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Retrospective Cohort Study

Improved scoring system for the electrocardiographic diagnosis of left ventricular hypertrophy

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Abstract

BACKGROUND

Left ventricular hypertrophy (LVH) is a common manifestation of cardiovascular disease and a risk factor for cardiovascular morbidity and mortality, but available methods for its electrocardiographic (ECG) diagnosis have limited accuracy.

AIM

To investigate findings associated with LVH on ECG and developed an improved system for the diagnosis of LVH.

METHODS

A cohort study comparing ECG data acquired within 30 days of transthoracic echocardiography (TTE) was performed. Multivariate regression analysis identified ECG findings associated with increased LV mass and mass index. A scoring system was derived and performance compared to established criteria for LVH.

RESULTS

Data from 5486 outpatients with TTEs and corresponding ECGs were included in the derivation cohort, 333 (6.1%) of whom had LVH by TTE. In the primary regression analysis, findings associated with LVH were amplitudes of Q in V3, R in V6, S in V3, T in V6, P' in V1, P in V6, as well as R and T-axis discordance, R peak time in V6, QRS duration, weight, height, sex, and age. From this we derived a score consisting of 5 criteria, and validated it in an independent cohort of 910 patients. With a threshold of 1.5 points, sensitivity and specificity were 67.9% and 81.4%, and 62.5% and 83.2% in the derivation and validation cohorts, respectively. With a threshold of 2 points, sensitivity and specificity were 42.3% and 93.0%, and 37.5% and 93.4% in these cohorts.

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CONCLUSIONS

This score had superior sensitivity for detection of LVH by ECG while making a modest sacrifice in specificity compared to conventional criteria.

Key words: Left ventricular hypertrophy; Electrocardiogram; Echocardiogram; Diagnostic criteria; Scoring system

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Core tip: In this study we performed analysis of a large number of echocardiograms with corresponding electrocardiographic (ECG), and though multivariate regression analysis identified ECG findings associated with left ventricular hypertrophy (LVH). Using these findings, a five-item scoring system was developed to diagnose LVH on ECG. The performance characteristics of the system were compared to several conventional criteria, and it was seen to have superior sensitivity, including in an independent validation cohort. Using this scoring system, we believe that the diagnosis of LVH on ECG will be more clinically applicable in certain patient populations given the enhanced sensitivity of this test.

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INTRODUCTION

Left ventricular hypertrophy (LVH) is a common consequence of various cardiovascular diseases, and has been associated with increased risks of morbidity and mortality. Specifically, LVH has been associated with several adverse cardiac outcomes including heart failure, angina pectoris, myocardial infarction, and sudden cardiac death^[1-5]. Upwards of 30 electrocardiographic (ECG) criteria have been proposed for diagnosis of LVH^[6], but most have low sensitivity in the general population. Transthoracic echocardiography (TTE) is often required to confirm the diagnosis^[7,8]. Antihypertensive treatment can promote regression of LVH and prevent adverse cardiovascular events in patients with hypertension^[9,10], and TTE is preferred over ECG to assess myocardial mass in this setting^[8,11], although detection of left ventricular electrical remodeling may have prognostic implications independent of mass^[12-16]. Despite the availability of multiple criteria for ECG diagnosis of LVH, relatively few are widely implemented in clinical practice. Several models have been correlated with echocardiographic, cardiac magnetic response imaging, and autopsy measurements of LV mass, but these have not been integrated into commonly used ECG analysis software, while others are too complex for practical use. The aim of this study was to identify ECG findings associated with increased LV mass and develop an improved and easy to use scoring system to facilitate the diagnosis of and screening for LVH.

MATERIALS AND METHODS

Data collection and processing

The Institutional Review Board approved the protocol in October 2015. Clinical data available in the information systems of the Mount Sinai Medical Center, a large urban academic medical center, were derived from two sources, one for ECGs, and another for echocardiographic data. Data from all standard 12-lead ECGs recorded between December 1, 2013 and January 31, 2015 was exported from the MUSE v8.0 SP2 system (GE Healthcare, Chicago, IL, United States). Computer performed measurements including ventricular rate, PR interval, QRS duration, R-axis, T-axis, P-, P'- (second phase of P-wave), Q-, R-, S-, R'- and T-wave maximum amplitude, duration, area and peak time, maximum and minimum ST-segment level, and ST-segment deviation at J-point, mid-ST-segment and end-ST-segment. Measurements in each standard lead

were averaged across the ECG by the MUSE software. ECGs were not manually verified or measured and all ECGs except for those noted below were included in analyses.

Data from all outpatient TTEs acquired from patients ≥ 18 yr of age between January 1, 2014 and December 31, 2014 were exported from a proprietary echocardiography reporting system. Two-dimensional echocardiograms were performed using Siemens SC-2000, Siemens Acuson Sequoia, Phillips IE-33 or GE Vivid 7 cardiac ultrasound equipment. Measurements of the left ventricle were made in the parasternal long-axis view perpendicular to the axis at or immediately below the level of the mitral valve leaflet tips. Internal ventricular dimensions were measured linearly from two dimensional (2D) echocardiographic images to avoid oblique sections, or from 2D-guided M-mode echocardiography. Posterior and septal wall thickness and left ventricular end-diastolic and end-systolic diameters were measured according to the recommendations of the American Society of Echocardiography^[17]. Measurements were made during routine clinical interpretation of the echocardiogram and were not repeated or verified for the purposes of this study. Demographic data including age, sex, height, and weight (patient reported at the time of the study) were also collected.

Left ventricular mass was calculated using the method of Devereux *et al*^[18]. Body mass index, body surface area, and LV mass index were calculated using the standard methods. LVH was defined by LV mass index one standard deviation above the mean, stratified by sex (145 g/m² for males, 125 g/m² for females). Data from the first 10 mo of the study period comprised the derivation set, while those from the final 2 mo were used to validate the derived model.

TTEs and ECGs were matched by selecting the ECG obtained most proximate to each TTE. When patients had more than one TTE during the study period, only the first was included for analyses. Echocardiograms with incomplete demographic or measurement data and those without a corresponding ECG within 30 d were excluded. Also excluded were ECGs showing complete (but not incomplete) left bundle branch block or a paced rhythm, as identified by the MUSE software and confirmed by a board-certified cardiologist.

Statistical analysis

A multivariate linear regression model was constructed using LV mass as the endpoint and covariates including P-, P'- (second phase of P-wave), Q-, R-, S-, R'- and T-wave amplitudes in each lead, R-wave peak time in each lead (intrinsicoid deflection), maximum and minimum ST levels in each lead, ST-segment deviation at the J-point and mid-ST-segment in each lead, QRS duration, PR interval, difference between R-axis and T-axis, and patient weight, height, sex and age (152 degrees of freedom). A similar model using LV mass index as the endpoint yielded similar output with reduced fit parameters. Another model constructed using wave-complex areas (as opposed to maximum amplitudes) was less strongly associated with the endpoint. Covariates most strongly correlated with LV mass (based on regression *P*- and *t*-values, and a *P*-value threshold set at $P \leq 0.005$ in the linear regression model) were retained for multivariate logistic regression analysis. Additional logistic regression models were constructed stratifying the data set by sex in order to assess differences in ECG findings between sexes.

As several of the amplitudes and durations included in the model are correlated, we minimized effects of multicollinearity by calculating variance inflation factors (VIF) for covariates likely to be correlated and manually removing colinear covariates (VIF > 5) in a stepwise fashion while maximizing fit parameters of the overall model. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, United States).

Scoring system development

A scoring system was derived using scaled and rounded regression Wald chi-square and beta-coefficients similar to the method of Sullivan *et al*^[19]. Thresholds for the prediction model were developed based on standard deviations of the covariates, established LVH criteria, and iteration. The derived diagnostic criteria as well as several accepted criteria for LVH (Cornell^[20], Sokolow-Lyon^[21], Cornell product^[22], Sokolow-Lyon product^[23], Gubner-Ungerleider^[24], Sum-of-12-lead^[25], Romhilt-Estes^[26], Framingham-adjusted Cornell^[27], R-wave amplitude in aVL, Peguero-Lo Presti^[28]) were evaluated. Sensitivity and specificity were calculated for each criterion in both cohorts, along with 95% confidence intervals using binomial proportions in the derivation cohort. Positive and negative predictive values were also calculated.

RESULTS

Patient characteristics

During the 1-yr inclusion period, 11087 outpatient TTEs were obtained, while 202706 ECGs were recorded during the bracketed 14-mo period for the study. After matching each TTE with available ECGs and excluding those with incomplete data ($n = 570$), subsequent TTE examinations in the same patients (695), those with left bundle-branch block (128) or paced rhythm (235), and those without corresponding ECGs within 30 days (1396), a total of 5486 cases were entered into the derivation cohort. Applying the same criteria, 910 cases comprised the validation cohort. Patients characteristics were similar between both cohorts, and patients included in analyses in the cohorts had mean age around 60, were on average overweight but not obese, and were about half male (Table 1).

Regression results

In the derivation cohort, 333 patients (6.1%) had LVH as defined by the foregoing TTE criteria. Utilizing the full set of 152 covariates available, multivariate logistic analysis for the endpoint of LV mass yielded a regression coefficient of 0.502. The most highly associated variables ($P \leq 0.005$) included Q-wave amplitude in V3, R-wave amplitude in V6, S-wave amplitude in V3, QRS duration, difference between R and T-wave axis, R-wave peak time in V6, T-wave peak amplitude in V6 (inversely associated with the outcome), P'-wave amplitude in V1 (inversely associated), P-wave amplitude in V6, weight, height, sex, and age. Using these covariates, a logistic regression model was constructed for LVH (Table 2) with area under the ROC curve estimated by the c-statistic at 0.867.

Scoring system development and evaluation

To derive a scoring system (Table 3), we summed the amplitude predictors and set a threshold of two standard deviations above the mean in the derivation cohort data, distinguished by sex. The QRS duration threshold was set arbitrarily at 100 ms, the upper limit of normal. The absence of a positive T-wave component in V6 was set based on the negative association of maximum T-wave amplitude in the regression model. Definition of R- and T-wave precordial axis discordance was set at $\pm 75^\circ$, although similar results were seen at $\pm 45^\circ$ and $\pm 90^\circ$. P-wave negative deflection greater than positive deflection in V1 was used due to the negative association of P'-wave amplitude in V1 in the model. Despite its association with LVH in the regression model, patient height was omitted from the scoring system to enhance clinical convenience.

Additional logistic regression models were constructed stratifying the data set by sex in order to assess differences in ECG findings between sexes (Table 4). Findings in these cohorts were similar to those in the overall analysis; however, notably discordance between R and T-wave axis was only found to be associated with LVH in men but not in women.

The derived prediction model and other criteria for ECG diagnosis of LVH were evaluated in the derivation and validation cohorts, calculating sensitivity and specificity as well as positive and negative predictive values (Table 5). Using a threshold of 2 points, the score exhibited sensitivity superior to previous methods while sacrificing little to no specificity; using a cutoff of 1.5 points, the score improved sensitivity while maintaining specificity $> 80\%$. Looked at another way, the score was also seen to have superior positive predictive values utilizing a cutoff of 2 points than established criteria while maintaining a high negative predictive value; all positive predictive values in this study for the derived and established criteria were relatively low because of the low overall prevalence of LVH in the studied population.

DISCUSSION

In this study of 5486 patients undergoing TTE within 30 d of a 12-lead ECG, several ECG findings were associated with increased LV mass from a set of 147 ECG variables, many of which are included in established criteria for LVH, along with several others heretofore unrecognized. In our model, QRS duration was independently associated with LVH, even when the voltage QRS duration products were tested as the other covariates. For this reason, we included QRS duration rather than a voltage duration product as an independent predictor. This independent association suggests that voltage duration products may not be optimal for identification of LVH. In contrast to established schema, R-wave amplitude in lead aVL was not independently associated with echocardiographic LVH in this analysis,

Table 1 Patient characteristics

Characteristic - no. (%) unless noted	Derivation cohort (n = 5486)	Validation cohort (n = 910)
Age (mean \pm SD)	59.1 \pm 15.8	58.6 \pm 15.2
18-29	265 (4.8)	30 (3.3)
30-39	408 (7.4)	91 (10.0)
40-49	708 (12.9)	105 (11.5)
50-59	1295 (23.6)	224 (24.6)
60-69	1358 (24.8)	242 (26.6)
70 +	1452 (26.5)	218 (24.0)
Male sex	2869 (52.3)	448 (49.2)
Body mass index		
mean \pm SD	28.0 \pm 6.6	28.5 \pm 6.5
Median (range)	26.9 (12.9-75.2)	27.5 (15.8-66.1)
Left ventricular mass by echocardiogram		
mean \pm SD	167.2 \pm 62.1	173.3 \pm 64.8
Median (intraquartile range)	155.4 (123.3-200.4)	163.0 (124.1-205.0)
Left ventricular hypertrophy present by echocardiogram	333 (6.1)	80 (8.6)
Time between echocardiogram and electrocardiogram in days (mean, intraquartile range)	6.7 (0-13)	5.9 (0-11)

possibly due to interactions with precordial lead amplitude.

P-wave amplitude in V6 and negative P-terminal force in V1 were associated with LVH, likely reflecting left atrial pathology. P-wave duration (encompassing both positive and negative components), however, was not associated with LVH. These variations suggest the need for further study of the ECG manifestations of left atrial conduction delay. Unlike previous systems for identification of LVH, which typically include only R and S-wave amplitudes, we found an association of Q-wave in addition to S-wave amplitude in V3 with LVH. This could indicate an association of the total negative QRS vector in this lead, rather than the S-wave alone, with LVH. Lead V3 was found to be more highly associated with LVH than lead V1 or V2 as is seen in many other LVH criteria; this may be due to the location of lead V3 being more in line with the LV septum and therefore a better representation of its thickness.

An additional analysis looking at differences in ECG findings associated with LVH between sexes found that although most factors remained similar, R- and T-axis discordance was found to be associated with LVH in men but not in women. This may highlight differences in electrical remodeling as it relates to repolarization between sexes, and could be the subject of further study.

Conventional ECG criteria have low sensitivity for diagnosis of LVH. Several regression equations have been developed to estimate LV mass directly, but are impractical except for implementation in computerized ECG software, and correlate poorly with measurements of LV mass made by echocardiography, cardiac magnetic resonance imaging (MRI), or autopsy. The scheme we derived was evaluated using two thresholds based on distinct objectives. A threshold of 2 points yielded high specificity (approximately 93%) with improved sensitivity (approximately 40%), while a cutoff of 1.5 points markedly improved sensitivity (approximately 65%) while maintaining sensitivity at $> 80\%$. The higher limit may be preferred for general use, while the lower value may be more applicable to patients with hypertension or clinical conditions associated with LVH. Further studies are needed to assess the utility of either cut-point for serial assessments in the same individual, or to identify those who may benefit from echocardiography or other imaging studies to assess LV mass or its response to therapeutic interventions.

The derived scoring system was compared to conventional criteria for the ECG diagnosis of LVH and our system was found to have increased sensitivity with a modest sacrifice in specificity. Most conventional LVH criteria have high specificity but low sensitivity which limits use as a screening test in a general population. The enhanced sensitivity of the presented scoring system may introduce improvement to clinical practice by aiding with patient risk stratification and preventing unnecessary additional testing.

An important limitation of this study was inclusion of only ambulatory outpatients. This was because fluctuating clinical circumstances in acute ill hospital inpatient could influence echocardiographic measurements of wall thickness or produce

Table 2 Multivariate logistic regression analysis for left ventricular hypertrophy

Characteristic	Wald Chi-Square	P value
Q-wave amplitude in V3	19.3	$P < 0.0001$
R-wave amplitude in V6	39.7	$P < 0.0001$
S-wave amplitude in V3	135	$P < 0.0001$
QRS Duration	115.4	$P < 0.0001$
Discordant R-axis and T-axis (difference ≤ 75 or > 75)	14.6	$P = 0.0001$
Maximum (positive deflection) T-wave amplitude in V6	38.5	$P < 0.0001$
Maximum P'-wave amplitude in V1	18.5	$P < 0.0001$
P-wave peak amplitude in V6	0.19	$P = 0.659$
Weight	0.008	$P = 0.927$
Height	25.2	$P < 0.0001$
Sex	6.3	$P = 0.012$
Age	0.03	$P = 0.864$

discordance with ECG's recorded within the requisite 30-d window. It is also worth noting that the ECG data we used was measured automatically, while the echocardiographic measurements were obtained manually. Echocardiographic measurement, while regarding as being relatively accurate, are not the gold standard for LV mass measurement; more accurate measurements of LV mass such as cardiac MRI were not able to be used in this study. We also were not able to collect data on patient race, cardiovascular risk factors, or comorbidities (*e.g.*, hypertension, diabetes), all of which are factors that may influence ECG estimations of LVH. Finally, while the Working Group on ECG diagnosis of LVH suggested that research on LVH focus on the potential relationship of electrical remodeling to clinical outcomes^[13], we lack long-term clinical follow-up of patients to correlate the LVH score with such outcomes.

In conclusion, we identified several ECG findings that are associated with LVH and incorporated them into a score to improve the ECG diagnosis of this common condition. The scoring system may help improve clinical utility by enhancing sensitivity whilst displaying a modest sacrifice in specificity compared to conventional criteria. Further studies are needed to determine whether this scheme optimally reflects changes in the electrical characteristics of the myocardium over time, and whether it may have value for predicting cardiovascular events that are not exposed by measurement of ventricular mass alone.

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Table 3 Components of the electrocardiographic diagnostic score for left ventricular hypertrophy

Criteria	Number of points
Sum of R-wave amplitude in V6 + S-wave amplitude in V3 + Q-wave amplitude in V3 > 4.0 mV in males and 3.2 mV in females	1
QRS duration > 100 ms	1
Absence of positive component of T-wave in V6 (maximum T-wave amplitude < 0) when overall QRS vector in V6 positive (i.e., R-wave larger than S-wave)	1
Discordant limb lead R- and T-wave axis (R- minus T-wave axis ≤ 75 or > 75 degrees)	0.5
Amplitude of negative terminal p-wave deflection in V1 greater than amplitude of positive deflection	0.5

Table 4 Multivariate logistic regression analysis for left ventricular hypertrophy stratified by sex

Characteristic	Male (n = 2869)		Female (n = 2617)	
	Wald Chi-Square	P value	Wald Chi-Square	P value
Q-wave amplitude in V3	14.7	P = 0.0001	5.0	P = 0.025
R-wave amplitude in V6	25.5	P < 0.0001	10.0	P = 0.001
S-wave amplitude in V3	77.0	p < 0.0001	53.6	P < 0.0001
QRS Duration	62.2	P < 0.0001	51.2	P < 0.0001
Discordant R-axis and T-axis (difference ≤ 75 or > 75)	17.8	p < 0.0001	0.63	P = 0.426
Maximum (positive deflection) T-wave amplitude in V6	16.0	P < 0.0001	26.1	P < 0.0001
Maximum P'-wave amplitude in V1	9.4	P = 0.002	4.6	P = 0.031
P-wave peak amplitude in V6	1.0	P = 0.314	3.5	P = 0.061
Weight	0.50	P = 0.477	0.9	P = 0.340
Height	6.8	P = 0.009	21.8	P < 0.0001
Age	1.4	P = 0.245	1.06	P = 0.303

Table 5 Sensitivity, specificity, and positive and negative predictive values of selected electrocardiographic criteria for left ventricular hypertrophy

Criteria	Cutoff	Derivation cohort				Validation cohort	
		Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	Sensitivity	Specificity
Derived Criteria	1.5 points	67.9 (62.6-72.9)	81.4 (80.3-82.4)	19.0	97.5	62.5	83.2
""	2 points	42.3 (37.0-47.7)	93.0 (92.3-93.7)	28.2	96.2	37.5	93.4
""	2.5 points	30.0 (25.2-35.3)	96.6 (96.1-97.1)	37.6	95.6	30.0	96.8
Cornell	-	37.8 (32.6-43.1)	92.3 (91.6-93.0)	24.1	95.8	36.2	90.3
Sokolow-Lyon	-	16.5 (12.5-20.5)	95.9 (95.4-96.5)	20.7	94.7	20.0	96.3
Cornell Product		55.0 (49.6-60.3)	88.3 (87.5-89.2)	23.3	96.8	53.8	88.1
Sokolow-Lyon Product		22.5 (18.0-27.0)	95.9 (95.3-96.4)	26.0	95.0	23.8	95.6
Gubner-Ungerleider		27.0 (22.3-31.8)	88.9 (88.0-89.8)	13.6	95.0	27.5	87.7
Sum-of-12-Lead		57.4 (51.9-62.7)	76.1 (74.9-77.3)	13.4	96.5	57.5	77.1
Romhilt-Estes	5 points	35.4 (30.3-40.8)	94.4 (93.7-95.0)	26.2	95.8	35.0	95.0
""	4 points	51.1 (45.5-56.5)	88.2 (87.3-89.0)	21.8	96.5	57.5	90.0
Framingham-adjusted Cornell		42.3 (37.0-47.7)	90.1 (89.3-90.9)	21.7	96.0	51.3	87.6
R-wave amplitude in aVL	1.1 mV	20.1 (16.0-24.8)	92.6 (91.8-93.3)	14.9	94.7	21.3	92.1
Peguero-Lo Presti		24.9 (20.3-29.6)	94.7 (94.1-95.3)	23.3	95.1	26.3	93.5

CI: Confidence interval; PPV: Positive predictive values; NPV: Negative predictive values.

ARTICLE HIGHLIGHTS

Research background

Left ventricular hypertrophy (LVH) is a common manifestation of cardiovascular disease and a risk factor for cardiovascular morbidity and mortality, but available methods for its electrocardiographic (ECG) diagnosis have limited accuracy.

Research motivation

Improvement in the ability of clinicians to diagnose LVH on ECG could aid with patient risk stratification and prevent unnecessary additional testing.

Research objectives

The aim of this study was to investigate findings associated with LVH on ECG and develop an improved system for the diagnosis of LVH.

Research methods

A cohort study comparing ECG data acquired within 30 days of transthoracic echocardiography was performed. Multivariate regression analysis identified ECG findings associated with increased LV mass and mass index. A scoring system was derived and performance compared to established criteria for LVH.

Research results

In regression analysis, findings associated with LVH were amplitudes of Q in V3, R in V6, S in V3, T in V6, P' in V1, P in V6, as well as R and T-axis discordance, R peak time in V6, QRS duration, weight, height, sex, and age. A score consisting of 5 criteria was derived and validated it in an independent cohort. This score had superior sensitivity for detection of LVH by ECG compared to conventional criteria whilst making a modest sacrifice in specificity compared to conventional criteria.

Research conclusions

We identified several ECG findings that are associated with LVH and incorporated them into a score to improve the ECG diagnosis of this common condition. The scoring system may help improve clinical utility by enhancing sensitivity whilst displaying a modest sacrifice in specificity compared to conventional criteria.

Research perspectives

Further studies are needed to determine whether this scheme optimally reflects changes in the electrical characteristics of the myocardium over time, and whether it may have value for predicting cardiovascular events that are not exposed by measurement of ventricular mass alone.

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