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Electrocardiographic prediction of left ventricular hypertrophy in women and men with left bundle branch block – Comparison of QRS duration, amplitude and voltage-time-integral

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Abstract

Background: Standard ECG criteria for left ventricular (LV) hypertrophy rely on QRS amplitudes. However, in the setting of left bundle branch block (LBBB), ECG correlates of LV hypertrophy are not well established. We sought to evaluate quantitative ECG predictors of LV hypertrophy in the presence of LBBB.

Methods: We included adult patients with typical LBBB having ECG and transthoracic echocardiogram performed within 3 months of each other in 2010–2020. Orthogonal X, Y, Z leads were reconstructed from digital 12-lead ECGs using Kors's matrix. In addition to QRS duration, we evaluated QRS amplitudes and voltage-time-integrals (VTIs) from all 12 leads, X, Y, Z leads and 3D (root-mean-squared) ECG. We used age, sex and BSA-adjusted linear regressions to predict echocardiographic LV calculations (mass, end-diastolic and end-systolic volumes, ejection fraction) from ECG, and separately generated ROC curves for predicting echocardiographic abnormalities.

Results: We included 413 patients (53% women, age 73 ± 12 years). All 4 echocardiographic LV calculations were most strongly correlated with QRS duration (all $p < 0.00001$). In women, QRS duration ≥ 150 ms had sensitivity/specificity 56.3%/64.4% for increased LV mass and 62.7%/

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Disclosures

None.

CRedit authorship contribution statement

Ashley DeBauge: Conceptualization, Methodology, Writing – original draft. **Tyan Fairbank:** Conceptualization, Methodology. **Christopher J. Harvey:** Methodology, Software. **Sagar Ranka:** Writing – original draft. **Sania Jiwani:** Writing – original draft. **Seth H. Sheldon:** Writing – review & editing. **Madhu Reddy:** Writing – review & editing. **Timothy A. Beaver:** Writing – review & editing. **Amit Noheria:** Conceptualization, Methodology, Software, Formal analysis, Writing – original draft, Supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jelectrocard.2023.03.004>.

67.8% for increased LV end-diastolic volume. In men, QRS duration ≥ 160 ms had a sensitivity/specificity 63.1%/72.1% for increased LV mass and 58.3%/74.5% for increased LV end-diastolic volume. QRS duration was best able to discriminate eccentric hypertrophy (area under ROC curve 0.701) and increased LV end-diastolic volume (0.681).

Conclusions: In patients with LBBB, QRS duration (≥ 150 in women and ≥ 160 in men) is a superior predictor of LV remodeling esp. eccentric hypertrophy and dilation.

Keywords

ECG; Left ventricular dilation; Left ventricular hypertrophy; Left ventricular remodeling; Left bundle branch block; QRS duration; QRS amplitude; QRS area; QRS voltage-time-integral

Introduction

Scientific and clinical background:

Left ventricular hypertrophy (LVH) is the increase in the mass of the left ventricle (LV) and is usually detected with echocardiography. LVH can be concentric (increase in LV wall thickness) or eccentric (dilation of the LV chamber) and usually occurs respectively in response to a chronic increase in pressure or volume load within LV [1]. LVH has consistently been shown to be an independent predictor of worse prognosis and early identification is an important first step in mitigating adverse cardiovascular outcomes [2]. Electrocardiography (ECG) is a simple, non-invasive and widely available modality to screen for cardiac abnormalities [3]. A multitude of reasonably specific ECG diagnostic criteria for LVH in setting of narrow QRS complex have been developed, such as Sokolow and Lyon, point score of Romhilt and Estes, Cornell criteria, and Peguero and Lo Presti, although they have limited sensitivity [4–7]. As LVH results in an overall increase in the QRS voltage, these criteria rely on different combinations of R and S amplitudes in the standard limb and/or precordial ECG leads [8]. However, none of these criteria are valid in the presence of left bundle branch block (LBBB), though prior publications have assessed the utility of these criteria in presence of LBBB [9,10]. The sequential anterior-to-posterior depolarization of the LV due to LBBB results in additive effects on the QRS voltage independent of LV hypertrophy, and we do not have established voltage-based criteria to detect LV hypertrophy in the setting of LBBB [9,11,12].

Published ECG criteria relying on QRS amplitudes for LVH in the setting of LBBB were obtained from small patient sample sets and have yielded limited sensitivity and specificity. Klein et al. developed the criteria S amplitude in lead V2 + R amplitude in lead V6 > 4.5 mV [13]. Kafka et al. published a complex sequential 4 component criteria (i) R amplitude in lead aVL ≥ 11 mV, (ii) QRS axis $\geq -40^\circ$, (iii) S amplitude in lead V1 + R amplitude in V5 or V6 ≥ 40 mV, (iv) and S in lead V2 ≥ 30 mV and in V3 ≥ 25 mV [14]. Subsequently, Haskell et al. determined that voltages were not sensitive or specific for LVH diagnosis in setting of LBBB [15]. Instead, they concluded that QRS duration was the best correlate of LVH, 160 ± 12 ms with LVH and 148 ± 11 ms without LVH. When Fragola et al. tried to validate different criteria for LVH in 100 patients with LBBB, they concluded that all aforementioned criteria were unreliable in predicting LVH [12].

QRS 3D-voltage-time-integral (VTI_{QRS-3D}) is a novel summary metric obtained by the integrating, over the duration of the QRS, the instantaneous absolute 3D ECG voltage (root-mean-square of orthogonal X, Y, Z coordinate instantaneous voltages) [16–20]. 3D QRS area, an approximation of VTI_{QRS-3D} , has been proposed as a marker for patient selection and evaluating response to resynchronization therapy [21–24]. VTI of the QRS can be obtained for any standard ECG lead, the reconstructed orthogonal X, Y and Z axes leads or the absolute 3D ECG.

Study objectives and hypothesis:

The presence of LBBB signifies conduction system disease. This can occur in association with structural heart disease, heart failure or cardiac ischemia, but can also occur independently related to age-related conduction system degeneration. The identification of LBBB may warrant evaluation for structural heart disease with cardiac imaging e.g. echocardiogram or magnetic resonance imaging (MRI). Regardless, there remains a large subset of patients with LBBB who are asymptomatic and have no identifiable structural cardiac abnormality on imaging [25]. Such patients, however, remain at risk of developing eccentric hypertrophy and systolic cardiomyopathy. Therefore, it would be useful to have ECG criteria to identify which patients with LBBB have LVH.

The increased myocardial mass in LVH would generate increased voltage, and it would take longer to activate the enlarged LV. We therefore hypothesized that presence of LV adverse remodeling with hypertrophy and dilation in presence of LBBB would increase the QRS duration, amplitude and the VTI. We sought to evaluate such quantitative ECG variables as predictors of structural LV abnormalities on echocardiography in a larger dataset of patients with LBBB, and compare to previously published criteria [26].

Methods

Study data and patient selection

All adult patients evaluated between January 1, 2010 to December 31, 2020 at The University of Kansas Medical Center with a diagnosis code for left bundle branch block who had a 12-lead ECG and comprehensive transthoracic echocardiogram within 3 months of each other were potential subjects. We utilized HERON (Healthcare Enterprise Repository for Ontological Narration), a search discovery tool that facilitates searches on various hospital electronic data sources, to query and retrospectively identify eligible subjects [27,28]. The study was conducted under an approval from the Institutional Review Board.

ECG criteria for LBBB: On manual review of the ECGs, only patients with typical LBBB per ACC/AHA criteria were included and those with atypical LBBB or non-specific intraventricular conduction delay were excluded. ACC/AHA criteria for left bundle branch block consist of QRS duration ≥ 120 ms, broad notched or slurred R waves in left-sided leads, small r waves in right-sided leads, R peak time > 60 ms in V_5 and V_6 , and ST and T waves in opposite direction to the QRS [29]. Of the remainder we further excluded patients who had a QRS duration less than the sex-specific 10th percentile (130 ms for women and 136 ms for men) as these may be incomplete LBBB.

Data extraction

ECG: The 12-lead ECGs were downloaded and were manually reviewed together by the AD, SR and AN to ensure they meet ACC/AHA criteria for LBBB and all disagreements resolved by mutual consensus. Subsequently, digital ECGs were processed in Python and converted to vectorcardiograms utilizing the Kors's regression matrix [30]. The root-mean-square of the instantaneous voltages from the orthogonal leads (X, Y and Z) was integrated over the QRS duration to obtain the VTI_{QRS-3D} (see Fig. 1). The QRS amplitude was obtained from the root-mean-square (3D) ECG (amplitudeQRS-3D). Similarly, VTIs and peak-to-peak amplitudes were obtained for all 12 standard ECG leads and the reconstructed X, Y and Z leads.

Echocardiogram: The echocardiographic calculations were obtained from the HERON search. These include LV mass, LV end diastolic volume (LVEDV), LV end systolic volume (LVESV) and LV ejection fraction (LVEF). American Society of Echocardiography definitions were used for all echocardiographic calculations including LV mass and concentric/eccentric hypertrophy based on relative wall thickness (RWT) [31]. We used the American Society of Echocardiography recommended formula for LV mass calculation from 2D echocardiographic measurements in parasternal long axis view i.e. $0.8 \times 1.04[(LVIDd + IVSd + PWd)^3 - LVIDd^3] + 0.6$ grams [32]. When LV mass is elevated, relative wall thickness is defined $2 \times PWd/LVIDd$. $RWT > 0.42$ defines concentric hypertrophy and $RWT < 0.42$ classifies eccentric hypertrophy.

Patient demographics—Patient demographics were also obtained from HERON.

Statistical analysis

Baseline demographics and echocardiographic continuous variables among men and women subjects are reported as medians with interquartile ranges. Unadjusted correlation coefficients and multivariate linear regressions adjusted for age, sex, and body surface area (BSA) were used to assess the associations of ECG QRS predictors with echocardiographic calculations (LV mass, LVEDV, LVESV and LVEF). In addition to the overall QRS duration, peak-to-peak QRS amplitudes and voltage-time-integrals (VTIs) from all 12 standard ECG leads, X, Y, Z vectorcardiographic leads and 3D ECG were individually evaluated as predictors for each of the 4 echocardiographic calculations. Two-tailed p -values < 0.05 were considered statistically significant. For each of the ECG predictors, we separately obtained receiver operator characteristic (ROC) curves to predict each of the sex-specific BSA-indexed echocardiographic calculation being increased out of normal range (decreased for LVEF). ROC curves were generated for the entire study population and separately for men and women. The statistical analyses were performed in JMP Pro 16.0.0 (SAS Institute, Cary, NC).

Results

We included 413 patients in our study, with a median age of 73 years with 53% women. The baseline characteristics are shown in Table 1. The absolute median difference between dates

of ECG and echocardiogram was 3 (interquartile range 1–19) days. All 4 echocardiographic calculations were correlated with each other (Supplementary Table 1).

After adjusting for age, sex, and BSA, among all ECG variables that were assessed, QRS duration was found to be the strongest predictor of all 4 echocardiographic calculations i.e., LV mass, LVEDV, LVESV and LVEF ($p < 0.00001$ for all, Table 2). Associations with LV calculations were weaker with QRS VTIs and weakest with QRS amplitudes. VTI_{QRS-3D} and $amplitude_{QRS-3D}$ respectively were generally the strongest VTI and amplitude predictors of LV calculations among the 16 ECG leads evaluated (12 standard, X, Y, Z and 3D ECG) and are also shown along with QRS duration in Table 2. VTI_{QRS-3D} was statistically associated with LV mass and volumes, but not LVEF. $Amplitude_{QRS-3D}$ was only associated with LV mass.

Among its associations with the echocardiographic LV calculations, QRS duration was most strongly correlated with LV mass and LVEDV (Table 2). Fig. 2 shows residual plots for QRS duration, VTI_{QRS-3D} and $amplitude_{QRS-3D}$ for predicting LV mass and LVEDV.

Similarly, unadjusted correlations with all 4 echocardiographic LV calculations were strongest for QRS duration (correlation coefficient with LV mass 0.49, LVEDV 0.48, LVESV 0.42 and LVEF -0.20 , see Table 2).

Out of all ECG predictors, QRS duration had the highest area under the ROC curve (AUC) to detect echocardiographic LV abnormalities, i.e. increased sex-specific BSA-indexed mass and volumes, and reduced LVEF (Table 3). For QRS duration, the highest AUCs were for detecting eccentric hypertrophy (0.701) and increased sex-specific LVEDVi (0.681). On the other hand, QRS duration was worse than VTI_{QRS-3D} and $amplitude_{QRS-3D}$ in predicting concentric hypertrophy (AUCs 0.567, 0.631 and 0.621 respectively), although this finding was inconsistent between men and women (Table 4A, 4B). In men, AUCs of QRS duration were reliably higher than AUCs of VTI_{QRS-3D} and $amplitude_{QRS-3D}$ for all echocardiographic LV abnormalities. However, in women, AUC of QRS duration was lower than AUCs of VTI_{QRS-3D} and $amplitude_{QRS-3D}$ for concentric hypertrophy (0.585, 0.687 and 0.686 respectively).

Among women, QRS duration ≥ 150 ms had a sensitivity 56.3% with specificity 64.4% for identifying increased LV mass index (>95 g/m²), and a sensitivity 62.7% with specificity 67.8% for increased LVEDVi (>61 mL/m²). In men, QRS duration ≥ 160 ms had a sensitivity 63.1% with specificity 72.1% for increased LV mass index (>115 g/m²) and sensitivity 58.3% with specificity 74.5% for increased LVEDVi (>74 mL/m²).

Discussion

Summary of our findings:

We found in our study that, among patients with LBBB, QRS duration ≥ 150 ms in women and ≥ 160 ms in men is a superior predictor of LV eccentric hypertrophy and dilation. QRS 3D-voltage-time-integral (VTI_{QRS-3D}) is a better predictor of LVH than QRS amplitudes; however, it is inferior to QRS duration. QRS duration was statistically significant at

predicting all 4 echocardiographic calculations i.e. LV mass, LVEDV, LVESV and LVEF; the correlation with LV mass and LVEDV being the strongest. QRS duration had a greater AUC for discriminating eccentric hypertrophy than concentric hypertrophy as opposed to VTI_{QRS}-3D or amplitude_{QRS}-3D that had a higher AUC for concentric than eccentric hypertrophy, especially in women.

Mechanistic insights:

It remains unclear if the weak correlation of LVH with QRS voltages in setting of LBBB is due to the dominant effect of electrical dyssynchrony rather than hypertrophy on voltage. In addition, the heterogeneous effects of myocardial fibrosis, infiltrative cardiomyopathy, epicardial adipose tissue, pericardial effusion, body habitus and LV dilation could also impact QRS voltages [16,33]. Further analyses are required to unravel the individual contributions of such variables on the QRS voltage. VTI_{QRS} remains a potential diagnostic and prognostic marker for LV structural abnormalities, but corrections for anthropo-metric, cardiac and extracardiac factors that impact the QRS voltage will have to be incorporated.

It intuitively makes sense that in presence of LBBB, QRS duration correlates with LV dilatation and eccentric hypertrophy. With LBBB, LV excitation is dependent on conduction within the working myocardium. Even assuming fixed intramyocardial conduction velocity, the larger the size of the LV, the longer it would take to activate it. Additionally, adverse remodeling results in impaired intraventricular conduction within the working myocardium prolonging QRS duration, a mechanism applicable on top of presence of LBBB but also seen as non-specific intraventricular conduction delay when left bundle branch conduction is intact [34,35]. On the other hand, LV dilation may not have a consistent effect on QRS voltage. In the unipolar precordial leads, the voltage may be increased due to the increase in the activated myocardial mass, however, the voltage in the bipolar limb leads may be paradoxically reduced [33].

Conversely, it is logical that concentric hypertrophy without LV dilatation may not result in an overall increase in the time for the activation wavefront originating in the right bundle branch to travel across the LV, and thereby have smaller impact on the QRS duration. Concentric hypertrophy is more likely to be reflected as an increase in the individual ECG lead QRS amplitude as the corresponding thicker LV wall gets activated.

Increase in QRS duration has previously been reported to identify LVH in smaller studies in patients with LBBB, though sex-specific cutoffs had not been established [15]. Additionally, in LBBB, prolonged QRS duration when coexistent with left axis deviation has been correlated with systolic cardiomyopathy [26]. The correlation of QRS duration with LVEF are weaker compared to the correlation with LV mass and volumes in our analyses and may be explained on account of high degree of collinearity between LVEF and LV mass/volumes (see Supplementary Table 1).

Sex differences:

Our data is novel that we have a majority representation of women. Beyond different sex-specific cutoffs for QRS duration identifying LVH, we also found interesting modification of ECG-LVH correlates based on sex in our data. Among women, QRS duration had

better discrimination of eccentric hypertrophy and QRS VTI/amplitude better discriminated concentric hypertrophy. However, among men, QRS duration always trumped QRS VTI/amplitude for all echocardiographic LV calculations. QRS duration was consistently the best discriminator of echocardiographic LV dilation but performed better in men compared to women.

Implications for practice:

This study incorporating >400 subjects with a majority women provides the largest LBBB patient population in comparison to previous studies, which ranged from 30 to 100 patients. As discussed in the introduction section, previous studies examining ECG criteria for diagnosis of LVH in the presence of LBBB have yielded conflicting results [9,10,12–15]. In our study we found sensitivities and specificities based on QRS duration cutoffs in patients with LBBB to be comparable to published ECG voltage criteria for LVH in patients with normal QRS duration [4–7]. QRS duration offers a quantitative, easy to use predictor for LV dilation (eccentric hypertrophy) with fair sensitivity and specificity. Current guidelines for screening for LVH in the presence of LBBB should be expanded to place a greater emphasis on QRS duration cutoffs. If a LBBB patient meets the QRS duration cutoff of 150 ms for women or 160 ms for men, then a follow up echocardiogram should be considered to rule out LVH and LV dilation. QRS duration dominantly trumps QRS VTI and voltage and there is no role for using measures like VTI_{QRS-3D} or $amplitude_{QRS-3D}$ for detecting adverse LV remodeling.

Limitations:

This study has many limitations. We do not have data on clinical outcomes. The LV mass formula is inherently susceptible to imprecise calculation. This involves assumption of the 3-dimensional shape and structure of the LV and relies on linear measurements made on a single parasternal long axis 2D image with slight measurement errors being compounded on account of taking cubes of the measurements. We therefore also validated the findings on LV volumes which are more precise and reproducible. We have no means to test biophysical causes for our findings and mechanistic insights remain speculative. The ECG and echocardiograms were not mandatorily obtained on the same date and there remains a possibility of temporal changes occurring between obtaining the 2 studies. Though the median absolute difference in acquiring these was 3 days, the separation was 19 days for a quarter of our study population. Even though we found statistically significant correlation between increased QRS duration and adverse LV remodeling, the AUC for ROC curves and sensitivity/specificity to detect echocardiographic LV abnormalities are modest, thereby limiting clinical utility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AUC	Area under the curve
ECG	Electrocardiogram
LBBB	Left bundle branch block
LV	Left ventricle
LVH	Left ventricular hypertrophy
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
LVEDV	Left ventricular end-diastolic volume
ROC	Receiver operator characteristic

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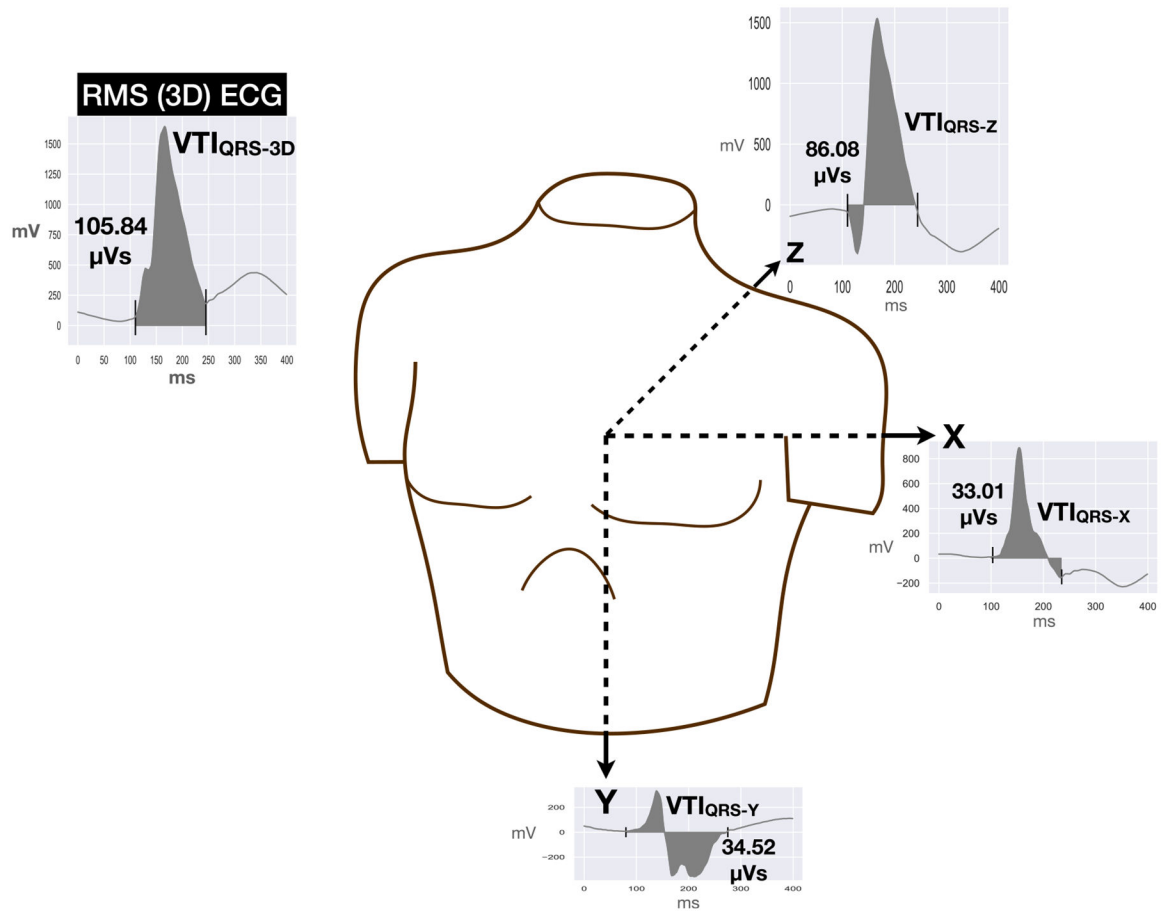


Fig. 1. Example of vectorcardiographic reconstruction from 12-lead ECG with X, Y and Z lead ECGs and root-mean-squared (3D) ECG. Voltage-time-integrals (VTIs) for the QRS in X, Y and Z leads and VTI_{QRS-3D} are shown.

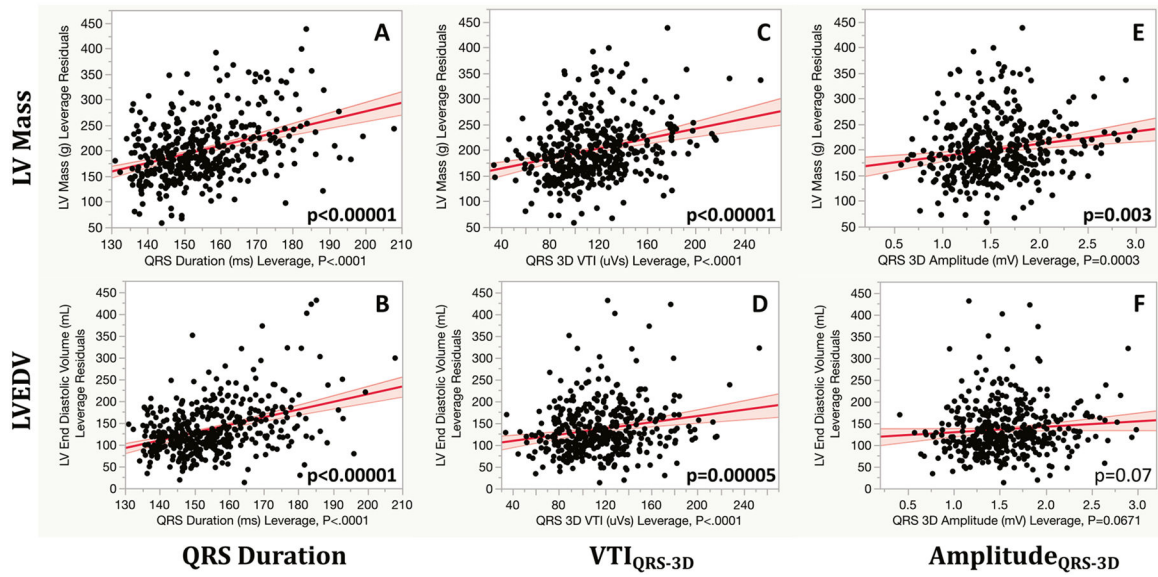


Fig. 2.

Leverage plots of QRS duration (Panels A and B), QRS 3D-voltage-time-integral (Panels C and D), and QRS 3D voltage (Panels E and F) with LV mass (top panels) and LVEDV (bottom panels) plotting residuals from multivariate linear regressions adjusting for age, sex and BSA.

Table 1

Study population characteristics.

Variable	Women (N = 219)	Men (N = 194)
	Median (IQR)	Median (IQR)
Age, years	74 (65–83)	72.5 (66–80)
BSA, m ²	1.9 (1.7–2.1)	2.1 (2.0–2.3)
LV Mass, g	164 (133–197)	227 (187–275)
LVEDV, ml	101 (76–138)	147 (113–199)
LVESV, ml	45 (31–71)	68 (48–105)
LVEF, %	54 (45–63)	53 (38–63)
QRS duration, ms	149 (140–158)	157 (150–168)
Amplitude _{QRS-3D} , mV	1.4 (1.2–1.7)	1.7 (1.3–1.9)
VTI _{QRS-3D} , μ Vs	102 (85–123)	124 (99–150)

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Table 2

Linear prediction of LV echocardiographic parameters by ECG ($N = 413$).

	QRS Duration			VTI _{QRS-3D}			Amplitude _{QRS-3D}		
	r^*	$t\text{-score}^\ddagger$	$p\text{-value}^\ddagger$	r^*	$t\text{-score}^\ddagger$	$p\text{-value}^\ddagger$	r^*	$t\text{-score}^\ddagger$	$p\text{-value}^\ddagger$
LV Mass	0.49	8.19	<0.00001	0.27	5.78	<0.00001	0.13	3.64	0.0003
LVEDV	0.48	8.52	<0.00001	0.22	4.12	0.00005	0.09	1.84	0.07
LVESV	0.42	8.04	<0.00001	0.22	3.51	0.0005	0.11	1.38	0.2
LVEF	-0.20	-4.48	<0.00001	-0.15	-1.84	0.07	-0.12	-0.88	0.4

VTI, voltage-time-integral; LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction.

* Unadjusted correlation coefficients.

[‡] From linear regression models adjusted for age, sex, BSA.

Table 3

Area under curve (AUC) from ROC curves for prediction of LV echocardiographic abnormalities by ECG in the overall population.

Echocardiographic Abnormality	AUC for Overall Population (N = 413)		
	QRS Duration	VTI _{QRS-3D}	Amplitude _{QRS-3D}
Increased LVMI (F > 95, M > 115 g/m ²)	0.646	0.636	0.603
Concentric Hypertrophy (LVH & RWT > 0.42)	0.567	0.631	0.621
Eccentric Hypertrophy (LVH & RWT < 0.42)	0.701	0.569	0.514
Increased LVEDVi (F > 61, M > 74 mL/m ²)	0.681	0.592	0.542
Increased LVESVi (F > 24, M > 31 mL/m ²)	0.640	0.591	0.561
Decreased LVEF (< 40%)	0.659	0.558	0.525

Table 4A

Area under curve (AUC) from ROC curves for prediction of LV echocardiographic abnormalities by ECG for women.

Echocardiographic Abnormality	AUC for Women (n = 219)		
	QRS Duration	VTI _{QRS-3D}	Amplitude _{QRS-3D}
Increased LVMI (> 95 g/m ²)	0.657	0.676	0.640
Concentric Hypertrophy (LVH & RWT > 0.42)	0.585	0.687	0.686
Eccentric Hypertrophy (LVH & RWT < 0.42)	0.714	0.535	0.554
Increased LVEDVi (> 61 mL/m ²)	0.668	0.556	0.501
Increased LVESVi (> 24 mL/m ²)	0.652	0.562	0.526
Decreased LVEF (< 40%)	0.683	0.508	0.562

Table 4B

Area under curve (AUC) from ROC curves for prediction of LV echocardiographic abnormalities by ECG for men.

Echocardiographic Abnormality	AUC for Men (n = 194)		
	QRS Duration	VTI _{QRS-3D}	Amplitude _{QRS-3D}
Increased LVMI (> 115 g/m ²)	0.703	0.616	0.567
Concentric Hypertrophy (LVH & RWT > 0.42)	0.651	0.603	0.548
Eccentric Hypertrophy (LVH & RWT < 0.42)	0.680	0.581	0.562
Increased LVEDVi (> 74 mL/m ²)	0.699	0.622	0.569
Increased LVESVi (> 31 mL/m ²)	0.634	0.615	0.587
Decreased LVEF (< 40%)	0.607	0.573	0.563