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ORIGINAL ARTICLE

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True complete left bundle branch block reveals dyssynchrony evaluated by semiconductor single-photon emission computed tomography

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Abstract

Background: Conventional complete left bundle branch block (CLBBB) criteria sometimes result in a false-positive diagnosis that does not represent dyssynchrony. Recently, true CLBBB criteria have been proposed to detect responders to cardiac resynchronization therapy (CRT), although their correlation with severity of dyssynchrony or natural prognosis is unclear.

Methods: Ninety-four consecutive patients (74 ± 9 years, 63 men) with conventional CLBBB during sinus rhythm underwent semiconductor SPECT. They were divided into two groups: patients with true CLBBB and others. True CLBBB was characterized by the mid-QRS notching/slurring and wide QRS duration (male, ≥140 milliseconds; female, ≥130 milliseconds). Multivariate analysis was performed to detect left ventricular dyssynchrony (LVD), defined as bandwidth ≥145° and/or phase standard deviation (SD) ≥43°. Primary endpoints (hospitalization for heart failure or cardiac death) were evaluated.

Results: True CLBBB had wider bandwidth (145 ± 83° vs 110 ± 64°, $P = 0.024$) and higher phase SD (48 ± 26° vs 35 ± 19°, $P = 0.007$). Ejection fraction (EF), end-diastolic volume (EDV), summed rest score (SRS), and the presence of ischemic heart disease (IHD) showed no differences between groups ($P = 0.401$, 0.591, 0.165, and 0.212, respectively). Multivariate analysis revealed that true CLBBB, EF, and EDV were significant predictors of LVD (odds ratio, 12.6, 0.90, 1.03; $P = 0.003$, 0.002, 0.022, respectively). At 3-year follow-up (median 667 days), primary endpoints were comparable in both groups (log-rank, $P = 0.92$).

Conclusions: Patients with true CLBBB had more severe dyssynchrony on single-photon emission computed tomography than patients with nontrue CLBBB. On the other hand, the two groups showed no differences in EF, EDV, the presence of IHD, hospitalization for heart failure, and cardiac death.

KEYWORDS

cardiac prognosis, cardiac resynchronization therapy, complete left bundle branch block, dyssynchrony, single-photon emission computed tomography

1 | INTRODUCTION

The impact of LV dyssynchrony was indicated that approximately 30-50% of patients with congestive heart failure (CHF) presents intraventricular conduction delay.[1] As patients of end-stage CHF accompanying LV dyssynchrony resists optimal medical therapy,[2] physicians had tried to improve cardiac function using cardiac resynchronization therapy (CRT).[3,4] It is recommended that patients with wide QRS duration and complete left bundle branch block (CLBBB), which seemed to present LV dyssynchrony, undergo CRT. Despite CLBBB representing a reliable surrogate of LV dyssynchrony, the cardiac prognosis of patients with CLBBB is not always improved by introducing CRT.[5,6] Therefore, it is crucial to verify why CLBBB patients do not always respond to CRT.

In fact, the diagnosis of CLBBB is still controversial. Especially, inclusion of mid-QRS notching/slurring in CLBBB criteria has been recommended repeatedly,[7,8] but not uniformly accepted. Therefore, most studies have avoided defining specific CLBBB.[9–12] A strict CLBBB definition (true CLBBB) was proposed by Strauss: QRS duration ≧140 milliseconds for men or 130 milliseconds for women, QS or rS in leads V1 and V2, and mid-QRS notching or slurring in ≧2 of the following V1, V2, V5, V6, I, and aVL.[13] The major emphasis in the criteria is that a wider QRS duration and mid-QRS notching/slurring should be included when diagnosing CLBBB. Subsequently, several studies examined whether true CLBBB criteria could predict responders to CRT,[14–17] although the mechanism why the true CLBBB could be a predictor for CRT responder is unclear. Previous reports mention the relationship between true CLBBB and the severity of dyssynchrony, however, it is not verified well. Furthermore, the attempt would be difficult because standard methods for evaluating dyssynchrony have not been established.

A phase analysis using gated myocardial perfusion single-photon emission computed tomography (SPECT) provides information on regional wall thickening, which represents cardiac synchrony rapidly and automatically with high reproducibility, regardless of the examiner.[18,19]

The purpose of the present study is to explore whether true CLBBB criteria could detect LV dyssynchrony, with evaluation using SPECT. We also verified the natural prognosis of patients with true CLBBB before introducing CRT.

2 | METHODS

2.1 | Study population

Ninety-four consecutive patients with conventional CLBBB in ECG during sinus rhythm underwent semiconductor SPECT at Yokohama Minami Kyosai Hospital between July 2013 and January 2017. Patients with decompensated CHF, pacemaker implantation, cardiac resynchronization therapy, and atrial fibrillation were not included in the study. We excluded three patients with an LV end-systolic volume ≤10 mL since LV volumes are underestimated. The primary causes of the examinations for the 94 patients were as follows: abnormal ECG in 20, CHF in 31, investigation for ischemic heart diseases in 22, preoperative examinations in 14, chest pain symptoms in 5, and dyspnea in 2. A total of 49 patients (52%) were diagnosed as ischemic cardiomyopathy by the attending doctor considering past medical history consistent with subsequent medical tests (such as 12-lead electrocardiogram, echocardiography, and SPECT). Patients were divided into two groups according to true CLBBB criteria[13]: true CLBBB group (t-CLBBB) and non-true CLBBB group (nt-CLBBB). The study protocol was approved by the ethics committee of Yokohama Minami Kyosai Hospital, and written informed consent was obtained from all participants before the study.

2.2 | ECG analysis

An ECAPS12c (Nihon Koden Co., Tokyo, Japan) 12-lead ECG system was used to record ECG on the same day of the SPECT examination. The following ECG parameters were calculated automatically by the machine: heart rate (HR), QRS duration, and Sokolow-Lyon index. These automatically calculated parameters were confirmed and validated manually by another expert cardiologist. QRS duration was measured from the earliest onset to the latest end of the QRS complex. The Sokolow-Lyon index, defined as the sum of SV1 + RV5 or V6, was used to estimate LV hypertrophy (LVH). All patients were in sinus rhythm with CLBBB morphology.[20] CLBBB morphology was defined according to conventional CLBBB criteria: QRS duration ≥120 milliseconds, QS, or rS complex in V1-V2, and a monophasic R wave with no Q waves in leads V6 and I.[21] True CLBBB was defined as follows: QRS duration ≧140 milliseconds for men or 130 milliseconds for women, QS or rS in leads V1 and V2, and mid-QRS notching or slurring in ≧2 of the following leads: V1, V2, V5, V6, I, and aVL.[13] Figures 1 and 2 exhibit the electrocardiogram with and without true CLBBB, respectively.

2.3 | SPECT analysis

The semiconductor SPECT system was a dedicated cadmium zinc telluride-based ultrafast cardiac camera (Discovery NM 530c®; GE Medical Systems, Milwaukee, WI, USA). The data were collected as described by Esteves et al.[22] They were analyzed using cardiac software (Auto QUANT 4.3.1®; Cedars-Sinai Medical Center and ADAC Laboratories, Los Angeles, CA, USA) operating on a Windows-based workstation (Xeleris® TM3; GE Medical Systems). ToolSync® software (Emory University, Atlanta, GA, USA) operating on the workstation was used to automatically measure LV dyssynchrony parameters according to the methodology of Chen et al.[23]

The phases of the regional LV count changes through the cardiac cycle were calculated, representing the regional LV onset of mechanical contraction. Phase histogram bandwidth (includes 95% of the elements of the phase distribution) and phase standard deviation (SD; the SD of the phase distribution) were calculated automatically.[23] In all cases, the summed rest score (SRS) of the 17-segment

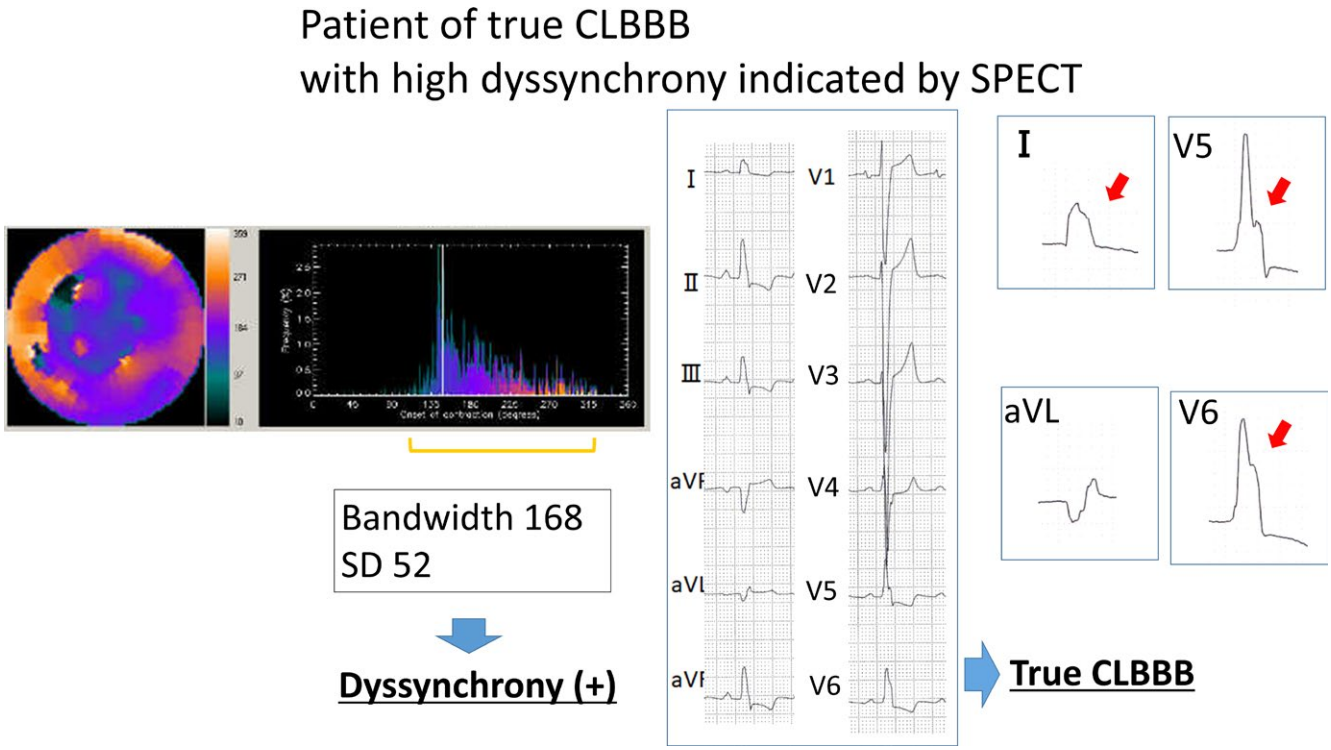


FIGURE 1 Example of true CLBBB with dyssynchrony defined by SPECT. (Left) LV dyssynchrony was demonstrated with quantitative gated SPECT. The phases of regional LV count changes through the cardiac cycle were calculated. Next, phase histogram bandwidth (includes 95% of the elements of phase distribution) and SD of the phase distribution were calculated. The present case had LV dyssynchrony, defined as phase histogram bandwidth ≥145° and/or phase SD ≥43°. (Right) The present case had wide QRS (≥150 ms) and mid-QRS notching in leads I, V5, and V6 (Red arrows), which define true CLBBB. CLBBB, complete left bundle branch block; LV, left ventricular; SD, standard deviation; SPECT, single-photon emission computed tomography

model of the myocardial perfusion map were calculated the method by Levine et al.[24]

2.4 | Evaluation of left ventricular dyssynchrony and outcomes

The present study used multivariate logistic regression analysis to predict left ventricular dyssynchrony (LVD), defined as bandwidth ≥145° and/or phase SD ≥43°.[18,19] Figures 1 and 2 exhibit the example case with and without LVD. We defined the primary endpoint as hospitalization for CHF or cardiac death.

2.5 | Statistical analysis

Parametrical continuous variables are shown as mean ± SD, while nonparametrical variables are shown as median (25% value, 75% value). Parametric variables were analyzed by a two-tailed *t* test, while nonparametric variables were analyzed by the Mann-Whitney test. Values of $P < 0.05$ were considered statistically significant.

We explored the overall population to identify variables correlated with LVD. Multivariate logistic regression with stepwise backward elimination was used to adjust for covariates that were found in univariate analyses to impact LVD with a *P* value of less than 0.05.

3 | RESULTS

The baseline characteristics of the 94 patients (mean age: 74 ± 9 years, 63 men) are summarized in Table 1. Fewer men had t-CLBBB (22 [54%] vs 41 [77%], $P = 0.026$), although there were no other differences in baseline characteristics between t-CLBBB and nt-CLBBB groups: hypertension (HTN) (25 [61%] vs 37 [70%], $P = 0.389$), diabetes mellitus (DM) (13 [32%] vs 21 [40%], $P = 0.518$), dyslipidemia (DLP) (17 [41%] vs 21 [40%], *P* = NS), chronic kidney disease (8 [20%] vs 17 [32%], $P = 0.234$), hemodialysis (HD) (1 [2%] vs 5 [9%], $P = 0.227$), known ischemic heart disease (IHD) (18 [44%] vs 31 [58%], $P = 0.212$), and past history of congestive heart failure (CHF) (23 [56%] vs 31 [58%], $P = 0.836$). In SPECT analysis, the two groups showed no differences in cardiac function and left ventricular size: ejection fraction (EF) (41 ± 17% vs 44 ± 17%, $P = 0.401$), end-diastolic volume (EDV) (103 ± 49 mL vs 109 ± 51 mL, $P = 0.591$), and end-diastolic volume (ESV) (67 ± 48 mL vs 67 ± 48 mL, $P = 0.922$). The presence of low EF (defined as <35%) showed no difference between the groups (14 [34%] vs 18 [34%], *P* = NS). The SRS was the same in both groups (10 vs 10, $P = 0.165$). The t-CLBBB group had wider bandwidth (145 ± 83° vs 110 ± 64°, $P = 0.024$) and high SD (48 ± 26° vs 35 ± 19°, $P = 0.007$). As defined, the t-CLBBB group had more LVD (24 [59%] vs 17 [32%], $P = 0.012$).

The ECG parameters according to the presence of LVD or t-CLBBB are shown in Table 2. The LVD group had high heart rate (HR) and wide

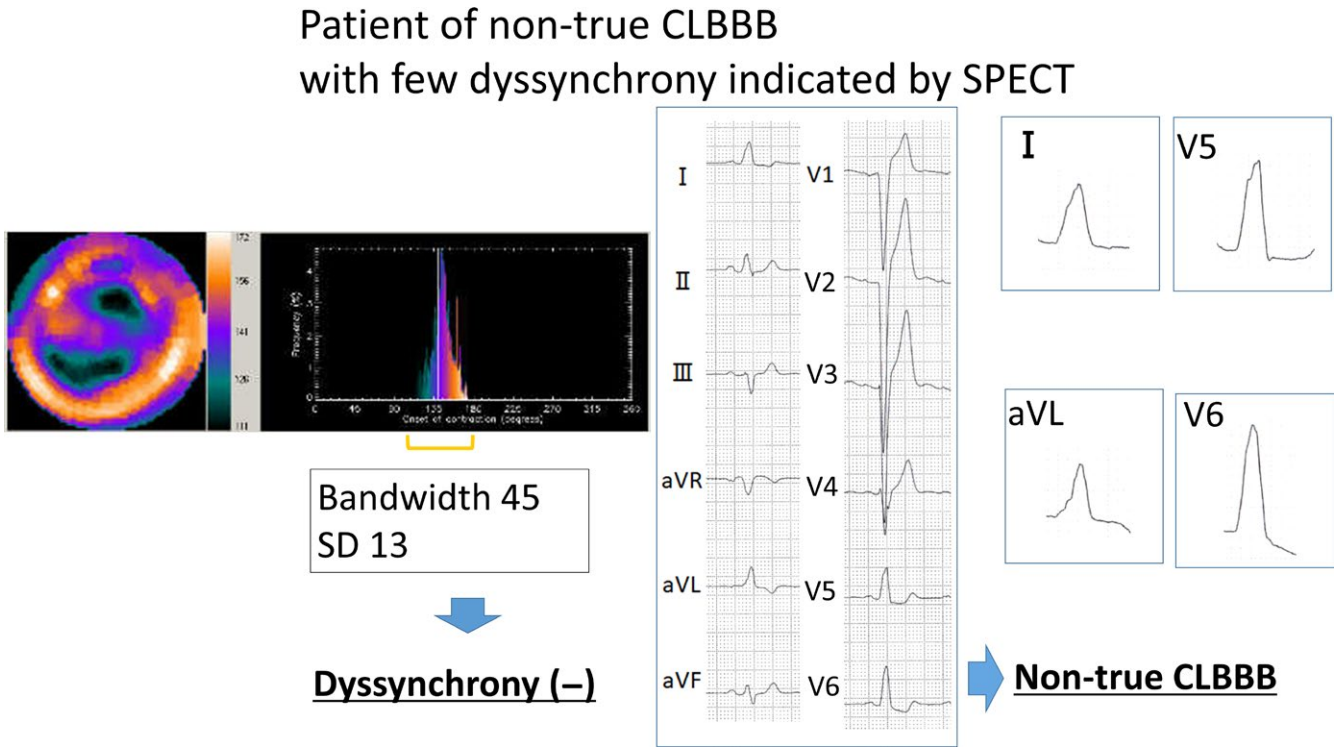


FIGURE 2 Example of nontrue CLBBB without dyssynchrony defined by SPECT. Evaluation of LV dyssynchrony by SPECT was described in Figure 1. (Left) The present case had a bandwidth of 45° and SD of 13°. Therefore, the LV dyssynchrony was not present. (Right) The present case had no obvious notching/slurring in a 12-lead electrocardiogram. CLBBB, complete left bundle branch block; LV, left ventricular; SPECT, single-photon emission computed tomography

QRS duration (HR, 81 ± 15/min vs 72 ± 13/min, $P = 0.002$, QRS duration, 148 ± 19 milliseconds vs 141 ± 13 milliseconds, $P = 0.027$). The presence of notching/slurring in the LVD group was more frequent in lateral leads (1, aVL, V5, and V6), inferior leads (2, 3, and aVF), and leads for t-CLBBB criteria (1, aVL, V1, V2, V5, and V6) ($P = 0.003$, 0.011, 0.003, respectively). The Sokolow Index was the same in groups with and without LVD (3.3 ± 1.4 mV vs 2.9 ± 0.9 mV, $P = 0.152$).

Multivariate logistic regression analysis with stepwise backward elimination revealed that t-CLBBB, EF, and EDV were significant and independent predictors of LVD (odds ratio, 12.6, 0.90, 1.03; $P = 0.003$, 0.002, 0.022, respectively) (Table 3). Among these variables, patients with t-CLBBB had wide bandwidth (146 ± 83° vs 113 ± 67°, $P = 0.035$), and correlation analysis revealed a moderate association between bandwidth and EDV/EF ($R = 0.711$, 0.766, $P = 0.001$, 0.001, respectively) (Figure 3).

During a median follow-up of 667 day (interquartile range 317-1045), 22 patients (8 with t-CLBBB) reached the primary endpoint. Kaplan-Meier analysis revealed that t-CLBBB was not associated with increased risk of reaching the primary endpoint (log-rank $P = 0.92$) (Figure 3).

4 | DISCUSSION

The present study had three important findings: t-CLBBB is associated with wide bandwidth and SD; low EF, high EDV, and the presence of t-CLBBB are independent predictors of dyssynchrony; and t-CLBBB itself was not associated with increased risk of either hospitalization for CHF or cardiac death (median follow-up of 667 days).

4.1 | Association between t-CLBBB and dyssynchrony

The major emphasis in the criteria for t-CLBBB is the presence of mid-QRS notching in several leads. Straus described the physiologic meaning of notching as follows: the first notch represents the time when the electrical depolarization wave front reaches the endocardium of the LV, whereas the second notch occurs when the depolarization wave front begins to reach the epicardium of the posterolateral wall.[13] He verified the meaning of the notches by computer simulation of LBBB, although the dispersion of depolarization had not been explored well in vivo.

Dyssynchrony has been evaluated using SPECT,[18,19,23,25,26] although definitive cutoff values for both bandwidth and SD had not been established. However, the presence of LVD in the present study is almost in line with previous reports (overall: 44%, t-CLBBB: 59%)[27,28] that mechanical dyssynchrony is not always seen in LBBB. We also quantified the correlation between t-CLBBB and bandwidth or SD ($P = 0.035$, 0.030, respectively, Table 1), and showed that t-CLBBB is associated with dyssynchrony using SPECT. Furthermore, the defined LVD were associated with the composite end points of cardiac failure and all-cause death (Supporting Information), indicating the LVD itself had impact on cardiac prognosis.

TABLE 1 Baseline characteristics in patients with/without true CLBBB

	Total (n = 94)	True CLBBB (N = 41)	Nontrue CLBBB (N = 53)	*P*
Age (y)	74 ± 9	75 ± 8	73 ± 10	0.213
Male (N, %)	63 (67%)	22 (54%)	41 (77%)	0.026*
BMI (kg/m^2)	22.5 ± 3.8	22.4 ± 3.3	22.6 ± 4.1	0.844
HTN (N, %)	62 (66%)	25 (61%)	37 (70%)	0.389
DM (N, %)	34 (36%)	13 (32%)	21 (40%)	0.518
DLP (N, %)	38 (40%)	17 (41%)	21 (40%)	1
CKD (N, %)	25 (27%)	8 (20%)	17 (32%)	0.234
HD (N, %)	6 (6%)	1 (2%)	5 (9%)	0.227
IHD (N, %)	49 (52%)	18 (44%)	31 (58%)	0.212
CHF (N, %)	54 (57%)	23 (56%)	31 (58%)	0.836
NYHA				
I (N, %)	64 (68%)	28 (68%)	36 (68%)	0.743
II (N, %)	27 (29%)	11 (27%)	16 (30%)	
III (N, %)	3 (3%)	2 (5%)	1 (2%)	
IV (N, %)	0	0	0	
LV EF (%)	43 ± 17	41 ± 17	44 ± 17	0.401
low EF (N, %)	32 (34%)	14 (34%)	18 (34%)	1
EDV (mL)	107 ± 50	103 ± 49	109 ± 51	0.591
ESV (mL)	67 ± 47	67 ± 48	67 ± 48	0.922
SRS	10 (6,19)	10 (6,23)	10 (6,16)	0.165
Bandwidth (°)	126 ± 75	145 ± 83	110 ± 64	0.024*
SD (°)	41 ± 23	48 ± 26	35 ± 19	0.007*
Dyssynchrony (N, %)	41 (44%)	24 (59%)	17 (32%)	0.012*

BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; DLP, dyslipidemia; CKD, chronic kidney disease; HD, hemodialysis; IHD, ischemic heart disease; CHF, past history of congestive heart failure; LVEF, left ventricular ejection fraction; low EF was defined as LVEF ≤35%; EDV, end-diastolic volume; ESV, end-systolic volume; SRS, summed stress score; SD, standard deviation of phase histogram; LV dyssynchrony was defined as both Bandwidth ≥143° and SD ≥45°.
Parametrical variables were shown as average ± SD, and nonparametrical variables as median (25%, 75% value).
*$P < 0.05$ was considered as significant.

The association between QRS duration and dyssynchrony has been reported repeatedly,[27,29] although the association is still unclear especially in patients with CLBBB.[28,30] Our study also revealed an association between QRS duration and dyssynchrony (OR 1.03, $P = 0.032$, Table 2), strongly supporting the idea that t-CLBBB criteria should include a wider QRS.[13]

Left ventricular volume evaluated by EDV and ESV was almost the same in t-CLBBB and nt-CLBBB (Table 1), possibly because we could not detect a difference in LV volume between these groups. It is hypothesized that t-CLBBB criteria exclude false positives by eliminating LV dilatation with LVH.[13,31,32] If the hypothesis is correct, the t-CLBBB group should have smaller LV volume compared with the nt-CLBBB group. On the other hand, we also demonstrated that EDV is an independent predictor of LV dyssynchrony (Table 2), which indicates that LV dilatation reflects the progression of LV dysfunction due to dyssynchrony.[28,33] Therefore, we speculate that patients with t-CLBBB had relatively severe progression of cardiac dilatation, conversely excluding LVH, which leads to the same EDV in both groups. As we did not evaluate LV thickness, further research is needed.

The present study revealed that t-CLBBB was more common in men (Table 1). However, previous reports did not detect a difference,[14,17] and we could not determine the basis for a sex-dependent difference. As our report included a relatively healthy population, differences in patient groups may influence the results. Table 1 also indicates that the t-CLBBB group had a greater tendency toward IHD. Although this was not statistically significant (41% vs 60%, $P = 0.092$), the result may also reflect the higher proportion of men.

4.2 | Prognosis of t-CLBBB

We demonstrated that t-CLBBB was not associated with increased risk of cardiac events in patients who had not undergone

TABLE 2 Distribution of ECG parameters in the presence of true CLBBB or LVD

	LVD (+) N = 41	LVD (–) N = 53	Sig (LVD (+) vs LVD (–))	T-CLBBB N = 41	Nt-CLBBB N = 53	Sig(t-CLBBB vs nt-CLBBB)
HR (bpm)	81 ± 15	72 ± 13	0.002*	76 ± 13	76 ± 16	0.936
QRS duration (ms)	148 ± 19	141 ± 13	0.027*	153 ± 16	137 ± 12	0.001*
Notching/slurring						
1, aVl, V5, V6	26 (63%)	17 (32%)	0.003*	41 (100%)	2 (4%)	0.001*
II, III, aVf	23 (56%)	15 (28%)	0.011*	27 (66%)	11 (21%)	0.001*
V1,2	1 (2%)	3 (6%)	1	4 (10%)	1 (2%)	0.164
V3,4	10 (24%)	19 (36%)	0.267	18 (44%)	11 (21%)	0.024*
1, aVl, V1, V2, V5, V6	26 (63%)	17 (32%)	0.003*	41 (100%)	2 (4%)	0.001*
Sokolow Index (mV)	3.3 ± 1.4	2.9 ± 0.9	0.152	3.1 ± 1.1	3.1 ± 1.2	0.744

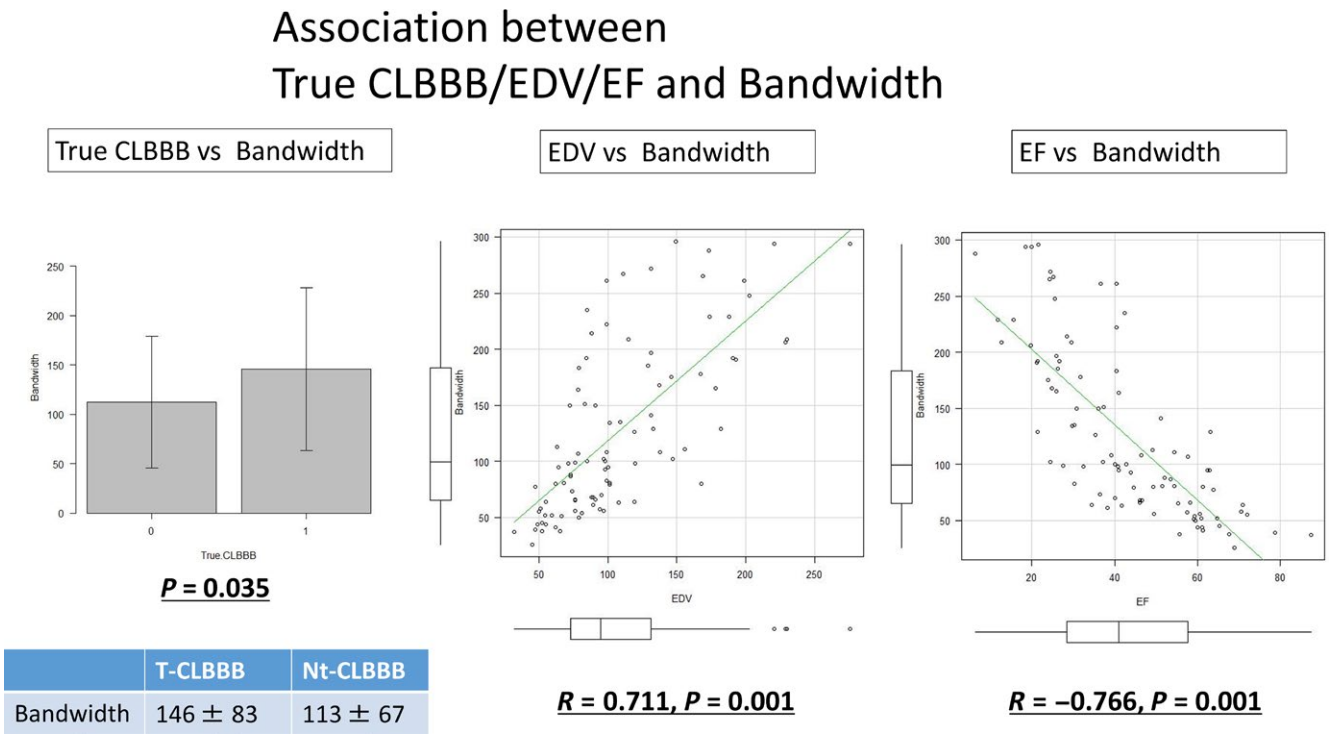
HR, heart rate; bpm, beats per minute; Sokolow Index: sum of SV1 + RV5 or RV6.
Parametrical variables were shown as average ± standard deviation.
*P < 0.05 was considered as significant.

TABLE 3 Multiple logistic regression analysis for LVD

	Univariate			Multivariate (step wised)		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (y)	1.01	0.97-1.06	0.607			
BMI (kg/m2)	1.04	0.93-1.16	0.464			
Male (N)	1.65	0.68-4.01	0.267			
CHF (N)	10.4	3.72-29.3	0.001*			
IHD (N)	2.26	0.98-5.22	0.056			
HTN (N)	0.99	0.42-2.34	0.985			
DM (N)	1.24	0.53-2.90	0.613			
DLP (N)	1.85	0.80-4.27	0.148			
CKD (N)	2.48	0.97-6.33	0.057			
HD (N)	1.32	0.25-6.89	0.745			
HR (bpm)	1.05	1.02-1.08	0.004*			
True CLBBB	2.99	1.28-6.98	0.011*	12.6	2.36-67.7	0.003*
QRS width (ms)	1.03	1.00-1.06	0.032*			
Mid-QRS notch	3.67	1.56-8.66	0.003*			
EF	0.88	0.83-0.92	0.001*	0.9	0.84-0.96	0.002*
EDV	1.04	1.02-1.05	0.001*	1.03	1.00-1.05	0.022*
SRS	1.12	1.05-1.20	0.001*			

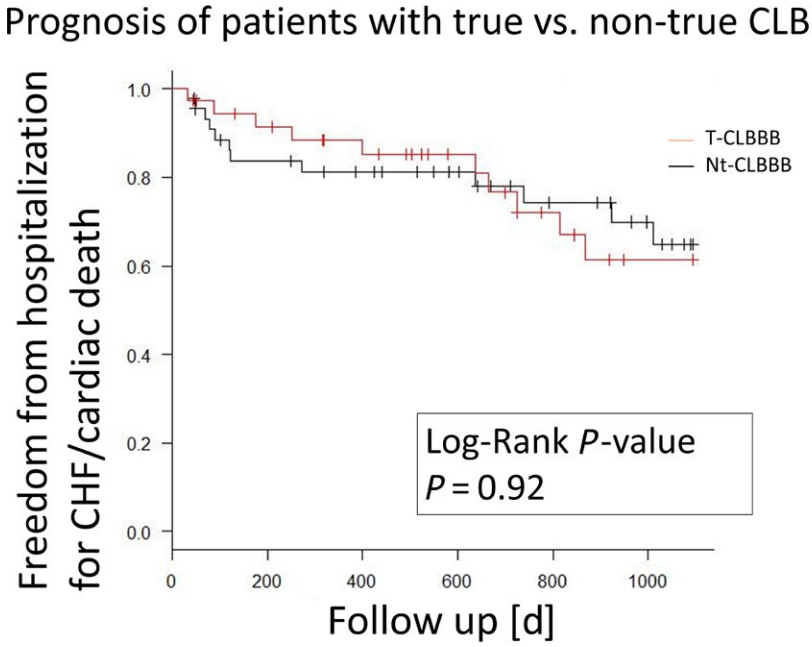
OR, odds ratio; 95% CI, confidence interval.
LVD was defined as Bandwidth of phase histogram ≥143° and/or phase standard deviation (SD) ≥45°.
Abbreviations were explained in Tables 1 and 2.
*P < 0.05 was considered as significant. Multivariate logistic regression with stepwise backward elimination was used to adjust for covariates that were found in univariate analyses to impact LVD with a P value of less than 0.05 (true CLBBB was included, on behalf of QRS width and/or mid-QRS notch).

CRT (Figure 4). The results have limited significance, although the prognostic value of t-CLBBB should be evaluated before introducing CRT. Previous studies demonstrated that t-CLBBB is associated with a preferable outcome following CRT,[14–17] although this remains controversial.[34] Furthermore, a limitation is that outcomes should be determined according to the natural prognosis, meaning whether patients with t-CLBBB have a prognosis comparable to those without t-CLBBB, before introducing CRT. The present study demonstrated



	T-CLBBB	Nt-CLBBB
Bandwidth	146 ± 83	113 ± 67

FIGURE 3 Associations between bandwidth and true CLBBB/EDV/EF. (Left) Patients with true CLBBB had larger bandwidth than patients without true CLBBB (146 ± 83° vs 113 ± 67°, *P* = 0.035). (Mid) EDV shows a moderate correlation with bandwidth (correlation coefficient [R], 0.711). (Right) EF shows a moderate correlation with bandwidth (*R* = 0.766). CLBBB, complete left bundle branch block; EF, ejection fraction; EDV, end-diastolic volume



	Baseline	1 year	2 years	3 years
T-CLBBB	33	25	15	9
Nt-CLBBB	49	34	21	9

FIGURE 4 Twelve patients who dropped out or reached the primary endpoint within 30 days were excluded. Finally, 82 patients were evaluated with Kaplan-Meier analysis. During a median follow-up of 667 days (interquartile range 317-1045), 22 patients (8 with true CLBBB) reached the primary endpoint. True CLBBB was not associated with increased risk of reaching the primary endpoint (log-rank *P* = 0.62). CLBBB, complete left bundle branch block

that patients with t-CLBBB do not have a better prognosis than those without t-CLBBB.

Our study had several important characteristics. First, the patients were relatively healthy, with no symptoms and normal EF. However, it has been demonstrated that the presence of LVD is associated with progression of LV dysfunction and cardiac failure.[35] Therefore, our population may represent an early stage of LVD. Furthermore, the nt-CLBBB group had a relatively high prevalence of IHD, which could demonstrate progression during a short follow-up period.

4.3 | Strength and clinical implication

The present study verified the association between true CLBBB criteria and dyssynchrony evaluated by SPECT. We enrolled only patients who had conventional CLBBB, and verified whether adding the true CLBBB criteria could improve to detect the dyssynchrony. The association between LVD and true CLBBB could support the adequacy introducing CRT to patients with true CLBBB.

5 | CONCLUSION

More patients with t-CLBBB had severe dyssynchrony than those with nt-CLBBB, as shown with SPECT. On the other hand, the two groups showed no difference in EF, EDV, ESV, the presence of IHD, hospitalization for heart failure, or cardiac death.

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CONFLICT OF INTEREST

Authors declare no conflicts of interest for this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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