Electrocardiogram Criteria to Diagnose Cardiac Amyloidosis in Men With a Bundle Branch Block

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Diagnosing cardiac amyloidosis is challenging and requires a high index of suspicion in patients with an increased left ventricular wall thickness (LVWT). Low QRS voltage on electrocardiogram (ECG) has been regarded as the hallmark ECG finding in cardiac amyloidosis; however, the presence of low voltage can range from 20-74% and the voltage/mass ratio carries a greater diagnostic accuracy than QRS voltage alone. Patients with cardiac amyloidosis can have conduction system infiltration and this may result in a BBB. Therefore, the ECG or mass/voltage criteria established for patients with a narrow QRS in the diagnosis of cardiac amyloidosis may not be applicable in patients with a BBB. We sought to identify criteria to aid in the diagnosis of cardiac amyloidosis in patients with increased LVWT on echocardiogram and with a BBB on ECG. We calculated the total QRS score/LVWT, limb lead QRS score/LVWT, R in lead aVL/LVWT, R in lead I/LVWT, and Sokolow index/LVWT. In patients with an increase in LVWT and BBB, total QRS voltage that is indexed to wall thickness can help distinguish between patients with increased wall thickness who have cardiac amyloidosis from those who have LVH related to a pressure overload state. A unique index of Total QRS Score/LVWT is the best predictor of cardiac amyloidosis with a cutoff value of 92.5 mV/cm which is 100% sensitive and 83% specific for the diagnosis of cardiac amyloidosis. This may be a useful screening tool in patients with an increased wall thickness to raise diagnostic suspicion for cardiac amyloidosis. **(Am J Cardiol 2021;146:89−94)**

Cardiac amyloidosis is an infiltrative cardiomyopathy caused by deposition of misfolded protein fibrils that can lead to heart failure, arrhythmias and conduction abnormalities.[1] The diagnosis of cardiac amyloidosis requires a high index of suspicion in order to prevent delays in treatment.[2−5] Although advances in the application of nuclear imaging have decreased the reliance on tissue biopsy for diagnosis, the initial index of suspicion continues to critically depend on clinical history, electrocardiogram (ECG), and echocardiographic findings. Low QRS voltage has been regarded as the hallmark ECG finding in cardiac amyloidosis; however, the presence of low voltage can range from 20% to 74%.[6−10] Given the discordance between QRS voltage and left ventricular (LV) wall thickness in cardiac amyloidosis, the mass/voltage ratio carries a greater diagnostic accuracy than QRS voltage alone.[11] Much of the data that has been published regarding QRS voltage in cardiac amyloidosis was derived from patients with a narrow QRS complex; therefore, the established ECG or mass/voltage criteria may not be applicable in patients with a bundle branch block (BBB). We sought to identify criteria to aid in the diagnosis of cardiac amyloidosis in patients with increased left ventricular wall thickness (LVWT) on echocardiogram and with a BBB on ECG.

Methods

We included all patients who were diagnosed with cardiac amyloidosis at Lahey Hospital & Medical Center between 2011-2017. The diagnoses were based either on endomyocardial biopsy, characteristic cardiac imaging findings in conjunction with non-cardiac biopsy or positive bone scintigraphy without evidence of a monoclonal gammopathy.[12,13] Patients were enrolled into a local registry, and all patients with cardiac amyloidosis and right bundle branch block (RBBB) or left bundle branch block (LBBB) using standard 12 lead ECG criteria were included (Figure 1).[14] Patients with cardiac amyloidosis (CA) and a BBB comprised our study population (+CA/+BBB). Our main comparison group included patients with left ventricular hypertrophy (LVH) secondary to severe aortic stenosis and a BBB (+LVH/+BBB). These patients were identified using a transcatheter aortic valve replacement registry at our institution. Patients were matched 1:1 for age, gender and body mass index . Patients were excluded if they had a moderate to large pericardial effusion or severe chronic obstructive pulmonary disease given the impact of these conditions on QRS voltage.[15] We also included 2 additional comparison groups. The third group included patients with a BBB with normal wall thickness and without a diagnosis of amyloidosis (−LVH/+BBB), and the fourth group included patients with cardiac amyloidosis and a narrow QRS complex (+CA/-BBB).

We performed a retrospective medical record review to obtain demographic and clinical data. QRS voltage was directly measured by one author (SS) and audited by a second author (SPS) for quality and accuracy based on

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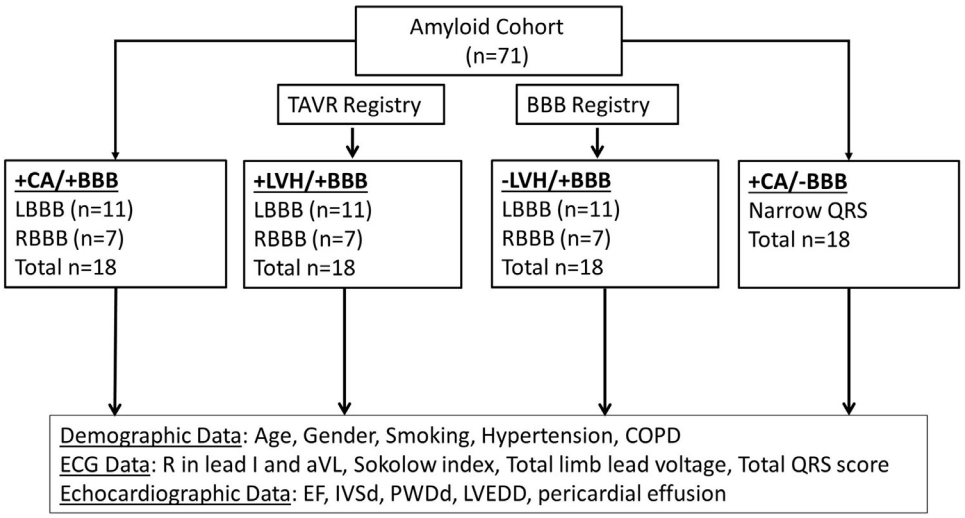

Figure 1. Study flow chart: study flow chart depicting the 4 groups of patients with inclusion and exclusion criteria and follow up data (WT = Wall thickness, COPD = Chronic obstructive pulmonary disease, EF = Ejection fraction, IVSd = Interventricular septal thickness at end-diastole, PWDd = Posterior wall thickness at end-diastole, EDD = End-diastolic dimension)

previously published criteria.[16] Individual lead QRS voltage was tabulated. In addition, we calculated a total QRS score and limb lead QRS score. The total QRS score was calculated as the sum of the total QRS amplitude in all 12 ECG leads (Figure 2), whereas the limb lead score was the sum of the total QRS amplitude in the 6 limb leads. In addition, the Sokolow criteria were calculated as the S in lead V1 plus the larger R wave in V5 or V6 ($\leq$ 15 mV would meet the Sokolow criteria for low voltage). We also evaluated various QRS voltage parameters that are indexed to the average LVWT. The average LVWT is equal to the average thickness of the anteroseptal wall and the inferolateral wall at end-diastole in the parasternal long axis view using 2-dimensinal echocardiography (Figure 2). We calculated the total QRS score/LVWT, limb lead QRS score/LVWT, R in lead aVL/LVWT, R in lead I/LVWT, and Sokolow index/LVWT. The LVWT and left ventricular end-diastolic dimension (LVEDD) on the echocardiogram were measured based on chamber

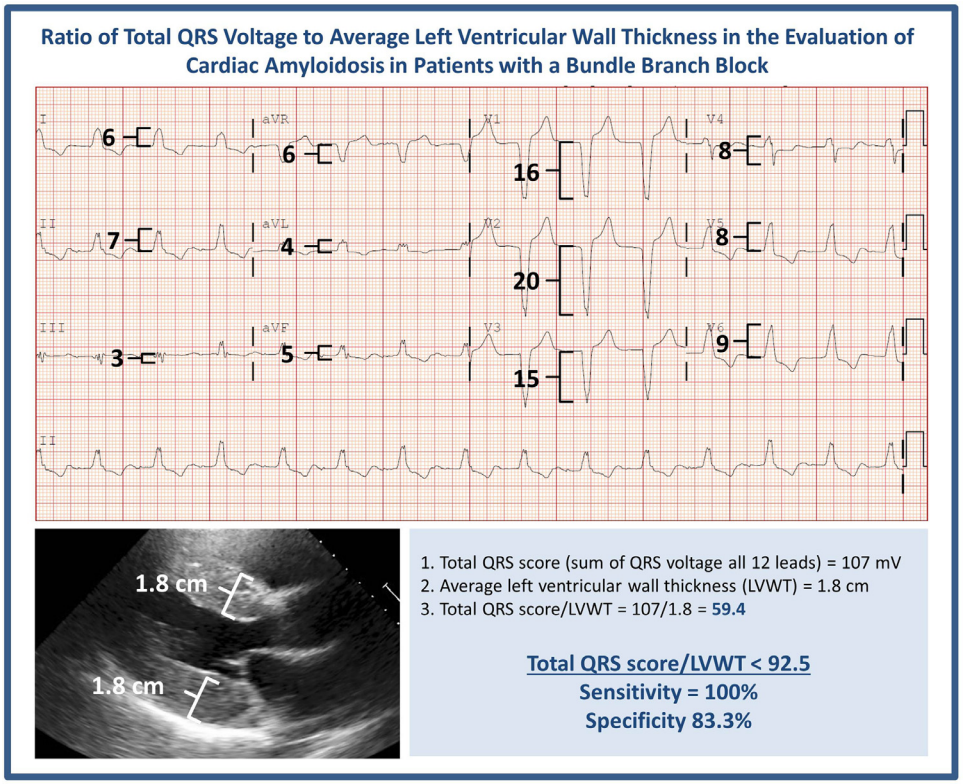

Figure 2. Ratio of total QRS voltage to average left ventricular wall thickness (LVWT) in the evaluation of cardiac amyloidosis in patient with a bundle branch block and increased wall thickness. Differentiating cardiac amyloidosis from left ventricular hypertrophy secondary to pressure overload.

quantification guidelines.[17] Left ventricular mass index (LVMI) was calculated by the method described by Devereux, et al (LVMI = (0.8 × 1.04 x [(IVSd + LVEDD + PWTd)^3 - LVEDD^3] + 0.6) / body surface area).[18] Repolarization changes were quantified by measuring the maximum degree of ST elevation in leads V1-V3 in patients with a left bundle branch block. P-wave amplitude was evaluated in patients in sinus rhythm, low P-wave amplitude was considered present if the P-wave was < 0.1 mV in lead I on a standard 12 lead ECG.

Continuous variables are expressed as mean ± standard deviation and compared using ANOVA. Categorical variables are reported as frequency (counts with percentages) and compared using chi-squared test and/or Fisher's Exact test, a p-value of <0.05 was considered statistically significant. Scatter plots are used to graphically represent data. Receiver operator characteristic curves are constructed to determine separate cutoff values for different ECG/echocardiographic derived indexes for the identification of cardiac amyloidosis in different subsets of patients. Sensitivity, specificity, positive likelihood ratios are calculated. Analysis was conducted using GraphPad Prism software. The study was approved by the Institutional Review Board at Lahey Hospital & Medical Center.

Results

From 2011 to 2017, there were 71 patients with a diagnosis of cardiac amyloidosis included in our database, 18 (25.3%) of these patients had a BBB (11 with a LBBB, 7 with a RBBB). Sixteen of these 18 (89%) patients had ATTR, 2 of the 18 (11%) had AL amyloidosis. The distribution of RBBB and LBBB was the same in all 3 groups with a BBB (Figure 1). Table 1 summarizes the baseline demographic data of these 4 groups.

ECG and echocardiographic data are depicted in Table 2. Total limb lead score was significantly lower in the amyloidosis groups with a BBB (+CA/+BBB) or without BBB (+CA/-BBB) as compared with the other 2 groups without amyloidosis. Total QRS score was significantly greater in BBB with increased wall thickness secondary to aortic stenosis (+LVH/+BBB) compared with all other groups. Based on ROC analysis, the index associated with the best diagnostic performance is Total QRS score/LVWT using a cutoff value of < 92.5mV/cm with a sensitivity of 100% and specificity of 83% in the identification of amyloidosis in a patient with a BBB and increased wall thickness. The area under the curve for this indexed parameter is 0.95, with a likelihood ratio of 6 of having amyloidosis. These findings are consistent irrespective of the type of BBB (RBBB or LBBB). We also performed a ROC analysis of Total QRS score/ LVMI, cutoff value of < 0.97 mV/g/m^2 with 100% sensitivity, 78% specificity, area under the curve of 0.91 and likelihood ratio of 4.5), which is similar to Total QRS/LVWT (Figure 3).

Other indices including limb lead QRS score, R in lead I, R in lead aVL, and Sokolow, which were all indexed to LVWT are displayed as a scatter plot. The Sokolow criteria, which is considered the most useful ECG index for diagnosis of amyloidosis, was not different among the 4 patient groups (Figure 4).

In addition, repolarization changes were less prominent in patients with CA and a LBBB compared with

Table 1
Baseline demographic data for patients in all 4 groups (bundle branch block with amyloidosis, bundle branch block with LVH, bundle branch block without LVH, and amyloidosis without bundle branch block)

Variable	±CA/±BBB (n=18)	±LVH/±BBB (n=18)	-LVH/±BBB (n=18)	±CA/-BBB (n=18)	p value
Age (years)	79 ± 8	80 ± 7	75 ± 12	78 ± 9	0.38
Men	100%	100%	100%	100%	NA
ATTR	83%	NA	NA	78%	NA
Hypertension	39%	83%	61%	44%	<0.05
Smoker	56%	56%	56%	61%	0.98
BMI (kg/m^2)	29 ± 5	30 ± 3	28 ± 4	28 ± 3	0.27
SBP (mm Hg)	123 ± 14	127 ± 18	131 ± 17	122 ± 15	0.29
DBP (mm Hg)	72 + 8	66 ± 18	70 ± 11	71 ± 11	0.29

ATTR = Transthyretin amyloidosis; BBB = Bundle branch block; CA = Cardiac amyloidosis; LVH = Left ventricular hypertrophy; BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure.

Table 2
ECG and echocardiographic data for patients in all 4 groups (bundle branch block with amyloidosis, bundle branch block with LVH, bundle branch block without LVH and amyloidosis without bundle branch block).

Variable	±CA/±BBB (n=18)	±LVH/±BBB (n=18)	-LVH/±BBB (n=18)	±CA/-BBB (n=18)	p value
QRSd (ms)	155 ± 21	150 ± 35	141 ± 12	101 ± 7*	<0.001
Total Limb Lead Score	30 ± 12*	52 ± 20	41 ± 11	22 ± 8*	<0.001
Total QRS Score	93 ± 29	150 ± 38*	108 ± 16	92 ± 24	<0.01
LVEF	46 ± 12%*	56 ± 19%	57 ± 7%	50 ± 15%	<0.05
LVWT (cm)	1.6 ± 0.2	1.3 ± 0.1 *	0.9 ± 0.1*	1.5 ± 0.2	<0.001
LVMI (g/m^2)	150 ± 36	128 ± 31	74 ± 15*	145 ± 34	<0.001
LV EDD (cm)	4.6 ± 0.5	5.0 ± 0.7*	4.5 ± 0.6	4.6 ± 0.4	<0.05

QRSd = QRS complex duration; LVEF = Left Ventricular ejection fraction; LVWT = Left ventricular wall thickness; LVMI = Left ventricular mass index; LVEDD = Left ventricular end diastolic dimension.

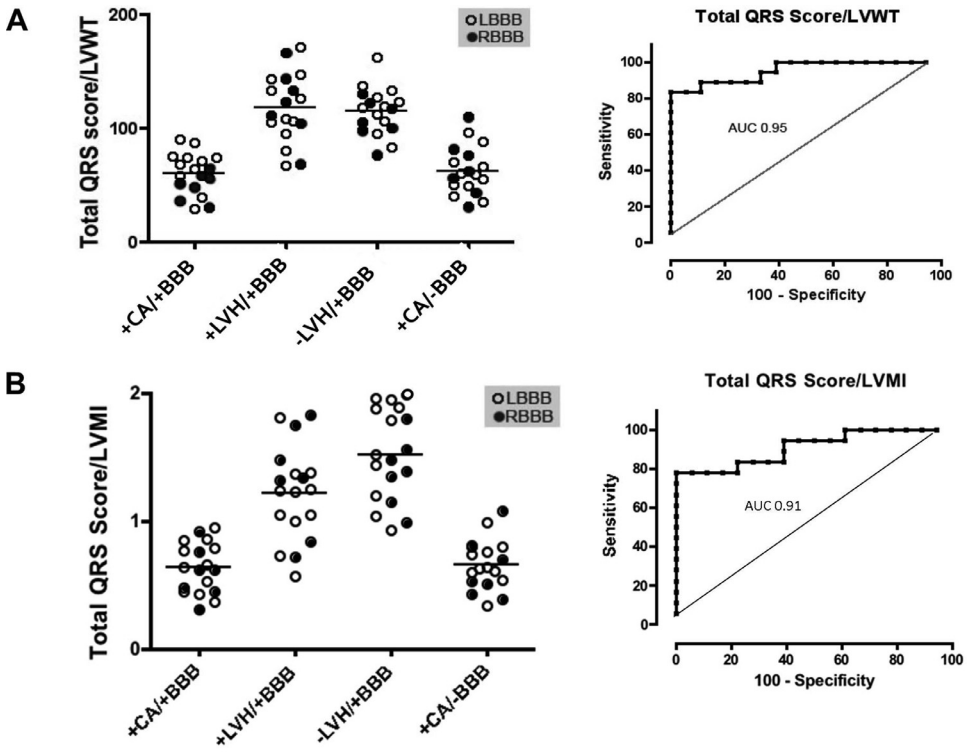

Figure 3. Scatter plot of Total QRS voltage/LVWT (A) and Total QRS/LVMI (B) all 4 groups. Open circles are patients with LBBB and closed circles are patients with RBBB, Line in the middle defines mean. The ratio in patients with cardiac amyloidosis with BBB is similar to patients with narrow complex amyloid but significantly ($p < 0.001$) lower in comparison to patients with BBB with LVH due aortic stenosis. ROC (Receiver Operator Curve) is on the right with AUC (area under the curve). The ROC is a comparison between Groups 1(+CA/+BBB) and 2 (+LVH/+BBB). (BBB = Bundle branch block, CA = Cardiac amyloidosis, LVH = Left ventricular hypertrophy, LVWT = Left ventricular wall thickness, LVMI = Left ventricular mass index)

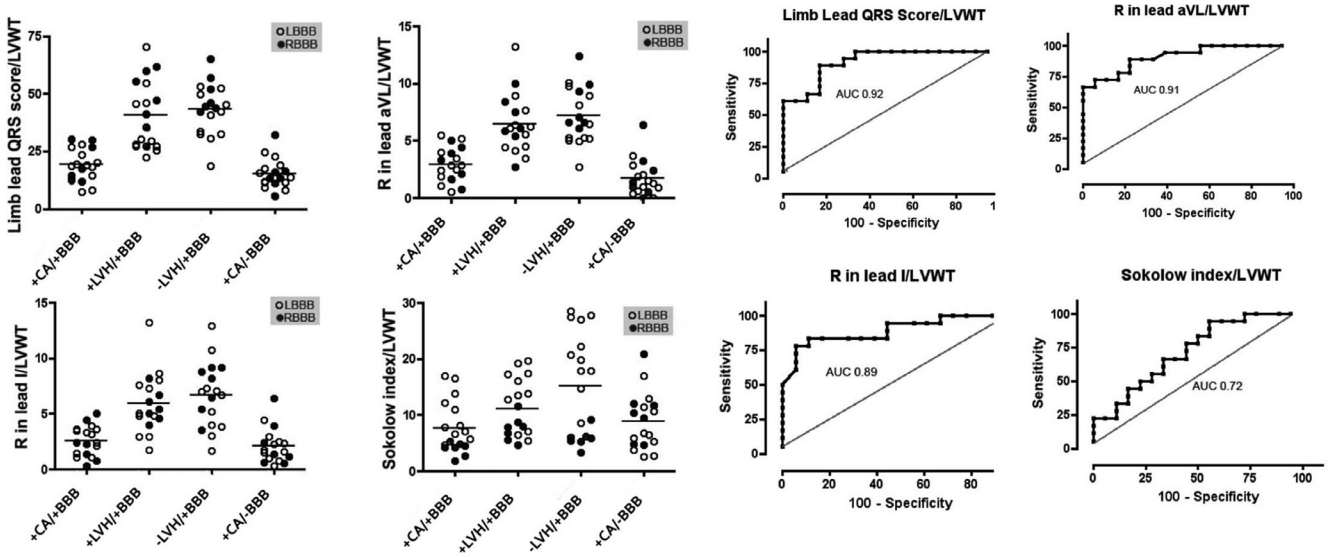

Figure 4. Scatter plot of four ECG criteria as indexed to LVWT in all groups. The indices include limb lead score, R in lead I, R in lead aVL and Sokolow indexed to LV wall thickness is shown. ROC figure for each index is on the right side of the scatter plot. Open circles are patients with LBBB and closed circles are patients with RBBB, Line in the middle defines mean. ROC (Receiver Operator Curve) is on the right with AUC (area under the curve). (BBB = Bundle branch block, CA = Cardiac amyloidosis, LVH = Left ventricular hypertrophy, LVWT = Left ventricular wall thickness

those with LVH and a LBBB. The maximal ST elevation in leads V1-3 were less in patients with +CA/+BBB than in patients with +LVH/+BBB (0.114 +/- 0.083 vs 0.200 +/- 0.100 mv, p=0.04). Eight of the 11 patients with +CA/+BBB in sinus rhythm had a low P-wave amplitude, compared with 4 of the 13 patients with +LVH/+BBB, this difference was not statistically significant (p=0.10).

Discussion

Cardiac amyloidosis is an infiltrative cardiomyopathy that is associated with an increase in LVWT and paradoxical low QRS voltage on ECG. BBB is not uncommon in patients with cardiac amyloidosis.[19] The main finding of our study is that ECG criteria indexed to LVWT can be utilized to distinguish cardiac amyloidosis from LVH related to a pressure overload state in patients with an increased LVWT and a BBB.

The initial index of suspicion of cardiac amyloidosis mainly depends on ECG and echocardiographic findings. Electrical insulation related to amyloid infiltration can lead to a low voltage on ECG in 20-74% of patients depending on the patient population and the ECG criteria used.[6–10] QRS voltage also varies depending on the type of amyloidosis, with AL amyloid demonstrating the greatest propensity for low QRS voltage (60% with AL amyloid, 25% with hereditary ATTR and 40% with wild-type ATTR).[7] The Sokolow-Lyon criteria for cardiac amyloidosis (S in lead V1 plus larger R wave in V5 or V6 $\leq$ 15) has been reported to have the greatest sensitivity (84%) for detection of cardiac amyloidosis, but has relatively low specificity (48%).[20] Importantly, however, none of these measures have been validated specifically in patients with a BBB.[21] In our study 25% of all cardiac amyloidosis patients had a BBB. This is similar to the 21% reported previously in patients with biopsy proven amyloidosis.[19]

The seminal work by Caroll et al, demonstrated that the sensitivity of low QRS voltage could be increased if this were incorporated in a mass to voltage ratio which helps expose the paradoxical relationship between QRS voltage and LVWT.[9,11] In addition, a study by Roberts, et al, found that total 12 lead QRS voltage is more reliable in predicting increased left ventricular mass than the previously recommended electrocardiographic criteria for LVH.[17] We have extended these concepts and tested several QRS voltage criteria to the average LVWT to identify a clinically useful parameter to aid in the diagnosis of cardiac amyloidosis. We have found that the Total QRS Score/LVWT is the best predictor (at a cutoff value of 92.5 mV/cm it is 100% sensitive and 83% specific) and it is very similar to Total QRS Score/LVMI in terms of sensitivity and specificity. We found that ECG criteria alone are inadequate for establishing a definitive diagnosis of cardiac amyloidosis; however, this index of Total QRS score/LVWT does have diagnostic utility.

Additionally, there are published reports establishing high sensitivity of Sokolow criteria for identification of patients with cardiac amyloidosis in the absence of BBB. Patients with a LBBB would be expected to have a higher QRS voltage by the Sokolow criteria, and those with a RBBB would be expected to have a much lower QRS voltage based on the RS relationship in the precordial leads in these conditions. As expected, we found that the Sokolow criteria are likely not supportive of diagnosis of cardiac amyloidosis in patients with a BBB and should not be used in the presence of a BBB.

Based on our findings, the Total QRS score and/or LVWT can be useful as a first line screening tool in the evaluation for cardiac amyloidosis in patients with an increased wall thickness on echocardiogram and a BBB on ECG.

There are several limitations of our study. Our primary study cohort was comprised of 18 men; therefore, the sample size of this study is a limitation and the findings may not be generalizable to women. The calculation of the total QRS score may be time consuming; however, it is conceivable that an automated calculation of this can be performed routinely by ECG interpretation software already in use. As this study was small and retrospective, the Total QRS score/LVWT will need to be validated in a larger population.

In conclusion, in patients with an increase in LVWT, total 12-lead QRS voltage is valuable despite the presence of a BBB. QRS voltage that is indexed to wall thickness appears more predictive than a low QRS voltage on ECG by conventional criteria. A unique index of Total QRS Score/LVWT is the best predictor of cardiac amyloidosis with a cutoff value of 92.5 mV/cm that is 100% sensitive and 83% specific.

Credit Author Statement

Sunita Sharma: Data Collection, Writing-original draft and preparation, Formal analysis. **Sherif Labib**: Visualization, Writing − Reviewing and Editing. **Sachin P. Shah**: Supervision, Conceptualization, Methodology, Writing − Reviewing and Editing.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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