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Electrocardiographic Identification of Increased Left Ventricular Mass by Simple Voltage–Duration Products

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Objectives. **This study was conducted to validate the hypothesis that the product of QRS voltage and duration, as an approximation of the time–voltage area of the QRS complex, can improve the electrocardiographic (ECG) detection of echocardiographically determined left ventricular hypertrophy and to further assess the relative contribution of QRS duration to the ECG detection of hypertrophy.**

Background. **The ECG identification of left ventricular hypertrophy has been limited by the poor sensitivity of standard voltage criteria alone. However, increases in left ventricular mass can be more accurately related to increases in the time–voltage area of the QRS complex than to changes in QRS voltage or duration alone.**

Methods. **Standard 12-lead ECGs and echocardiograms were obtained for 389 patients, including 116 patients with left ventricular hypertrophy. Simple voltage–duration products were calculated by multiplying Cornell voltage by QRS duration (Cornell product) and the 12-lead sum of voltage by QRS duration (12-lead product).**

Results. **In a stepwise logistic regression model that also included Cornell voltage, Sokolow–Lyon voltage, age and gender, QRS duration remained a highly significant predictor of the presence of left ventricular hypertrophy (chi-square 26.9, $p < 0.0001$). At a matched specificity of 96%, each voltage–duration product significantly improved sensitivity for the detection of left ventricular hypertrophy compared with simple voltage criteria alone (Cornell product 37% vs. Cornell voltage 28%, $p < 0.02$, and 12-lead product 50% vs. 12-lead voltage 43%, $p < 0.005$). Sensitivities of both the Cornell product and the 12-lead product were significantly greater than the 27% sensitivity of QRS duration alone ($p < 0.01$ vs. $p < 0.001$), the 20% sensitivity of a Romhilt–Estes point score >4 ($p < 0.001$) and the 33% sensitivity of the best-fit logistic regression model in this cohort ($p < 0.05$ vs. $p < 0.001$).**

Conclusions. **QRS duration is an independent ECG predictor of the presence of left ventricular hypertrophy, and the simple product of either Cornell voltage or 12-lead voltage and QRS duration significantly improves identification of left ventricular hypertrophy relative to other ECG criteria that use QRS duration and voltages in linear combinations.**

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Standard 12-lead electrocardiography remains the most widely used initial screening test for the noninvasive detection of left ventricular hypertrophy. However, electrocardiographic (ECG) criteria based only on QRS voltage have exhibited poor sensitivity for left ventricular hypertrophy at the high levels of specificity necessary for adequate clinical utility (1–6), and more complex ECG scores that incorporate QRS duration, repolarization abnormalities, P wave findings and demographic variables in multivariate regression equations or as linear scores have only marginally improved the overall accuracy of the ECG for identification of increased left ventricular mass (1,2,7–10). Nonetheless, the increased cardiac morbidity and mortality associated with the presence of echocardiographically detected left ventricular hypertrophy (11–13) make the accurate and cost-effective identification of left ventricular hypertrophy a clinical priority (14).

Increased left ventricular mass has been associated separately with increased QRS amplitude and duration (1–9,15–24) and with an increased time–voltage integral of the QRS complex (23–26). It has recently been demonstrated (22) that the simple product of QRS duration and voltage, as an approximation of the time–voltage area under the QRS complex, can significantly improve the ECG identification of left ventricular hypertrophy as defined at autopsy. The present study was conducted to test these simple voltage–duration product criteria for the identification of increased left ventricular mass detected by echocardiography in living subjects and to examine further the relative contribution of QRS duration to the ECG detection of left ventricular hypertrophy.

Methods

Study patients. Standard 12-lead ECGs were acquired in 389 patients who underwent echocardiography at The New

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York Hospital-Cornell Medical Center as part of several ongoing, longitudinal studies. The control group included 273 normotensive or mildly hypertensive patients (208 men, 65 women; mean [±SD] age 51 ± 12 years) with normal echocardiographic left ventricular mass indexed to body surface area, as defined later. The second group included 116 patients with echocardiographic left ventricular hypertrophy (69 men, 48 women, mean age 53 ± 15 years), including 48 normotensive or mildly hypertensive patients and 68 patients with chronic, regurgitant valvular heart disease. Because of the absence of any patients with left or right bundle branch block in the control group, patients with bundle branch blocks were excluded from the present study. The study was performed in accordance with protocols approved by the Committee on Human Rights in Research of Cornell University Medical College, and written informed consent was obtained from all patients.

Electrocardiography. Standard 12-lead ECGs were recorded at 25 mm/s and 1 mV/cm standardization with equipment whose frequency response characteristics met recommendations of the American Heart Association (27). All ECGs were digitized at 250 or 500 Hz, and all measurements were performed by computer from median complexes with verification by a single investigator who had no knowledge of calculated left ventricular mass; QRS duration was measured by computer to the nearest 2 ms, and QRS amplitudes were measured to the nearest microvolt.

Several widely used ECG criteria for the detection of left ventricular hypertrophy were examined. These included QRS duration; the amplitude of the R wave in lead aVL; Gubner–Ungerleider voltage (sum of the amplitude of R wave in lead I and the amplitude of the S wave in lead III) (16); Sokolow–Lyon voltage (sum of amplitude of the S wave in lead V_1 and the R wave in lead V_5 or V_6) (10); gender-specific Cornell voltage (sum of the amplitude of the R wave in lead aVL and the amplitude of the S wave in lead V_3, adjusted by the addition of 800 μV for female gender) (2,22); the sum of QRS voltage in all 12 leads (28); the Romhilt–Estes point score (29), a complex ECG criterion for left ventricular hypertrophy based on a weighted score that incorporates QRS duration, QRS voltages, QRS axis, repolarization changes and P wave abnormalities; and the Sokolow–Lyon score, a grading system of from 0 to 4 based on the presence of abnormal voltage alone (grade 1), abnormal voltage and low-amplitude T waves (<10% of the R waves, grade 2), abnormal voltage and biphasic T waves (grade 3) or abnormal voltage and inverted T waves (grade 4) (10,15). A voltage–duration product was calculated for each simple voltage criterion as the product of QRS duration and voltage (22).

Echocardiography. All subjects underwent standard M-mode and two-dimensional echocardiography performed by a skilled research technician using a commercially available echocardiograph equipped with 2.5- and 3.5-MHz imaging transducers. Left ventricular dimensions were obtained from two-dimensionally guided M-mode tracings according to the recommendations of the American Society of Echocardiography (30). Measurements were performed on multiple cardiac cycles by use of a digitizing tablet and were averaged. If M-mode tracings were technically inadequate, left ventricular wall thicknesses and internal dimensions were measured from the two-dimensional study by the method recommended by the American Society of Echocardiography (31). Left ventricular mass was calculated according to an anatomically validated formula (32), and left ventricular hypertrophy was considered present if the left ventricular mass index was >110 g/m^2 in women or >125 g/m^2 in men, partition values based on the distribution of values in employed normotensive and hypertensive adults (33) and subsequently shown to be related to prognosis (10,11).

Table 1. Univariate Relations of Electrocardiographic and Demographic Variables With Left Ventricular Mass Index

	Correlation Coefficients With Left Ventricular Mass Index			
	Voltage Alone	p Value	Voltage–QRS Duration Product	p Value
Voltage criteria				
Skolow–Lyon voltage	0.57	< 0.0001	0.64	< 0.0001
12-lead QRS sum of voltage	0.55	< 0.0001	0.61	< 0.0001
Cornell voltage	0.52	< 0.0001	0.56	< 0.0001
Gubner–Ungerleider voltage	0.31	< 0.0001	0.36	<0.0001
R wave amplitude in lead aVL	0.26	< 0.0001	0.31	< 0.0001
Other criteria				
QRS duration	0.46	< 0.0001		
Romhilt–Estes point score	0.52	< 0.0001		
Sokolow–Lyon score	0.50	<0.0001		
Age	0.09	0.06		
Body surface area	−0.10	0.05		

Data analysis and statistical methods. Definitions of test sensitivity and specificity conform to standard use. The ECG partitions defining upper limits of normal under the present experimental conditions were calculated from data in the 273 patients without left ventricular hypertrophy by the method of percentile estimation (34,35), which requires no assumption regarding the normal distribution of individual test values. Test partitions were selected to incorporate the lowest 96% of ECG data in these patients as normal. Test sensitivities of the derived partition values, as indicators of the presence of left ventricular hypertrophy, were compared in the 116 patients with left ventricular hypertrophy using the McNemar modification of the chi-square method for paired proportions. Because sensitivity and specificity of a test are dependent on the partition values chosen for test positivity, test accuracy of ECG criteria was also compared using receiver operating characteristic curve analysis. Receiver operating characteristic curves

Table 2. Multivariate Linear Relations of Electrocardiographic and Demographic Variables With left Ventricular Mass Index

Dependent Variable	Beta Coefficient	Partial R^2 Value	p Value
Sokolow-Lyon voltage	0.016	0.25	0.0001
Cornell voltage	0.013	0.10	0.0001
QRS duration	0.896	0.08	0.0001
Age	0.351	0.02	0.005
Intercept	−68.241	—	—

Overall R = 0.71 (R^2 = 0.51), p < 0.00001.

compare sensitivity and specificity of different tests over a wide range of possible partition values and can be used to compare differences between methods independent of empirically derived criteria, with greater area under a method's performance curve indicative of superior test performance (36). Receiver operating characteristic curves were generated using maximal likelihood estimation techniques (36) and were compared statistically by means of a univariate *z* score test of the difference between the areas under two performance curves (36).

The relation between ECG and demographic variables and indexed left ventricular mass was evaluated by linear regression; independence of association was assessed by stepwise multiple regression, with the contribution of individual variables reported as the partial R^2. The relation between ECG and demographic variables and the presence or absence of left ventricular hypertrophy was assessed by stepwise logistic regression analysis. For all tests, $p < 0.05$ was required for rejection of the null hypothesis.

Results

Relation of ECG and demographic criteria to left ventricular mass index and left ventricular hypertrophy. The univariate linear correlates of ECG and demographic variables with left ventricular mass index are shown in Table 1. There were modest relations between indexed left ventricular mass and QRS duration or voltage criteria alone and only a minimal relation between left ventricular mass index and age or body surface area. Of note, correlation with left ventricular mass index was improved by the product of QRS duration with each of the simple voltage criteria. In a multivariate analysis that excluded the voltage-duration products, QRS duration remained an independent predictor of indexed left ventricular mass (partial $R^2 = 0.08$, $p < 0.0001$) along with Sokolow-Lyon voltage, Cornell voltage and age (Table 2). When QRS duration, voltages, age, gender and body surface area were entered into a stepwise logistic regression model for the prediction of left ventricular hypertrophy (Table 3), QRS duration was a strong predictor of left ventricular hypertrophy in the present population (chi-square = 26.9, $p < 0.0001$).

Electrocardiographic identification of left ventricular hypertrophy. Relative performance of ECG criteria for the identification of left ventricular hypertrophy and the effect of the simple product of QRS duration with voltage on test performance are examined in Table 4 and Figures 1 to 4. At matched specificity of 96%, individual QRS voltage and duration criteria had only moderate sensitivity for left ventricular hypertrophy, ranging from 20% for the R wave amplitude in lead aVL to 43% for Sokolow-Lyon voltage and the 12-lead sum of voltage. Test sensitivity of the 12-lead sum of voltage was enhanced by multiplication by QRS duration; at matched specificity of 96%, the 12-lead voltage-duration product identified left ventricular hypertrophy with a sensitivity of 50% (58 of 116), which was significantly higher than the sensitivity of either QRS duration (27%) or 12-lead sum (43%) criteria alone. Relative to simple voltage criteria, test sensitivity of Cornell voltage, Gubner-Ungerleider voltage and the amplitude of the R wave in lead aVL were also improved by creation of a voltage-duration product, but there was no significant improvement in sensitivity with the Sokolow-Lyon voltage-duration product. Comparison of receiver operating characteristic curves confirmed that the superior performance of the 12-lead product (Fig. 1) and Cornell product (Fig. 2) relative to simple voltage and QRS duration was independent of partition value selection. In addition, overall performance of the Sokolow-Lyon product was also significantly greater than that of simple QRS duration or Sokolow-Lyon voltage alone (Fig. 3) because of greater increments in sensitivity of the Sokolow-Lyon product at levels of specificity lower than 96% (Table 4).

The performance of the 12-lead voltage-duration product relative to complex electrocardiographic criteria that incorporate QRS voltages, QRS duration, repolarization changes, P wave abnormalities and demographic variables is examined in

Table 3. Multivariate Logistic Regression Model of Left Ventricular Hypertrophy

Variable	Beta Coefficient	Chi-Square Analysis†	p Value	Standard Deviation	Odds Ratio (95% CI)
Sokolow-Lyon voltage	0.0014	48.5	< 0.0001	1,154	5.27 (3.28–8.47)
QRS duration	0.010	26.9	< 0.0001	11.6	3.19 (2.06–4.94)
Cornell voltage	0.0008	13.4	0.0002	918	2.14 (1.42–3.24)
Gender*	1.37	11.3	0.0008	—	3.93 (1.77–8.75)
Age	0.038	9.4	0.0021	12.9	1.64 (1.20–2.24)
Intercept	−20.46	63.8	< 0.0001	2.56	

*Male = 1, female = 2. †Overall model chi-square 231.5, $p < 0.0001$. Odds ratios calculated as risk associated with a 1 SD increase for continuous variables and for female gender. CI = confidence interval.

Table 4. Sensitivity of Electrocardiographic Criteria for Identification of Left Ventricular Hypertrophy at Partitions With Matched Specificity of 96%

	Voltage Alone			Voltage–Duration Product	
	Partition (μV)	Sensitivity (%)	p Value	Partition (μV·s)	Sensitivity (%)
Voltage criteria					
12-lead QRS sum	20,758	43*	< 0.005	1,995	50
Sokolow-Lyon voltage	3,808	43*	NS	371	45‡
Cornell voltage	2,961	28†	< 0.02	286	37†
Gubner-Ungerleider voltage	2,226	22†	< 0.002	207	30†
R wave in lead aVL	1.139	20†	< 0.001	103	29†
Other criteria					
QRS duration	108 ms	27†			
Romhilt-Estes point score	4	20†			
Sokolow-Lyon score	1	35*			
Current logistic regression model	0.475	33†			

*p < 0.01, †p < 0.001, ‡p < 0.05 versus sensitivity of the 12-lead product.

Table 4 and Figure 4. At matched specificity of 96%, the 50% sensitivity of the 12-lead product for the detection of left ventricular hypertrophy was significantly greater than the 29% to 45% sensitivity of the other voltage–duration products, than the 20% sensitivity of a Romhilt–Estes point score >4, than the 35% sensitivity of a Sokolow–Lyon score >1, and even than the 33% sensitivity of the best-fit logistic regression model (Table 3) that was derived in the present population. Comparison of receiver operating characteristic curves confirmed the superior overall performance of the 12-lead product relative to the Romhilt–Estes point score and the logistic regression model (Fig. 4), both of which include QRS duration as part of the weighted scores.

The relation of test sensitivity of electrocardiographic criteria to the severity of left ventricular hypertrophy is examined in Table 5. When patients with hypertrophy were classified according to whether indexed left ventricular mass was higher or lower than the median value (152.8 g/m^2), sensitivity of the 12-lead product was significantly higher, and there was a trend toward higher sensitivity for the other electrocardiographic criteria among patients with more severe left ventricular hypertrophy.

Figure 1. Receiver operating characteristic curves demonstrating the superior overall performance of the 12-lead product for the identification of left ventricular hypertrophy compared with simple QRS duration and the 12-lead sum of voltage. *p < 0.001 versus the 12-lead product.

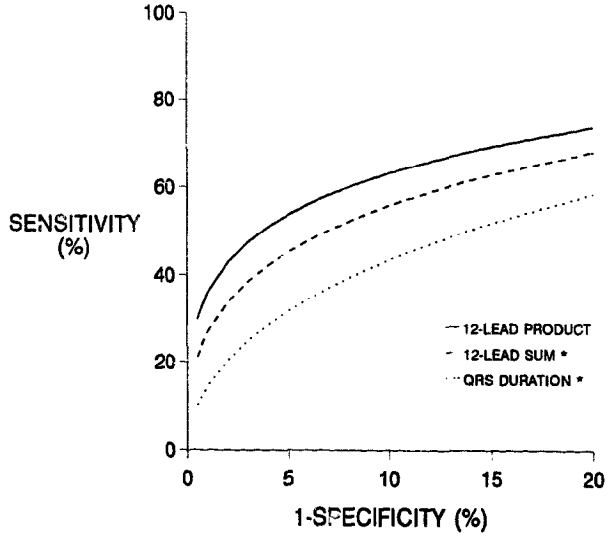
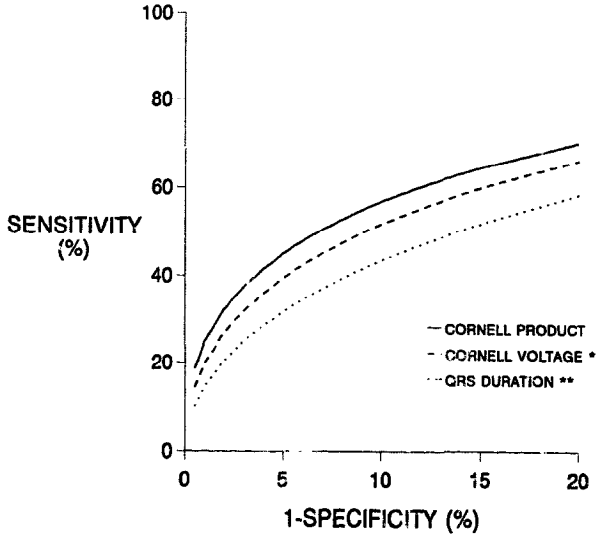


Figure 2. Receiver operating characteristic curves demonstrating the superior overall performance of the Cornell product for the identification of left ventricular hypertrophy compared with simple QRS duration and Cornell voltage. *p < 0.01, **p < 0.001 versus the Cornell product.



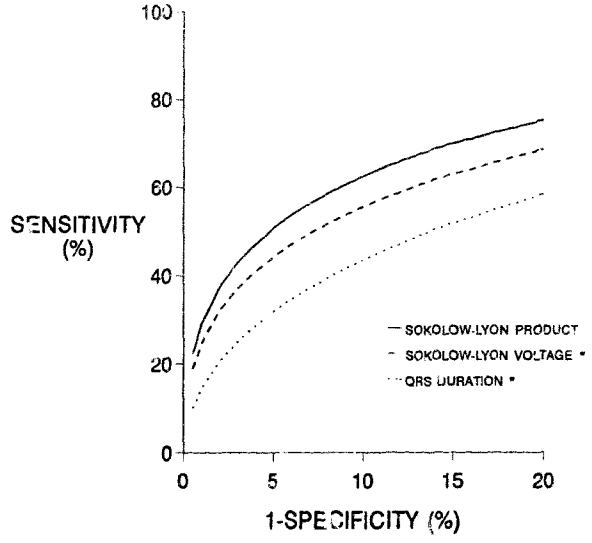


Figure 3. Receiver operating characteristic curves demonstrating the superior overall performance of the Sokolow-Lyon product for the identification of left ventricular hypertrophy compared with simple QRS duration and Sokolow-Lyon voltage. *p < 0.001 versus the Sokolow-Lyon product.

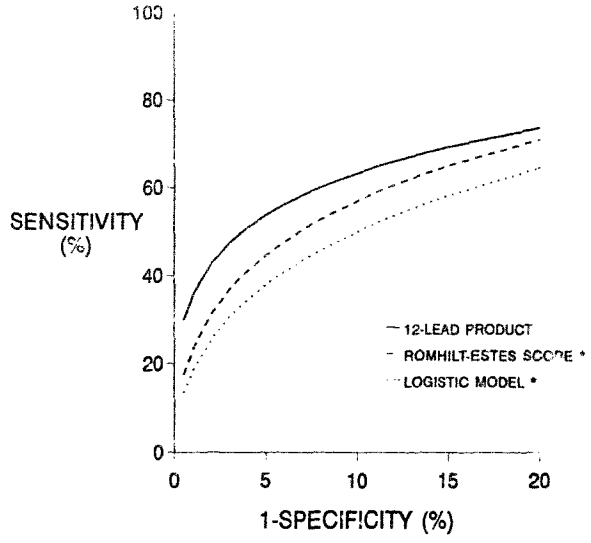


Figure 4. Receiver operating characteristic curves demonstrating the superior overall performance of the 12-lead product for the identification of left ventricular hypertrophy compared with the Romhilt-Estes point score and the multivariate logistic regression model derived in the current population. *p < 0.05 versus the 12-lead product.

Discussion

Improved ECG sensitivity for left ventricular hypertrophy. Although the standard 12-lead ECG remains the most widely utilized initial diagnostic test in the screening process for left ventricular hypertrophy, the relatively poor sensitivity of both simple and complex ECG criteria for left ventricular hypertrophy has limited the clinical utility and cost-effectiveness of the ECG (14). In a previous study (22) in which autopsy determination of left ventricular mass in highly selected patients was used as the reference standard, we found that the simple product of several standard voltage criteria with QRS duration could improve the ECG identification of left ventricular hypertrophy. Results of the present study confirm this finding in living subjects, using echocardiographically measured left ventricular mass index as the reference standard (31-33) in an ambulatory cohort representative of clinically normal subjects and of patients with hypertensive or valvular heart disease.

The voltage-duration product approximates the precise time-voltage integral of the QRS (22,26). Observations that the time-voltage integral of the orthogonal lead vectorcardiographic QRS complex and the time-strength left ventricular dipole derived from the 126-lead multiple dipole ECG can improve ECG correlation with indexed left ventricular mass (17-20,23-26) suggest that an ECG representation of the time-voltage integral of ventricular activation should more accurately reflect the presence of left ventricular hypertrophy than scores that sum QRS voltage and duration. The present study supports this conclusion. Because even a simple approximation of the time-voltage area of the QRS complex can improve the ECG identification of left ventricular hypertrophy relative to criteria incorporating both QRS voltages and duration as linear weighted sums, further investigation of more precise measures of the time-voltage integral of depolarization is warranted (25,26).

Relation of QRS voltage and duration to left ventricular hypertrophy. Increased QRS voltage, attributed to increased size of the electrical activation boundary according to solid-

Table 5. Sensitivity of Electrocardiographic Criteria for Identification of Left Ventricular Hypertrophy According to Severity of Hypertrophy at Partitions With Matched Specificity of 96%

Criteria	Sensitivity (%) LVMI ≤ 152.8 g/m² (n = 58)	p Value	Sensitivity (%) LVMI > 152.8 g/m² (n = 58)
12-lead QRS sum	36	NS	50
Sokolow-Lyon voltage	38	NS	48
Cornell voltage	28	NS	29
Gubner-Ungerleider voltage	19	NS	24
R wave in lead aVL	16	NS	24
QRS duration	26	NS	28
12-lead product	38	0.02	62
Sokolow-Lyon product	41	NS	48
Cornell product	33	NS	41
Gubner-Ungerleider product	29	NS	31
Lead aVL product	28	NS	31
Romhilt-Estes point score	19	NS	21
Sokolow-Lyon score	29	NS	40
Current logistic regression model	34	NS	52

Partitions as in Table 4. LVMI = left ventricular mass index.

angle theory (37), is a highly specific but poorly sensitive finding in left ventricular hypertrophy (1–6). Increased QRS duration has also been found to correlate with the presence of left ventricular hypertrophy (17–24,38). Potential mechanisms underlying the QRS prolongation associated with left ventricular hypertrophy include the longer time required to activate myocardium that is increasingly distant from specialized conduction tissue (18,38), decreased conduction velocity in hypertrophied myocardium (39), and changes in activation sequence or changes in the relative conductivity of fibrotic intracellular and extracellular spaces (17,40,41). However, QRS duration alone has also proved to be poorly sensitive for left ventricular hypertrophy at clinically relevant levels of specificity (22). The low sensitivity of Cornell voltage criteria relative to the sensitivity of both the 12-lead sum and Sokolow–Lyon criteria stands in contrast to previous reports from our laboratory (1,2,22), which were based on study patients with a high prevalence of concentric rather than eccentric geometric forms of left ventricular hypertrophy. The lower accuracy of Cornell voltage in the present study is most likely explained by the high proportion of patients with dilated left ventricles and eccentric left ventricular hypertrophy in the current population and reflects the recognized relatively lower overall performance of Cornell criteria in this particular form of cardiac enlargement (42).

Attempts to increase sensitivity of the ECG for the identification of left ventricular hypertrophy by combining QRS duration and voltages with additional electrocardiographic and demographic variables into complex linear scores have only modestly improved performance of the ECG for the detection of left ventricular hypertrophy (1–9). The present study demonstrates similarly modest improvements in ECG accuracy for left ventricular hypertrophy when QRS duration and voltages are combined in a logistic score. However, QRS duration appears to correlate more strongly with indexed left ventricular mass in a multivariate regression analysis than was found in a recent analysis of the Framingham population (9), with QRS duration adding an 8% increase in the coefficient determination (R^2) in the current study compared with only 1% to 3% increases in the Framingham population (9).

Clinical implications. The present study suggests that the simple product of QRS voltage and duration can significantly improve sensitivity of the ECG identification of left ventricular hypertrophy at acceptably high levels of specificity, enhancing the clinical utility of the ECG as the initial screening test for the detection of left ventricular hypertrophy. Because the voltage-duration product can be readily calculated by most commercially available ECG systems and can be easily calculated even in the absence of computer-measured QRS duration and voltage, this method is readily implemented in most physicians' practices. These findings further suggest that more accurate determination of the true time–voltage integral of individual QRS complexes may further enhance the ECG recognition of left ventricular hypertrophy.

The partitions derived in the current patient cohort without echocardiographic left ventricular hypertrophy compare favorably with partitions derived from 125 autopsied patients without left ventricular hypertrophy in a previous study (22). The slightly higher partitions found in the present study reflect the slightly higher specificity (96% vs. 95%), the use of percentile estimation to derive the partitions and the use of computerized measurements throughout the current study and may additionally be related to both differences in the left ventricular mass indexes used to define left ventricular hypertrophy and differences in the study patients (22). Further validation of these methods and partitions in larger, more heterogeneous patient groups, including patients with bundle branch blocks, will be necessary.

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