Relationships between electrical and mechanical dyssynchrony in patients with left bundle branch block and healthy controls

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Background. **Abnormal electrical activation may cause dyssynchronous left ventricular (LV) contraction. In this study, we characterized and analyzed electrical and mechanical dyssynchrony in patient with left bundle branch block (LBBB) and healthy controls.**

Methods. **Myocardial perfusion imaging (MPI) data from 994 patients were analyzed. Forty-three patient fulfilled criteria for LBBB and 24 for controls. Electrical activation was characterized with vector electrocardiography (VECG) and LV function including mechanical dyssynchrony with ECG-gated MPI phase analysis.**

Results. **QRS duration (QRSd; $r = 0.69$, $P < .001$) and a few other VECG parameters correlated significantly with phase bandwidth (phaseBW) representing mechanical dyssynchrony. End-diastolic volume (EDV; $r = 0.59$, $P < .001$), ejection fraction and end-systolic volume correlated also with phaseBW. QRSd ($\beta = 0.47$, $P < .001$) and EDV ($\beta = 0.36$, $P = .001$) were independently associated with phaseBW explaining 55% of its variation. Sixty percent of patients with LBBB had significant mechanical dyssynchrony. Those patients had wider QRSd (159 vs 147 ms, $P = .013$) and larger EDV (144 vs 94 mL, $P = .008$) than those with synchronous LV contraction. Cut-off values for mechanical dyssynchrony seen in patients with LBBB were QRSd $\geq$ 165 ms and EDV $\geq$ 109 mL.**

Conclusions. **Despite obvious conduction abnormality, LBBB is not always accompanied by mechanical dyssynchrony. QRSd and EDV explained 55% of variation seen in phaseBW. These two parameters were statistically different between LBBB cases with and without mechanical dyssynchrony. (J Nucl Cardiol 2019;26:1228–39.)**

Key Words: Myocardial perfusion imaging · SPECT · Left bundle branch block · Phase analysis · Gated SPECT · Vector electrocardiography

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Abbreviations	
LBBB	Left bundle branch block
MPI	Myocardial perfusion imaging
VECG	Vector electrocardiography
SPECT	Single photon emission computerized tomography
QRSd	QRS duration
EDV	End-diastolic volume
phaseBW	Phase bandwidth (phase analysis parameter describing mechanical dyssynchrony)
$LBBB_{nor}$	Left bundle branch block patient with normal (synchronous) left ventricular contraction
$LBBB_{abn}$	Left bundle branch block patient with abnormal (dyssynchronous) left ventricular contraction

See related editorial, pp. 1240–1242

INTRODUCTION

The left bundle branch block (LBBB) is defined as prolonged QRS duration (QRSd) with specific features seen in the ECG.[1] In addition to electrical changes, mechanical function is often distorted in LBBB. In LBBB, the electrical activation reaches first the right ventricle, and then the electrical front usually transmits through the interventricular septum towards the lateral wall of the left ventricle (LV).[2] This abnormality in electrical conduction can result in mechanical dyssynchrony, myocardial remodeling and decreased cardiac function.[3] The variability in the location of the block and diversity in conduction path is seen among patients with LBBB,[4] and for that reason its influence on mechanical function can be diverse.

Cardiovascular diseases are common in patients with conduction abnormalities.[5] In patients with LBBB, myocardial contraction may also be disturbed by non-electric mechanisms, e.g., as result of myocardial infarction. Myocardial perfusion imaging (MPI) is used for diagnosing coronary artery disease (CAD). In addition to information of myocardial perfusion acquired from MPI; ECG-gated data can also been used for estimating LV mechanical dyssynchrony. With phase analysis method, three-dimensional view of the LV can be produced to match different phases of the cardiac cycle.

During recent years, the vector electrocardiography (VECG) has gained new attention in the electrocardiographic literature. A few study reports suggest that novel VECG parameters could be used as an indicator of left ventricular (LV) mechanical dyssynchrony[6] and even predict cardiac resynchronization therapy (CRT) response.[7] However, the electrical and mechanical dyssynchrony do not always go hand in hand. This is important to keep in mind when considering novel treatment options for the electrical dyssynchrony. For reasons mentioned above, our interest is to study VECG parameters ability to identify mechanical dyssynchrony seen in patients with LBBB.

METHODS

The study was approved by the Ethics Committee of the Northern Savo Hospital District.

The Study Population

We analyzed retrospectively 994 patients who underwent MPI single photon emission computer tomography (SPECT) study during April 2009 and May 2011 at Kuopio University Hospital. Control and LBBB groups were formed from the study population with precisely selected criteria.

The inclusion into LBBB group was based on Strauss criteria.[1] Criteria for LBBB included QRS duration (QRSd) $\geq$ 140 ms for men and $\geq$ 130 ms for women, along with mid-QRS notching or slurring observed at least in two contiguous leads in V_1, V_2, V_5, V_6, I, and aVL, and QS or rS in leads V_1 and V_2. Forty-five patients fulfilled these criteria. The inclusion criteria for control group (no history of cardiac diseases, normal ECG and only mild coronary artery calcification according to lowdose computer tomography (CT), and no history of hypertension, diabetes, pulmonary diseases, cerebrovascular disorders, obesity, significant cancer or cancer treatments, and normal stress and rest in MPI results) were fulfilled in 27 subjects.

Three patients were discarded from the control group, and two from LBBB group due to technical problems in SPECT scanning and the final study population consisted of 43 patients with LBBB and 24 controls. Due to limited sample size, women and men were pooled together. The upper limit of the highest normal for phase analysis results was defined as controls mean values plus two standard deviations. Further, we divided patients with LBBB into two subgroups according to normal ($LBBB_{nor}$, N = 17) and abnormal phase analysis results ($LBBB_{abn}$, N = 26).

Myocardial Perfusion Imaging Protocol

As our normal MPI protocol, one-day adenosine MPI protocol was used for this study. Caffeine-containing products were avoided 24 hour before and during the study. Patients were given adenosine (140 μg/kg/minute) intravenously for 6 min. Intravenous tetrofosmin (300 MBq/8.1 mCi ^{99m}Tc-tetrofosmin) injection was given within 4 min from the start of adenosine administration. Patients with LBBB were lying in the supine position and control subjects were riding on a bicycle ergometer with 20 to 60 W loads during the pharmacological stress with adenosine. The scanning was performed

30 min post injection at the stress phase and the rest acquisition 45 min after the second tetrofosmin (700 MBq/18.9 mCi ^{99m}Tc-tetrofosmin) injection.

MPI scans were performed in supine position with a dual-detector SPECT/CT system (Philips Precedence; Royal Philips N.V., Amsterdam, Netherlands). The image acquisition was carried on with detectors in 90° configurations using 180° body contour orbits with 64 projections. Energy window with a width of 20% was centered on 140 keV and images were acquired with 128 × 128 matrix size. Also, a low-dose CT scan was acquired. Reconstructions were made with HERMES Hybrid Recon Cardiology (Hermes Medical Solution AB, Stockholm, Sweden). The LV perfusion was analyzed from non-gated MPI data using QPS2012-program (Cedars-Sinai Medical Center, Los Angeles, CA). Stress and rest images were scored according to the 17-segment LV model and a five-point scale (0; normal to 4; absence tracer uptake). Summed rest score (SRS) equal to or above two was considered to represent myocardial scar, and summed difference score (SDS) above two was considered to represent myocardial ischemia.[8]

Phase Analysis of MPI

Phase analysis data were collected with rest perfusion scanning. The gated MPI data were acquired with 16-time bins, and with 25 or 30 second per angle depending on patient's weight (if weight was < 100 kg 25 second/angle was used, and if weight was ≥ 100 kg 30 second/angle was used).

Phase parameters were analyzed from ECG -gated MPI data using QGS2012-program (Cedars-Sinai Medical Center, Los Angeles, CA). The myocardial surfaces were presented using 2D ellipsoidal coordinate systems with 36 longitudes and 28 latitudes leading to 1008 surface sampling points. Myocardial contraction onset time was detected with changes observed in myocardial pulse quantity. Five percent of phase angles corresponding to sampling points with the lowest periodic myocardial count variation was discarded. Contraction onset times were presented in phase histogram. The phase bandwidth (phaseBW), phase distribution standard deviation (phaseSD) and phase entropy (Entropy%) of the histogram were calculated as dyssynchrony measures. PhaseSD represents the heterogeneity of LV myocardial contraction onset times and phaseBW stands for the distribution of time during which 95% of the LV is starting the contraction.[9] Also, information about LV volumes (end-diastolic volume; EDV and end-systolic volume; ESV) and ejection fraction (EF) was gained.

Synthesizing VECG from Conventional 12 Lead Measurements

12-lead ECG was recorded at rest before adenosine administration. Mason–Likar leads were used. VECG parameters were produced with in-house developed semiautomatic VECG analysis tool. The R-wave fiducial points were detected from lead V_5 using Kubios HRV software [10] and detections were verified by visual inspection. Kors matrix [11] was used to synthesize VECG from conventional 12-lead ECG recordings (Figure 1). Kors regression-based matrix was selected because it has shown to approximate Frank's lead system more precisely as compared to other methods.[12–14] Averaged beat segments (P-QRS-T) were produced and a median beat was calculated. Averaged P-QRS-T segments were produced for *x*-, *y*- and *z*-leads using the selected segments. Onset and offset times of P-, QRS- and T-waves were approved by a trained specialist.

The mean QRS- and T-wave vector loop angles were defined in frontal, transverse and sagittal planes. QRS-T angle (QRSTα) was defined as an angle between the resultant vectors of the QRS and T wave vector loops. cosRT was defined as the mean of cosines of the angles between the dominant QRS-complex loop vectors and T-wave loop vector. QRSTα and cosRT describe uniformity of repolarization and depolarization forces. The QRS-angle in the frontal plane was defined as the angle between the x-axis and the QRSloop in the frontal plane, the QRS angle in the horizontal plane as the angle between the *x*-axis and the QRS loop in the horizontal plane and the QRS angle in the sagittal plane as the angle between *z*-axis and the QRS loop in the sagittal plane. The QRS loop width, length and 2D area (QRS area 2D) were defined by reducing QRS loop into a two-dimensional space.[15] QRS vector loop total area (QRS area 3D) was determined in tri-dimensionally.[16] Normal spatial QRS loop lies approximately in a single plane. Non-planarity of the loop was estimated using ratio between area 2D and area 3D (QRS area 2D/QRS area 3D).

Generally, Cornell voltage (CorV) is used for estimating LV hypertrophy (LVH).[17] In this study, we used it to describe the overall electrical activity. Because obesity can affect QRS amplitudes due to attenuation, we also used weight-corrected Cornell voltage in the analyses.[18] Also, Sokolow–Lyon index was calculated.[19]

Statistical Methods

Shapiro–Wilk's test and visual evaluation of histogram were used to determine normal distribution. In the case of non-normally distributed variables, logarithmic transformation was performed. Correlations for phase analysis results and VECG parameters were calculated in the whole study population and its subgroups. Descriptive data were expressed as mean ± SD. When two independent groups were compared, we used independent samples *T* test for continuous parameters and χ^2 test for class variables. Pearson's correlation was conducted to investigate univariate linear correlations. ECG/VECG parameters association with phaseBW was estimated with multivariable regression analysis. Statistical significance level was set at $P < .05$. To estimate best cut-off values for studied variables, ROC analysis (receiver operating characteristic) was used. The optimal cut-off value was detected according to the maximal sum of sensitivity and specificity. Statistical analyses were performed using SPSS software (IBM SPSS Statistics, 2013, version 22.0).

RESULTS

Clinical characteristics of the study population are presented in Table 1. Compared to patients with LBBB,

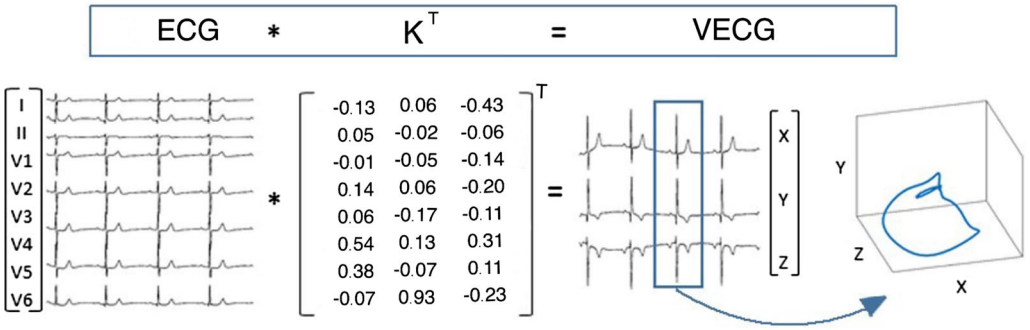

Figure 1. Synthetization of VECG from 12 lead ECG using Kors matrix. *VECG*, vector electrocardiography; *KT*, Kors transpose; *T*, transpose.

control subjects were younger and their BMI (body mass index) was significantly lower. There was no significant difference in gender distribution between the two groups ($P = .506$). Patients in the LBBB group were on more medications (heart, diabetes and cholesterol medication was taken into account) than controls (average number of medication used; 4.5 vs 0.5, $P < .001$). In the LBBB group, there were also more patients who had a history of CAD and heart failure. They also had a higher prevalence of hypertension and diabetes ($P < .001$). Patients with LBBB had more scar and ischemia findings in MPI study than controls ($P < .001$). All parameters reflecting mechanical dyssynchrony in phase analysis were significantly higher ($P < .001$) in the LBBB group than among controls (Table 2). Also EDV and ESV were higher ($P = .001$) and EF% lower ($P < .001$) in LBBB group. Almost all ECG/VECG parameters were significantly different between controls and patients with LBBB (Table 2). Controls and $LBBB_{nor}$ were also compared: $LBBB_{nor}$ had significantly higher phaseBW ($P = .029$) and Entropy% ($P = .001$) than controls. PhaseSD was not statistically different between two groups ($P = .321$).

Limit of the highest normal phase parameters gained from the controls was 126 ms (48°) for phaseBW, 44 ms (17°) for phaseSD and 63% for Entropy%.

$LBBB_{nor}$ had synchronous (phaseBW ≤ 126 ms and phaseSD ≤ 44 ms) and $LBBB_{abn}$ had dyssynchronous (phaseBW > 126 ms or/and phaseSD > 44 ms) LV contraction. There were no significant differences between the two LBBB subgroups in age, gender, height, weight, the medication used or prevalence of comorbidities. EDV and ESV were significantly higher and EF% lower in $LBBB_{abn}$ group than in $LBBB_{nor}$ group. The QRSd was the only ECG/VECG parameter that was significantly different between the two LBBB subgroups (Table 2). $LBBB_{abn}$ patients had more abnormal MPI findings classified as scars than $LBBB_{nor}$ patients, but there was no difference in the prevalence of ischemia (Table 1). Patients with LBBB were also divided into two groups; those with (N = 20) and those without (N = 23) myocardial scar. Patients with myocardial scar (SRS ≥ 2) had statistically more mechanical dyssynchrony (phaseBW 43 vs 40, $P = .012$) and their EDV was higher (86 vs 32 mL). However, there were no statistical differences between these two groups according to QRSd (158 vs 150 ms, $P = .126$).

In the pooled population (consisting of both control subjects and patients with LBBB), there was moderate correlation ($r = 0.63$-0.72, $P < .001$ for all) between phase parameters (phaseBW, phaseSD and Entropy%) and QRSd (Table 3, Figure 2). A statistically significant correlation was also seen between QRSd and all phase parameters among patients with LBBB ($r = 0.39$ to 0.55, $P < .01$ for all) as well as in its subgroup $LBBB_{abn}$ ($r = 0.46$ to 0.67 $P < .02$ for all). However, in the control group and subgroup $LBBB_{nor}$, there were no significant correlations between phase parameters and QRSd. In pooled population, the correlation between CorV and all phase analysis parameters was moderate ($r = 0.54$ to 0.62, $P < .001$ for all) (Table 3, Figure 2). In subgroups analysis, significant correlation was seen between phaseBW and CorV among $LBBB_{nor}$ patients ($r = 0.50$, $P = .040$). Also, when all patients with LBBB were studied CorV correlated with phaseBW ($r = 0.34$, $P = .024$) and Entropy% ($r = 0.33$, $P = .033$). The Cornell voltage-BMI product correlated significantly with all phase parameters ($r = 0.51$ to 0.65, $P < .001$ for all) in the pooled population. When study population was divided into subgroups correlations were non-significant. There was no significant correlation between phase analysis results and Sokolo–Lyon index.

The morphology and the orientation of the QRS vector loop of patients with LBBB differed from the control one (Table 2). The average QRS loop was longer and narrower in patients with LBBB than in control

Table 1. Clinical characteristics in control, LBBB group and LBBB subgroups

	Control group	LBBB group	Sig. (controls vs LBBB)	$LBBB_{nor}$	$LBBB_{abn}$	Sig. ($LBBB_{nor}$ vs $LBBB_{abn}$)
Background information						
Number of study subjects	24	43		17	26	
Men/Women	7/17 (29%/71%)	16/27 (37%/63%)	$P = .506$	5/12 (29%/71%)	11/15 (42%/58%)	$P = .392$
Age (years)	58.3 ± 8.6	68.5 ± 10.2	$P < .001$*	71.5 ± 7.3	66.5 ± 11.5	$P = .063$
Weight (kg)	71.9 ± 9.7	84.4 ± 16.4	$P = .001$*	82.2 ± 15.8	85.8 ± 17.0	$P = .152$
Height (cm)	169.1 ± 8.8	165.8 ± 9.9	$P = .172$	163.5 ± 10	167.2 ± 10.0	$P = .323$
BMI (kg/m^2)	25.1 ± 2.8	30.8 ± 5.8	$P < .001$*	30.9 ± 6.6	30.7 ± 5.4	$P = .986$
Medication used						
ACE/ARB	0 (0%)	30 (70%)	$P < .001$*	10 (59%)	20 (77%)	$P = .206$
ASA	4 (17%)	30 (70%)	$P < .001$*	13 (77%)	17 (65%)	$P = .439$
Beta blocker	4 (17%)	31 (72%)	$P < .001$*	10 (59%)	21 (81%)	$P = .280$
Calcium blocker	0 (0%)	9 (21%)	$P = .016$*	5 (29%)	4 (15%)	$P = .269$
Cholesterol medication	5 (21%)	35 (81%)	$P < .001$*	21 (81%)	14 (82%)	$P = .896$
Diabetes medication	0 (0%)	8 (19%)	$P = .024$*	4 (24%)	4 (15%)	$P = .502$
Diuretic	0 (0%)	19 (44%)	$P < .001$*	10 (59%)	9 (35%)	$P = .118$
Nitrate	0 (0%)	16 (37%)	$P < .001$*	8 (47%)	8 (31%)	$P = .280$
Comorbidities						
CAD	0 (0%)	22 (51%)	$P < .001$*	10 (59%)	12 (46%)	$P = .416$
PCI	0 (0%)	8 (19%)	$P = .024$*	3 (18%)	5 (19%)	$P = .896$
Infarction	0 (0%)	7 (16%)	$P = .037$*	2 (12%)	5 (19%)	$P = .517$
CABG	0 (0%)	4 (9%)	$P = .123$	1 (6%)	3 (12%)	$P = .531$
Pacemaker	0 (0%)	1 (2%)[a]	$P = .453$	1 (6%)[a]	0 (0%)	$P = .413$
Hypertension	0 (0%)	32 (74%)	$P < .001$*	15 (88%)	17 (65%)	$P = .093$
Heart failure	0 (0%)	22 (51%)	$P < .001$*	6 (35%)	16 (62%)	$P = .092$
Pulmonary disease	0 (0%)	14 (33%)	$P = .002$*	7 (41%)	7 (27%)	$P = .329$
Obesity (BMI ≥ 30 kg/m^2)	0 (0%)	22 (51%)	$P < .001$*	8 (47%)	14 (54%)	$P = .663$
Diabetes	0 (0%)	12 (28%)	$P < .001$*	6 (35%)	6 (23%)	$P = .383$
Kidney disease	0 (0%)	2 (5%)	$P = .283$	1 (6%)	1 (4%)	$P = .757$
MPI findings						
SRS	0.0 ± 0.2	2.4 ± 4.1	$P < .001$*	0.7 ± 1.2	3.6 ± 4.9	$P = .008$*
Scar[b]	0 (0%)	20 (47%)	$P < .001$*	4 (24%)	16 (62%)	$P = .015$*

Table 1 continued

	Control group	LBBB group	Sig. (controls vs LBBB)	$LBBB_{nor}$	$LBBB_{abn}$	Sig. ($LBBB_{nor}$ vs $LBBB_{abn}$)
SDS	0.5 ± 0.6	1.9 ± 1.9	$P < .001$*	1.8 ± 1.6	1.9 ± 2.1	$P = .894$
Ischemia[c]	0 (0%)	9 (21%)	$P = .016$*	3 (18%)	6 (23%)	$P = .669$

LBBB, left bundle branch block; *$LBBB_{nor}$*, patients with LBBB and normal phase analysis results (phase analysis bandwidth and it´s standard deviation); *$LBBB_{abn}$*, patients with LBBB and abnormal phase results; *Sig.*, statistical significance; *ACE/ARB*, angiotensin converting enzyme/angiotensin receptor blocker; *ASA*, acetylsalicylic acid; *CAD*, coronary artery disease; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *BMI*, body mass index; *MPI*, myocardial phase imaging; *SRS*, summed rest score; *SDS*, summed difference score

*Statistically significant finding ($P > .05$)

[a]Pacemaker (synchronize only if severe arrhythmia detected, no synchronization observed during the study)

[b]Scar is defined from MPI data (SRS ≥ 2)

[c]Ischemia is defined from MPI data (SDS > 2)

subjects. The angle between the x-axis and the QRS loop in the horizontal plane was wider in patients with LBBB, and the angle between the z-axis and the QRS loop in the sagittal plane was smaller (Table 2). Those findings designate that the average QRS-loop of patient with LBBB is pointing more downward, posteriorly and medial in patients with LBBB than in control patients. When $LBBB_{abn}$ and $LBBB_{nor}$ were compared to each other, no statistically significant difference was detected in orientation or morphology of the QRS-vector loop (Table 2). There was a significant correlation between all phase parameters and the QRS angle in the frontal, horizontal and sagittal planes (Table 3). When correlations were studied in subgroups, only significant correlation was seen among patients with LBBB (N = 43) between QRS angle in the horizontal plane and phaseBW ($r = 0.31$, $P = .044$), as well as between QRS angle in the horizontal plane and Entropy% ($r = 0.35$, $P = .028$).

QRS-loop area estimated in 2D plane was smaller in group consisting of patients with LBBB than among controls ($P = .002$) but larger when estimated tridimensionally ($P < .001$). Ratio between 2D and 3D QRS area (QRS area 2D/QRS area 3D) was smaller in patients with LBBB than controls (Table 2). QRS loop diameter was longer in LBBB group ($P = .019$) There was no significant difference between LBBB subgroups considering these parameters.

ECG/VECG parameters ability to explain phaseBW variation among patients with LBBB was analyzed by multivariate analysis (Table 4). QRSd and EDV were independently associated with phaseBW. QRSd ($\beta = 0.45$, $P < .001$) explained 47% of variation seen in phaseBW. When EDV ($\beta = 0.36$, $P = .001$) was added to the model, explanation of phaseBW variation was increased to 55%. Univariate analysis results and other parameters in the model are demonstrated in the Table 4. Optimal cut-off values (maximal sum for sensitivity and specificity) for detection of mechanical dyssynchrony among patients with LBBB were determined by ROC analysis (Figure 3). For QRSd, the optimal cut-off value was 165 ms, with the sensitivity of 42% and specificity of 100%. Cut-off value for EDV was 109 mL, with sensitivity of 69% and specificity of 71%.

DISCUSSION

In this study, we found out that even though Strauss criteria [1] were used for patient selection, only 60% of patients with LBBB had mechanical dyssynchrony in MPI phase analysis. Several ECG/VECG parameters correlated significantly with mechanical dyssynchrony when the whole population (consisting of both control

Table 2. Phase analysis and VECG parameters in controls and patients with LBBB

	Controls	LBBB group	Sig. (controls vs LBBB)	$LBBB_{nor}$	$LBBB_{abn}$	Sig. ($LBBB_{nor}$ vs $LBBB_{abn}$)
Number of study subjects	24	43		17	26	
Rest MPI phase parameters						
PhaseBW (ms)	79 ± 23	136 ± 46	$P < .001$*	94 ± 17	164 ± 36	$P < .001$*
PhaseSD (ms)	25 ± 11	40 ± 13	$P < .001$*	28 ± 7	48 ± 10	$P < .001$*
Entropy%	56 ± 4	65 ± 5	$P < .001$*	60 ± 4	68 ± 3	$P < .001$*
Rest MPI volumetric parameters						
EDV (mL)	77 ± 16	125 ± 67	$P = .001$*	97 ± 27	144 ± 79	$P = .008$*
ESV (mL)	29 ± 10	76 ± 69	$P = .001$*	49 ± 24	94 ± 83	$P = .015$*
EF (%)	63 ± 8	45 ± 15	$P < .001$*	51 ± 12	42 ± 16	$P = .048$*
VECG parameters						
QRS duration (ms)	93 ± 12	154 ± 15	$P < .001$*	147 ± 8	159 ± 17	$P = .013$*
QRS-T-angle (deg.)	70 ± 39	164 ± 19	$P < .001$*	165 ± 7	163 ± 25	$P = .716$
cosRT	0.31 ± 0.55	− 0.93 ± 0.16	$P < .001$*	− 0.96 ± 0.03	− 0.92 ± 0.20	$P = .336$
QRS angle in frontal plane (deg.)	48 ± 20	75 ± 18	$P < .001$*	73 ± 20	77 ± 18	$P = .430$
QRS angle in horizontal plane (deg.)	36 ± 25	81 ± 10	$P < .001$*	79 ± 12	83 ± 9	$P = .198$
QRS angle in sagittal plane (deg.)	60 ± 16	27 ± 6	$P < .001$*	28 ± 8	27 ± 6	$P = .646$
QRS-vector loop length (mV)	1.91 ± 0.46	2.50 ± 0.88	$P = .001$*	2.50 ± 0.78	2.50 ± 0.95	$P = .996$
QRS-vector loops width (mV)	0.84 ± 0.38	0.47 ± 0.22	$P < .001$*	0.44 ± 0.21	0.49 ± 0.23	$P = .472$
QRS-loop diameter (mV)	5.0 ± 1.2	5.8 ± 1.6	$P = .019$*	5.6 ± 1.5	5.9 ± 1.7	$P = .610$
QRS area 2D (mV^2)	1.20 ± 0.76	0.63 ± 0.47	$P = .002$*	0.60 ± 0.54	0.65 ± 0.43	$P = .774$
QRS area 3D (mVs)	0.036 ± 0.013	0.167 ± 0.060	$P < .001$*	0.174 ± 0.063	0.157 ± 0.055	$P = .368$
QRS area 2D/area 3D (mV/s)	33.9 ± 17.4	3.7 ± 2.2	$P < .001$*	3.7 ± 2.3	3.6 ± 2.3	$P = .905$
Sokolow-Lyon (mm)	23 ± 6	26 ± 9	$P = .132$	28 ± 10	25 ± 8	$P = .385$
Cornell voltage (mm)	8 ± 4	22 ± 9	$P < .001$*	20 ± 7	24 ± 10	$P = .153$

VECG, vector electrocardiography; *LBBB*, left bundle branch block; *Sig.*, statistical significance; $LBBB_{nor}$, patients with LBBB and normal phase analysis results (phase analysis bandwidth and it´s standard deviation); $LBBB_{abn}$, patients with LBBB and abnormal phase results; *MPI*, myocardial perfusion imaging; *phaseBW*, phase analysis bandwidth; *phaseSD*, phase analysis standard deviation; *Entropy%*, phase analysis entropy percent; *EDV*, end-diastolic volume; *ESV*, end-systolic volume; *EF*, ejection fraction; *cosRT*, cosine of the angle between QRS and T-loops; *2D*, two-dimensional; *3D*, tridimensional
*Statistically significant finding ($P > .05$)

subjects and patients with LBBB) was studied. In multivariate analysis, independent predictors of mechanical dyssynchrony were QRSd and EVD. QRSd variation was able to explain 47% of the variation in phaseBW. Together, QRSd and EDV explained 55% of the phaseBW variation.

Normally, the LV contraction occurs nearly simultaneously in all LV segments. A wide range of contraction patterns are seen among patients with LBBB influencing in the electrical and the mechanical function of LV.[4,20] Also, pathophysiology of dyssynchrony is multifactorial, and several cellular and molecular changes have been seen.[21] Furthermore, LBBB may cause structural changes in the myocardium through remodeling.[3] Studies of endocardial mapping and simulation have demonstrated that about a third of patients interpreted to have a complete LBBB, might have false-positive finding. In these cases, LV conduction can be delayed due to LV dilatation, hypertrophy, or incomplete LBBB.[22,23] In this study, we demonstrated that although electrical and mechanical dyssynchrony has a significant association, mechanical dyssynchrony is not always seen in LBBB. This observation is in line with the previous study.[24] When whole study population was pooled, several ECG and VECG parameters had a statistically significant correlation with mechanical dyssynchrony measures. However, the statistical significance of these results was generally lost in subgroup analyses. The aetiological diversity of LBBB might explain why electrical dyssynchrony is not always connected to mechanical one. According to multivariate regression analysis, ECG/VECG parameters explained about half of the variation seen in mechanical dyssynchrony (phaseBW). Taken together our findings suggest

Table 3. Correlation between phase analysis results and VECG and MPI parameters among all study participants

	PhaseBW (ms)	Sig.	PhaseSD (ms)	Sig.	Entropy (%)	Sig.
VECG parameters						
QRS duration (ms)	0.690	$P < .001$*	0.628	$P < .001$*	0.721	$P < .001$*
QRS-T-angle (degrees)	0.454	$P < .001$*	0.380	$P < .001$*	0.585	$P < .001$*
cosRT	− 0.447	$P < .001$*	− 0.374	$P = .002$*	− 0.586	$P < .001$*
QRS angle in frontal plane (degrees)	0.431	$P = .001$*	0.368	$P = .002$*	0.464	$P < .001$*
QRS angle in horizontal plane (degrees)	0.515	$P < .001$*	0.451	$P < .001$*	0.556	$P < .001$*
QRS angle in sagittal plane (degrees)	− 0.504	$P < .001$*	− 0.423	$P < .001$*	− 0.565	$P < .001$*
QRS-vector loop length (mV)	0.309	$P = .011$*	0.355	$P = .003$*	0.318	$P = .009$*
QRS-vector loops width (mV)	− 0.242	$P = .049$*	− 0.219	$P = .075$	− 0.356	$P = .003$*
QRS-loop diameter (mV)	0.367	$P = .011$*	0.338	$P = .005$*	0.276	$P = .024$*
QRS 2D area (mV^2)	− 0.206	$P = .094$*	− 0.167	$P = .178$	− 0.299	$P = .014$*
QRS area 3D (mVs)	0.635	$P < .001$*	0.567	$P < .001$*	0.632	$P < .001$*
QRS Area 2D/QRS area 3D (mV/s)	− 0.559	$P < .001$*	− 0.491	$P < .001$*	− 0.579	$P < .001$*
Sokolow-Lyon (mm)	0.097	$P = .437$	0.153	$P = .217$	0.037	$P = .769$
Cornell voltage (mm)	0.577	$P < .001$*	0.542	$P < .001$*	0.622	$P < .001$*
Parameters gained from MPI study						
EDV	0.592	$P < .001$*	0.563	$P < .001$*	0.595	$P < .001$*
SRS	0.475	$P < .001$*	0.457	$P < .001$*	0.562	$P < .001$*

VECG, vector electrocardiography; *MPI*, myocardial perfusion imaging; *phaseBW*, phase analysis bandwidth; *Sig.*, statistical significance; *phaseSD*, phase analysis standard deviation; *Entropy%*, phase analysis entropy; *cosRT*, cosine of the angle between QRS and T-loops; *2D*, two-dimensional; *3D*, tridimensional; *EDV*, end-diastolic volume; *SRS*, summed rest score
*Statistically significant finding ($P > .05$)

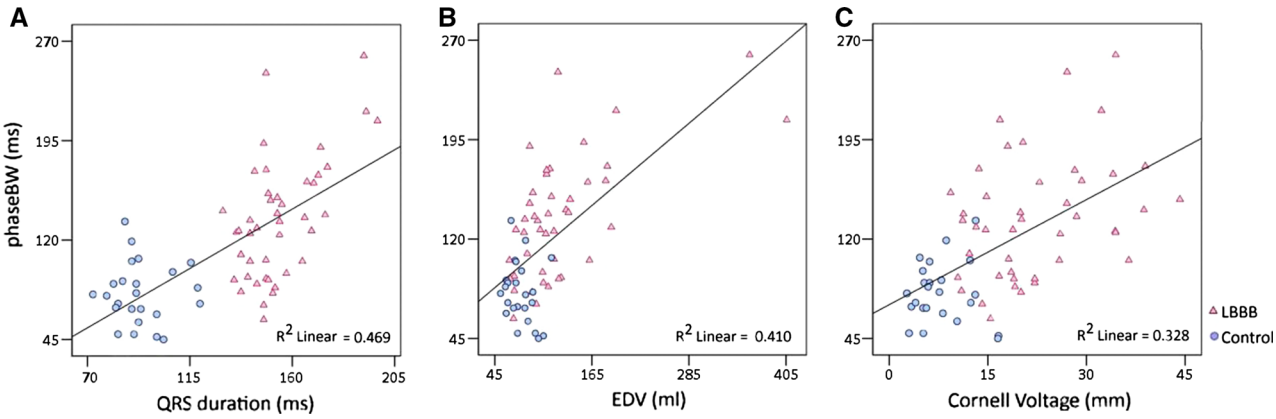

Figure 2. Correlations between phase analysis bandwidth and QRS duration, EDV as well as Cornell voltage. Controls are marked with blue circles and patients with left bundle branch block (LBBB) with red triangles. The *P* value was <.001 for all presented parameters. *PhaseBW*, bandwidth; *EDV*, end-diastolic volume.

Table 4. Results of univariate (enter) and multivariate (stepwise) analysis of selected parameters ability to predict phaseBW variance

	Univariate			Multivariate		
	B	β	**Sig.**	**B**	β	**Sig.**
QRS duration (ms)	0.995	0.685	$P < .001$	0.683	0.470	$P < .001$
EDV (mL)	0.516	0.641	$P < .001$	0.291	0.360	$P = .001$
Cornell voltage (mV)	2.642	0.573	$P < .001$			
SRS	7.238	0.525	$P < .001$			
Gender	10.572	0.106	$P = .185$			
Total R^2				55%, $P < .001$		
Total R^2 adjusted				54%, $P < .001$		

phaseBW, phase analysis bandwidth; *EDV*, end diastolic volume; *SRS*, summed rest score (defines myocardial scaring); *B*, unstandardized coefficient; β, standardized coefficients; *Sig.*, significance

that LBBB should not be considered as one homogenous group and as a certain indicator of mechanical dyssynchrony.

LBBB associates with increased mortality.[5,25] According to a study by Hess and co-workers, mechanical dyssynchrony estimated by gated MPI has a stronger relationship with outcome than QRSd among patient with significant CAD. After adjustment for baseline characteristics and LVEF, neither mechanical nor electrical dyssynchrony is independently associated with death. However, among patients with EF > 35%, QRSd and phaseBW together provide value above that provided by LVEF alone.[26] For these reasons, it is important to study more the relationship between QRSd and mechanical dyssynchrony. Previously, mild to moderate correlations have been shown to exist between electrical (QRSd) and mechanical dyssynchrony assessed with phase analysis in association with ECG-gated MPI.[27] In our study, the correlations between QRSd and mechanical dyssynchrony were slightly higher. The difference might be due to a non-identical patient material used for the study. In Trimble´s study, all studied patients had EF ≤ 35%. In our study, the patient population was more heterogeneous.

In LBBB, the thick posterobasal wall is activated before the thinner anterolateral wall, and for that reason, the frontal plane of the QRS axis shifts leftward and results in greater amplitude in S waves in the right precordial leads. This distorts traditional LVH estimation algorithms like CorV or Sokolow–Lyon, and they cannot be used in patients with LBBB on hypertrophy estimation. However, these algorithms can be used to describe electrical activity in the heart. In a previous study performed on patients with LBBB, CorV has

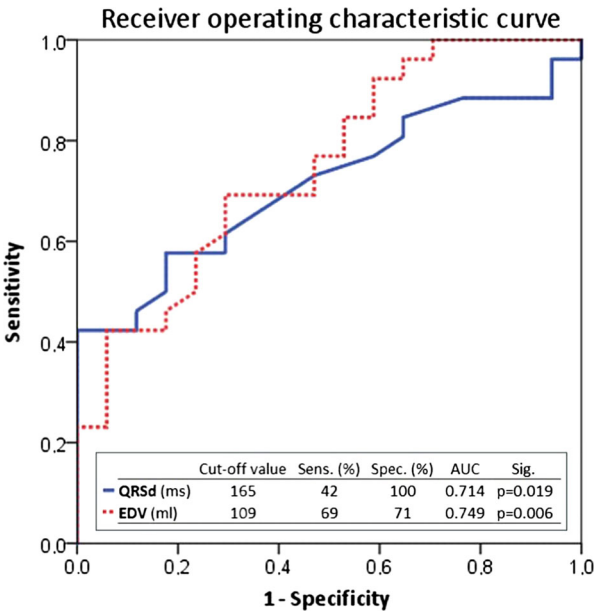

Figure 3. Cut-off values, sensitivity and specificity were determined from receiver operating characteristic curve. *QRSd*, QRS duration; *EDV*, end-diastolic volume; *Sens.*, sensitivity; *Spec.*, specificity; *AUC*, area under the curve; *Sig.*, significance. Values determined from patients with left bundle branch block.

shown to have a weak correlation ($r = 0.30$) with the LV dyssynchrony assessed by tissue Doppler imaging.[28] In our study, the correlation with CorV and dyssynchrony assessed with MPI phase analysis parameters were moderate ($r = 0.54$ to 0.62, $P < .001$ for all). Differences in the significance of correlations between these studies may be explained by a different method used to estimate mechanical dyssynchrony (echocardiogram vs MPI phase analysis) and differences in patient material. In this study, there was no correlation between phase analysis parameters and Sokolow–Lyon.

The heterogeneity of the repolarization and depolarization sequences was presented using the QRSTα and cosRT parameters. The wide QRSTα has been associated with increased incidence of the heart failure,[29] cardiac mortality,[30] CAD and all-cause mortality.[31] A previous study shows that QRSTα predicted more accurately poor prognosis than other traditional ECG indicators including ST-depression, T-wave inversion, LVH seen in ECG, abnormal T-wave axis and prolonged QTc.[30] In line with the preceding observation, the QRSTα was significantly higher in patients with LBBB compared to controls (164° ± 19 vs 70° ± 39, $P < .001$) in our study. Rautaharju et al[29] studied patients free of CAD and heart failure and reported the average QRSTα as 74° ± 27 for men and 61° ± 26 for women. Also, it has been shown that in LBBB QRSTα increases significantly.[31] Therefore, our result corresponded well with the previous results. In our study, QRSTα correlated with phaseBW representing LV synchrony ($r = 0.45$, $P < .001$). Ratio between 2D and 3D QRS area (QRS area 2D/QRS area 3D) was smaller in the group consisting of patients with LBBB than among controls (Table 2). This suggests that depolarization front differs from main vector plane more among LBBB than among healthy controls.

Because the study is based on a relatively limited sample of study subjects, statistical calculations are based on the characteristics of the sample we have taken and the probability of association with the normal curve. Since the distributions of the data values do not always strictly fulfill the assumptions of the statistical methods, the methods may not always be able to reflect accurately the values of parameters and the interpretation made may or may not accurately reflect the reality. Because for previously mentioned reasons, the study is low powered and results of this paper must be confirmed in a larger population. In ROC analysis, selection of right patients with and without heart disease is important. Some tests recognize well severely diseased patients, but fail to detect mild diseases. Upper limit for normal values was determined with mean + 2SD because phase parameters were normally distributed in original or logarithmic form. The upper limit would be same or almost the same if 95% percentile would have be used; for Entropy% (63% vs 63%) for phaseBW (128 vs 126 ms). PhaseSD upper limit would have been somewhat lower (38 vs 44 ms).

The Mason–Likar lead system was used for original ECG recording in this study. Unlike in conventional 12-lead ECG recording; extremity electrodes are placed into torso near limbs. This might have some impact on registration. However, all ECG registrations were performed in the same way so this is not explaining differences between study groups. We also have to remember that the surface ECG is a reflection of true ventricular activation and therefore, the representation of LV activation is always somehow restricted. The advantage of this study was that Strauss criteria were used to detect LBBB and therefore, our study population is likely to represent "true LBBB". Stricter criteria for QRS duration and results of MPI phase analysis have been shown to be promising for predicting CRT response,[32–34] nonetheless also opposite results have been published.[35]

Findings of this study are important because association between electrical and mechanical dyssynchrony has been somewhat poorly understood. Still, more studies are required to clarify the association, especially in CRT patients. This finding demonstrates that patients with LBBB and wider QRS have more mechanical

dyssynchrony and that might explain why wider QRSd have been shown to predict CRT response in previous studies. Lack of mechanical dyssynchrony in some patients with LBBB might partly explain why some patients do not gain benefit from CRT device. For CRT implantation, LV mechanical function is nowadays estimated only with EF. So far, no specific information of mechanical dyssynchrony is required.

CONCLUSIONS

In this study, we distinguished two types of patients with LBBB; those with (60%) and those without (40%) mechanical dyssynchrony. This indicates that LBBB should not be considered as one homogenous phenomenon and that LBBB is not a definite signal of mechanical dyssynchrony. The QRSd was the only ECG/VECG parameter that differed statistically significantly between these two groups and optimal cut-off value for estimating mechanical dyssynchrony was 165 ms for patients with LBBB. Also EDV was found to be independently associated with phaseBW. Together these two parameters explained 55% of phaseBW variation. Results of this study give new information about the relationship between electrical and mechanical dyssynchrony.

NEW KNOWLEDGE GAINED

- We found that QRSd, LV volumes and EF were statistically different between $LBBB_{abn}$ and $LBBB_{nor}$.
- Together QRSd and EDV predicted 55% of the phaseBW variation.
- QRSd 165 ms and EDV 109 mL were optimal cut-off values for estimating mechanical dyssynchrony in patients with LBBB.

Disclosure

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