Comparison of the Relation Between Left Ventricular Anatomy and QRS Duration in Patients With Cardiomyopathy With Versus Without Left Bundle Branch Block

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Abstract

QRS duration (QRSd) is used to diagnose left bundle branch block (LBBB) and is important for determining cardiac resynchronization therapy eligibility. The same QRSd thresholds established decades ago are used for all patients. However, significant inter-individual variability of normal QRSd exists and individualized QRSd thresholds may improve diagnosis and intervention strategies. Prior work reported left ventricular (LV) mass and papillary muscle location predicted QRSd in healthy subjects, but the relationship in diseased ventricles is unknown. We aimed to determine the association between LV anatomy and QRSd in cardiomyopathy patients. Patients referred for primary prevention implantable defibrillators (n=166) received cardiac magnetic resonance imaging and those with normal conduction (without bundle branch or fascicular block) and LBBB were studied. LV mass, length, internal diameter, end diastolic volume (LVEDV), septal and lateral wall thickness, and papillary muscle location were measured. In normal conduction patients, LV length (r=0.35, p<0.001), mass (r=0.32, p<0.001), diameter (r=0.20, p=0.03) and septal wall thickness (r=0.20, p=0.03) had positive correlations with QRSd. In LBBB patients, LV length (r=0.32, p=0.03), mass (r=0.39, p=0.01), diameter (r=0.34, p=0.02), and LVEDV (r=0.32, p=0.04) had positive correlations with QRSd. Contrary to prior studies in healthy subjects, papillary muscle angle (location) was not associated with QRSd in normal conduction or LBBB cardiomyopathy patients. In conclusion, increasing LV anatomical measurements are

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associated with increasing QRSd in cardiomyopathy patients. Future work should investigate the use of LV anatomical measurements in developing individualized QRSd thresholds for diagnosing conduction abnormalities such as LBBB and identifying candidates for cardiac resynchronization therapy.

Keywords

Left Ventricular Anatomy; QRS Duration; Cardiomyopathy; Left Bundle Branch Block

Introduction

Conventional QRS duration (QRSd) thresholds for diagnosis of cardiac disease were established decades ago and the same thresholds are used for all patient types. For example, QRSd thresholds are used to diagnose left bundle branch block (LBBB) as well as to determine patient eligibility for treatments such as cardiac resynchronization therapy (CRT). Since QRSd inter-individual variability can make diagnosis difficult, determining an individualized baseline QRSd could aid in determining the onset and progression of cardiac conditions. Causes of QRSd variability include differences in cardiac anatomy. Prior work in healthy subjects demonstrated that left ventricular (LV) mass, length, and papillary muscle location predicted QRSd.[1] Previous studies also showed that QRSd prolongation is associated with LV structural changes including increases in wall thickness.[2,3,4] Other anatomical factors that influence QRSd include fiber orientation, LV geometry, the complexity of the Purkinje network, and the shape of the LV wall.[5] However, it is not known if LV anatomical characteristics correlate with QRSd in cardiomyopathy patients referred for primary prevention implantable defibrillators or CRT. The aim of this study was to evaluate the association between LV anatomy and QRSd in cardiomyopathy patients, specifically those with normal conduction and those with LBBB.

Methods

The study was approved by the Johns Hopkins Hospital Institutional Review Board and the FDA Research in Human Subjects Committee. Patients referred to the Johns Hopkins Medical Institutions for implantable cardioverter-defibrillator (ICD) placement for primary prevention of sudden cardiac death and were enrolled between November 2003 and December 2010. This is a retrospective analysis of the cardiovascular magnetic resonance (CMR) arm of the PROSE-ICD study (Prospective Observational Study of Implantable Cardioverter Defibrillators) which has been previously described.[6] The inclusion and exclusion criteria have been described previously.[7] In brief, patient inclusion required 1) left ventricular ejection fraction (LVEF) 35% measured by a clinically indicated non-CMR study (echocardiography, nuclear scintigraphy or ventriculography), 2) coronary angiography, 3) no other indications for ICD placement (e.g. syncope, sustained ventricular arrhythmias, or cardiac arrest), and 4) no contraindications to CMR (e.g. existing cardiac device). Patients were classified as having ischemic cardiomyopathy if they had a history of myocardial infarction or revascularization, evidence of coronary artery stenosis >50% of the left main or proximal left anterior descending coronary arteries, or >50% stenosis of two or

more epicardial vessels. Other patients were classified as having non-ischemic cardiomyopathy. Acute myocarditis, congenital heart disease, hypertrophic cardiomyopathy, and infiltrative heart disease were excluded.[8] Patients were divided into normal His-Purkinje conduction (normal conduction) and LBBB using the criteria below. Patients not matching the defined normal conduction or LBBB classes and those with right bundle branch block or left anterior fascicular block were excluded from the analysis.

Clinically indicated 12-lead ECGs were acquired with a GE-Marquette system before ICD implantation as previously described.[7] ECGs were analyzed by two observers and classified in consensus by the following criteria.[7] 1) Normal Conduction: QRSd < 120 ms and 2) LBBB: QRS duration 140 ms (men) or 130 ms (women), QS or rS in V1 with mid-QRS notching/slowing in 2 of the leads I, aVL, V1, V2, V5 or V6. The new strict LBBB criteria, with different thresholds for men and women, were proposed previously because men have larger ventricles and longer QRS duration than women.[7,9,10] Multiple independent studies have shown that they improve prediction of which patients benefit from CRT,[11,12,13] likely identifying which patients have a true LBBB.[14,15]

Of the 235 primary prevention ICD patients available for analysis, 167 met the inclusion criteria for this study and had analyzable data. One LBBB patient was excluded because his LV mass was >8 standard deviations and QRSd was >5 standard deviations from the mean of other LBBB patients (subject LV mass = 525.30 g, QRSd = 244 ms).

The cine and CMR protocol have been described previously.[7,16,8] In summary, patients were imaged with a 1.5T scanner (Signa CV/I, GE Healthcare Technologies, WI, USA or Avanto, Siemens Medical Systems, Erlangen, Germany). LV mass and end diastolic volume measurements (LVEDV) were performed with CINEtool (GE Healthcare, WI, USA), as previously described. All images were analyzed subsequently using the image analysis program Segment (Segment 1.9, Medviso, AB, Lund, Sweden) to determine LV papillary muscle angle, LV length, LV diameter, ventricular septal wall thickness, and LV lateral wall thickness (Figure 1). Papillary muscle angle was measured as previously described, in the short axis view in the plane where the papillary muscle inserts into the LV wall (Figure 1B).[5,1] LV diameter and wall thicknesses were measured at this level at end-diastole. LV length was measured from the four-chamber long axis view (Figure 1A). In brief, papillary muscle angle was determined by defining anterior and posterior papillary muscle insertion points (P1 and P2) along with ventricular septal wall border points (W1 and W2) where the right ventricle meets the left ventricle. A perpendicular bisector line was then drawn between the W1W2 segment and is used to determine the free wall midpoint (F). Two segments (P1F and P2F) are drawn between the midpoint (F) and the papillary muscle insertion points (P1 and P2). The papillary muscle angle is defined as the angle between P1F and P2F segments.

Baseline patient characteristics were compared between ECG conduction types with oneway ANOVA (Kruskal-Wallis). Associations between LV anatomical measurements and QRSd were assessed by linear regression. Categorical variables were evaluated by Chi-square. All statistical analyses were performed using SigmaPlot (version 11.0, CA, USA). P-values <0.05 were considered statistically significant.

Results

The 166 patients had a mean age of 56 years, were 23% female, had a mean LVEF of 28%, had 49% ischemic cardiomyopathy etiology, and had a distribution of NYHA heart failure classes of: 23% Class I, 48% Class II and 29% Class III. LBBB patients, n=44 (compared to non-bundle/fascicular block patients, n=122) were older, more commonly female and Caucasian, had smaller LV scar size, higher QRSd, less ischemic and had higher NYHA heart failure class (Table 1). LBBB patients also had larger LV mass, LV length and LVEDV, but smaller LV wall thicknesses. There was no significant difference in LV diameter or papillary muscle angle between groups (Table 1).

Figure 2 shows scatterplots and linear regression results for the correlation between each anatomical measurement and QRSd. LV length, LV diameter, and LV mass all had positive correlations with QRSd in both the normal and LBBB conduction groups. In the normal conduction patients, there was a 10 ms QRSd increase per 3.9 mm increase in LV length (r=0.35, p<0.001), 10 ms QRSd increase per 2.4 mm LV diameter increase (r=0.20, p=0.02), and 10 ms QRSd increase per 0.8 g increase in LV mass (r=0.32, p<0.001). In the LBBB patients, the increase in QRSd per change in length (10 ms per 4.4 mm; r=0.32, p=0.03) was similar to that in the normal conduction group, while the increase in QRSd per change in LV diameter (10 ms per 5.4 mm; r=0.34, p=0.02) and LV mass (10 ms per 1.5 g; r=0.39, p=0.01) was approximately double that in the normal conduction group.

QRSd was also associated with ventricular septal wall thickness in the normal conduction (10 ms per 8.1 mm; r=0.20, p=0.03), but not in the LBBB group; while QRSd was associated with LVEDV in the LBBB (10 ms per 0.5 mL; r=0.32, p=0.04), but not in the normal conduction group. We found no correlation between QRSd and LV lateral wall thickness or papillary muscle angle in either conduction type group. Sub analyses of the normal conduction group stratified by scar, ischemic etiology, gender, and mass did not increase the correlation of LV anatomical measurements with QRSd.

Discussion

This retrospective analysis of PROSE-ICD trial data determined that LV anatomical measurements correlate with QRSd in cardiomyopathy patients with normal conduction and with LBBB. Specifically, LV length, LV diameter, and LV mass increase with prolonged QRSd in all cardiomyopathy patients. Additionally, LVEDV correlates with QRSd in LBBB patients, while the ventricular septal wall thickness correlates with QRSd in normal conduction patients. Overall, considering both groups, LV dilation is more closely associated with QRSd than is LV wall thickness in cardiomyopathy patients. Larger LVEDV prolonged QRSd more than increases in LV wall thickness did. This agrees with electrocardiographic simulation studies where ECGs were produced from anatomical models of dilated and hypertrophied hearts.[17] In addition, the LV walls in LBBB patients were significantly thinner compared to those of normal conduction patients, which is consistent with a prior study in which LV walls in LBBB patients were thinner than in healthy subjects.[18]

The degree of correlation between QRSd and significant anatomical measurements in cardiomyopathy patients is consistent with that found in healthy patients. Previous studies in healthy subjects with normal conduction demonstrated that LV mass,[2,1] LV length[1], LV diameter,[2] and LV wall thickness[2] all correlated with QRSd. Our findings are also consistent with results of previous studies in patients with known cardiovascular disease, where QRS duration was associated with LV mass and LVEDV.[19] QRSd also correlated also LV mass, LV diameter, and ventricular septal and LV lateral walls in Framingham Heart study participants without heart failure or myocardial infarction.[2]

The correlation between papillary muscle angle and QRSd in healthy patients[1] was not present in cardiomyopathy patients. Figure 3A shows electrical activation in normal conduction patients starting in the endocardium and papillary muscles. Figure 3B depicts electrical activation in LBBB where activation begins in the RV and must proceed through the septum before reaching the LV endocardium. It was expected that there would be no correlation between papillary muscle angle and QRSd in LBBB patients; however, in normal conduction patients, it can be postulated that as papillary muscle angle increases, the insertion point of the papillary muscle moves towards the lateral wall. Therefore QRSd would be shorter because there is less distance for the electrical wavefront to travel before reaching the LV lateral wall. In our study, dilation of the LV in cardiomyopathy patients may have confounded the relation between the papillary muscle angle and QRSd.

While individualized baseline QRSd could aid in the diagnosis of cardiac conditions, the causes of inter-individual variability are numerous. Cardiomyopathy patients can have large variation in QRSd due to several factors including differences in conduction velocity due to fibrosis or scarring.[20] QRSd is prolonged with slower conduction velocities in myocardial tissue.[19] Conduction velocity can also be slowed in the Purkinje network[21] and with LBBB, there may be inter-individual variability with re-entry into the LV Purkinje network.[22] Fiber orientation, which can also influence conduction velocity, has been shown to impact electrical excitation both in simulation and in vivo studies.[23,24]

A limitation of this study is the relatively small number of cardiomyopathy patients with LBBB and p-values should be interpreted with caution due to the multiple comparisons. Larger numbers of patients will be necessary to determine if individual LV anatomic characteristics could have clinical applications for ECG diagnosis. However, to our knowledge, this is the first study to determine the correlation between LV anatomy and QRSd in cardiomyopathy patients referred for primary prevention ICDs with or without CRT.

This study supports that QRSd is associated with LV structural parameters. The importance of individualized QRSd thresholds is already evident by the introduction of new strict LBBB criteria that require a QRSd   130 ms in women or   140 ms in men due to men having larger heart sizes than women.[9] Further research is necessary to determine if individualized QRSd thresholds can be used to improve the diagnosis of LBBB and select patients for CRT.

Acknowledgments

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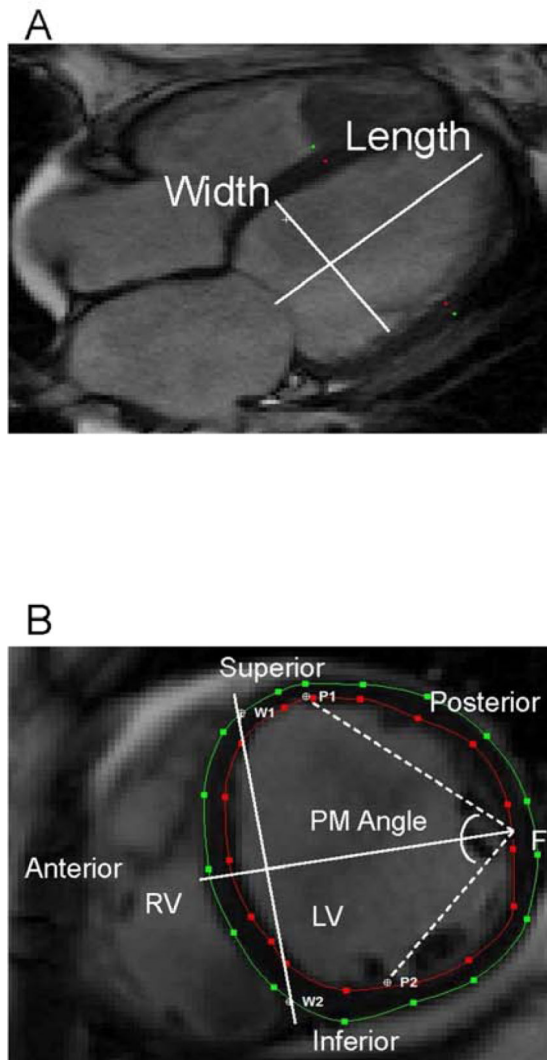
Figure 1.
LV anatomical and papillary muscle angle measurements. (A) The long axis view was used to measure LV length. (B) Short axis view, at the level of endocardial insertion of the papillary muscle, was used for the measurement of LV wall thicknesses, LV diameter, and papillary muscle angle. PM-angle papillary muscle angle; W1, W2-ventricular septal wall border points; P1-Anterior papillary muscle; P2- Posterior papillary muscle; F-Free wall midpoint.
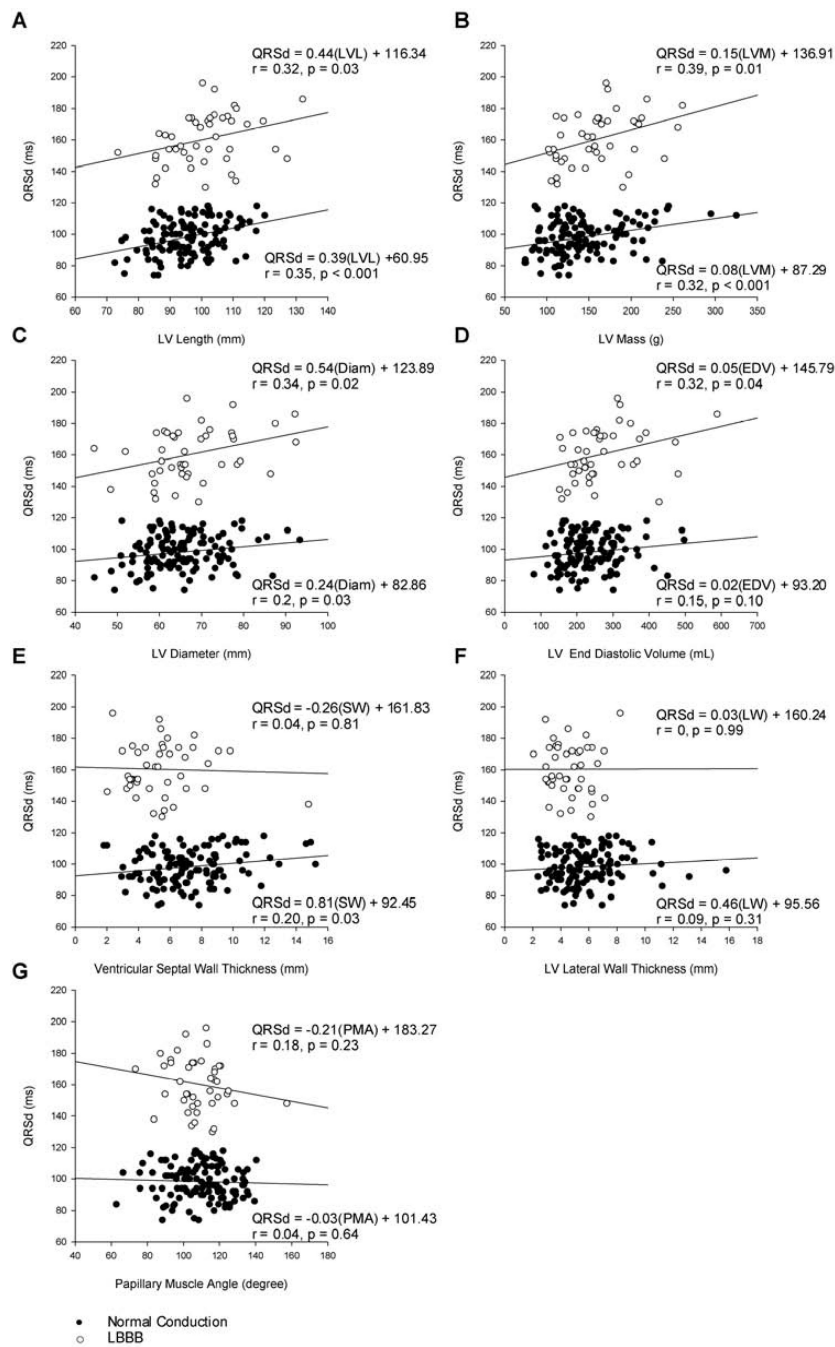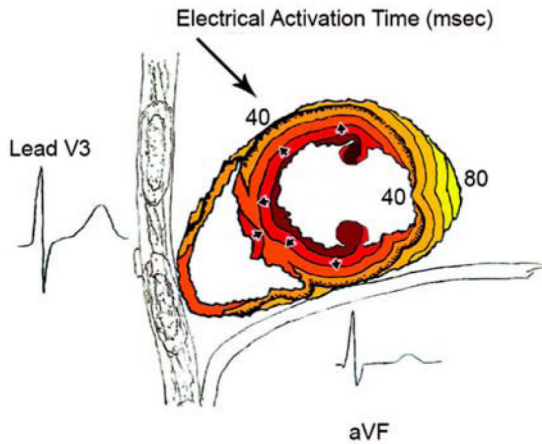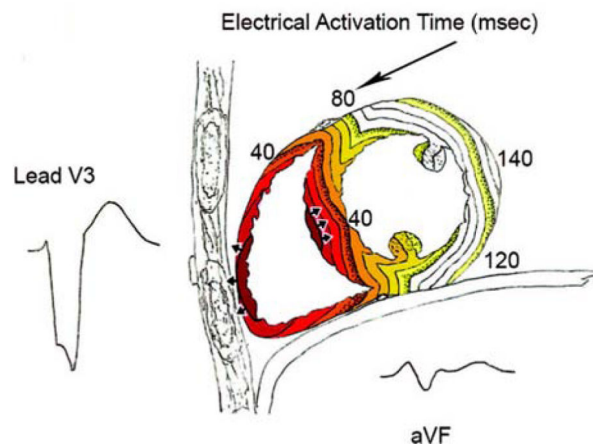
Figure 2.
Correlation between QRSd and left ventricle A) Length (LVL), B) Mass (LVM), C) LV Diameter (Diam), D) LV End Diastolic Volume (EDV), E) Ventricular Septal Wall (SW), F) LV Lateral Wall (LW), and G) Papillary Muscle Angle (PMA).

Figure 3.
(Reprint from *Circ Arrhythmia Electrophysiol* 2008;1:327-336.) Timing of electrical activation (depolarization) wavefronts in normal conduction (A) and LBBB (B). For reference, 2 QRS-T waveforms are shown in their anatomic locations (V3 on the chest and aVF inferiorly). Electrical activation starts at the small arrows and spreads in a wavefront with each colored line representing successive 10 ms. In normal conduction, activation begins within both the LV and RV endocardium. In LBBB, activation only begins in the RV and must proceed through the septum before reaching the LV endocardium (i.e., this pattern in the septum is opposite to that seen in normal conduction).

Table 1

Baseline Characteristics by Conduction Type

Characteristics	Normal Conduction (n=122)	LBBB (n=44)	P-value
Age (years)	54.4 ± 12.1	59.6 ± 11.5	0.01
Female	22 (18%)	16 (36%)	0.01
Left Ventricular Ejection Fraction (%)	28.4 ± 9.0	25.4 ± 8.6	0.06
Scar size (%LV)	13.9 ± 13.4	6.6 ± 9.5	0.001
QRS duration (ms)	98.2 ± 10.8	160.4 ± 16.2	<0.001
Ischemic etiology	68 (55.7%)	13 (30%)	0.003
New York Heart Association			<0.001
Class I	37 (30%)	2 (5%)	
Class II	64 (52%)	15 (34%)	
Class III	21 (17%)	27 (61%)	
Body Surface Area (m^2)	2.07 ± 0.3	2.04 ± 0.3	0.47
Caucasian	78 (64%)	34 (77%)	
African American	39 (32%)	9 (20%)	0.13
Other	5 (4%)	0 (0%)	
LV length (mm)	95.7 ± 9.8	101.0 ± 11.9	0.004
LV diameter (mm)	65.4 ± 8.8	67.7 ± 10.3	0.18
LV mass (g)	144.5 ± 45.2	159.3 ± 42.3	0.04
Ventricular septal wall thickness (mm)	7.1 ± 2.6	5.5 ± 2.3	<0.001
LV lateral wall thickness (mm)	5.8 ± 2.2	4.7 ± 1.4	0.002
Papillary Muscle Angle (°)	108.8 ± 16.0	107.9 ± 14.0	0.73
LV End Diastolic Volume (mL)	236.7 ± 75.6	271.0 ± 95.2	0.04

LBBB=Left Bundle Branch Block, LV=Left Ventricle

Continuous variables are reported as mean ± standard deviation and categorical variables are reported as n (% of population).