Time-Voltage QRS Area of the 12-Lead Electrocardiogram
Detection of Left Ventricular Hypertrophy

Peter M. Okin, Mary J. Roman, Richard B. Devereux, Thomas G. Pickering, Jeffrey S. Borer, Paul Kligfield

Abstract—Identification of left ventricular hypertrophy (LVH) using 12-lead ECG criteria based primarily on QRS amplitudes has been limited by poor sensitivity at acceptable levels of specificity. Because the product of QRS voltage and duration, as an approximation of the time-voltage area of the QRS complex, can improve accuracy of the 12-lead ECG for LVH, we examined the diagnostic value of true time-voltage area measurements of QRS complexes from the standard 12-lead ECG. Standard 12-lead ECGs and echocardiograms were obtained in 175 control subjects without LVH and in 74 patients with regurgitant valvular heart disease and LVH defined by echocardiographic criteria (indexed LV mass >110 g/m² in women and >125 g/m² in men). Standard voltage criteria, voltage-duration products (voltage multiplied by QRS duration), and true time-voltage areas of the QRS were calculated for Sokolow-Lyon criteria (SV₁ + RV₅₆) and the 12-lead sum of voltage criteria. Test sensitivities were compared using gender-specific partitions with matched specificity of 98% in the 175 subjects without LVH. Measurement of the time-voltage area significantly improved sensitivity for both criteria. The 76% sensitivity of the 12-lead sum area and 65% sensitivity of Sokolow-Lyon area were significantly greater than the 54% sensitivity of the approximation of QRS area provided by each voltage-duration product (P < .001 and P = .021) and than the 46% and 43% sensitivities of the respective simple voltage criteria (each P < .001). Comparison of receiver operating characteristic curves confirmed the superior overall performance of time-voltage area criteria compared with both voltage-duration products and simple voltage criteria. These results suggest that use of time-voltage areas can dramatically improve identification of LVH by 12-lead ECG. Further study of this approach is needed to identify optimal criteria for LVH based on the time-voltage area measurements from the 12-lead ECG. (Hypertension. 1998;31:937-942.)

Key Words: echocardiography · electrocardiography · hypertrophy

The standard 12-lead ECG remains the most widely used initial diagnostic test in the screening process for LVH. However, both simple voltage criteria based on measured QRS amplitudes¹-⁶ and more complex ECG criteria that incorporate QRS voltages, QRS duration, P-wave amplitudes, repolarization abnormalities, and demographic variables in linear scores⁷-¹⁰ have exhibited relatively poor sensitivity at high levels of specificity, limiting the clinical utility and cost-effectiveness of the ECG for the detection of hypertrophy.¹¹

Previous studies have demonstrated that accuracy of the ECG for the detection of LVH can be improved based on observations that relate increased LV mass to increases in the time-voltage area of the QRS complex.¹²-¹⁸ For example, the simple product of QRS voltage and duration, as an approximation of the time-voltage area of the QRS, improves ECG identification of LVH compared with standard voltage criteria.¹⁵,¹⁶ In addition, more precise quantification of QRS area by measurement of the time-voltage integral of the horizontal plane vector using the orthogonal-leading signal-averaged ECG further improves ECG identification of LVH.¹⁷,¹⁸ However, generalized clinical applicability of this approach will only be possible if accurate time-voltage area criteria can be developed using the standard 12-lead ECG. Accordingly, the present study was performed to assess the initial value of true time-voltage QRS area criteria derived from the 12-lead ECG for the identification of LVH in comparison with standard 12-lead ECG voltage and voltage-duration product criteria and, in addition, to compare these criteria with the performance of the time-voltage integral of the horizontal plane vector derived from the signal-averaged ECG.

Methods

Study Population
Standard 12-lead and signal-averaged ECGs were obtained in 249 subjects who underwent echocardiography at The New York Hospital-Cornell Medical Center as part of several ongoing longitudinal studies as previously described.¹⁶ Group 1 consisted of 175 normotensive or mildly hypertensive subjects (132 men and 43 women; mean ± SD age, 48 ± 10 years) with normal LV mass indexed to body surface area as defined below. Group 2 consisted of 74 subjects (49 men and 25 women; mean age, 51 ± 16 years) with chronic regurgitant valvular heart disease as the cause of LVH. Because of the
absence of any subjects with right or left bundle branch block in group 1, subjects with bundle branch blocks were excluded from group 2. All subjects gave informed consent to participation in these studies, which were performed in accordance with protocols approved by the Committee on Human Rights in Research of Cornell University Medical College. Data on performance of the horizontal plane vector integral of the signal-averaged ECG for the detection of LVH have been previously reported.17,18

**Time-Voltage Area of the QRS**

The time-voltage area of each Q, R, and S wave in all 12 leads was measured by the Marquette MUSE system, and the measurements were performed by computer from median complexes with visual verification by a single investigator who had no knowledge of the echocardiographic findings; QRS duration was measured to the nearest 2 ms and QRS amplitudes were measured to the nearest microvolt from the signal-averaged median digitized complexes.

Two widely used ECG criteria for the detection of LVH were examined: Sokolow-Lyon voltage (sum of the amplitude of the S wave in lead V1 and the R wave in lead V5 or V6)14 and the sum of QRS voltage in all 12 leads.20,21 Because Cornell voltage criteria have previously been shown to have poor sensitivity for the detection of the eccentric geometric pattern of LVH associated with regurgitant valvular heart disease,16 these criteria were not used in the present study. Based on previous observations that the product of QRS duration and voltage, as an approximation of the time-voltage area, improves ECG identification of LVH,15,16 a voltage-duration product was calculated for Sokolow-Lyon voltage and the 12-lead sum of QRS voltage.

The time-voltage area of each Q, R, and S wave in all 12 leads was measured by the Marquette MUSE system, and the measurements were accessed using custom software. This measurement process is graphically illustrated in Fig 1. For the purposes of the present study, two new time-voltage area criteria were derived from the individual 12-lead QRS complex measurements: Sokolow-Lyon area and the 12-lead sum area. Sokolow-Lyon area was calculated as the sum of the area of the S wave in lead V1 and the area of the R wave in lead V5 or V6, whichever was greater. The 12-lead sum area was calculated as the sum of Q, R, and S wave areas in all 12 leads in a manner parallel to the calculation of the 12-lead sum of QRS voltage.20,21

**Signal-Averaged Electrocardiography**

After careful skin preparation, with the patient lying quietly in the supine position, three orthogonal X, Y, Z leads were acquired (Predictor Signal Averaging ECG, Arrhythmia Research Technology, Inc) using an operator-selected template at a sampling frequency of 2000 Hz. Signal averaging was terminated when the residual root mean square noise in the ST segment was no more than 1 μV and, in the majority of cases, when the residual noise reached 0.3 μV. Digital filtering was performed on averaged orthogonal lead complexes with a standard frequency (0 to 100 Hz) low-pass filter. Vector QRS complex onset and offset were calculated with a computer algorithm that determined the first and last points at which voltage exceeded the mean of the baseline noise level plus three times the standard deviation, to the nearest 0.5 ms. Vector magnitudes were calculated for each filtered orthogonal lead as ($X^2 + Y^2 + Z^2$)1/2, which were then used to calculate the horizontal plane vector integral ($X^2 + Z^2$)1/2 to the nearest 0.01 μV · s by integrating voltage measurements over time as previously described.17,18

**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. LV dimensions were obtained from two-dimensionally guided M-mode tracings according to the recommendations of the American Society of Echocardiography.22 Measurements were performed on multiple cardiac cycles by use of a digitizing tablet and were averaged. If M-mode tracings were technically inadequate, LV wall thicknesses and internal dimensions were measured from the two-dimensional study by the method recommended by the American Society of Echocardiography.22 LV mass was calculated according to an anatomically validated formula,24 and LVH was considered present if the LV mass indexed to body surface area exceeded 110 g/m2 in women or 125 g/m2 in men, partition values chosen based on the distribution of values in employed normotensive and hypertensive adults25 and subsequently shown to be related to prognosis.26,27

**Data Analysis and Statistical Methods**

Mean values and standard deviations are reported for each variable by group and by gender. Comparison of mean ECG values between men and women was performed after first adjusting for the presence or absence of LVH using two-way ANOVA with inclusion of an interaction term between gender and hypertrophy. Definitions of test sensitivity and specificity conform to standard use.25 Test specificity of each ECG method for the identification of LVH was assessed in the 132 men and 43 women without LVH to produce gender-specific test criteria with matched specificities of 98%. Comparisons of test sensitivity were performed using McNemar’s modification of the $\chi^2$ method for paired proportions. Because sensitivity and specificity of a test are dependent on the partition values chosen for test positivity, test accuracy was also compared using ROC curve analysis. ROC curves 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.25 ROC curves were compared statistically by means of a univariate $z$ score test of the difference between the partial areas under two performance curves at specificities between 80% and 100%,24 which is a clinically relevant range of specificity for the identification of LVH. For all comparisons, a value of $P<.05$ was required for rejection of the null hypothesis.

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**Selected Abbreviations and Acronyms**

ECG = electrocardiogram, electrocardiographic
LV = left ventricular
LVH = left ventricular hypertrophy
ROC = receiver operating characteristic

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**Figure 1.** A typical QRS complex illustrating measurement of the time-voltage area of each QRS complex used to derive time-voltage area criteria for LVH. The computer measures the area inscribed by each individual Q, R, and S wave as denoted by the shaded areas.
Results
Mean values of QRS duration, simple voltage criteria measurements, voltage-duration products, and time-voltage area criteria in men and women according to the presence or absence of LVH are presented in Table 1. After adjustment for gender, both men and women with LVH had significantly greater mean values of all variables than their counterparts without hypertrophy. In addition, women both with and without hypertrophy had significantly shorter QRS durations and lower voltages, voltage-duration products, and time-voltage area than did men, although there was only a trend toward lower Sokolow-Lyon voltage in women. The mean LV mass index was 79±15 (median, 78; range, 47 to 123) g/m² in the 175 subjects without LVH and was 157±34 (median, 148; range, 110 to 267) g/m² in the 74 subjects with LVH.

Performance of time-voltage area criteria derived from the 12-lead ECG for the identification of LVH relative to their respective voltage-duration product and simple voltage criteria is examined in Table 2 and Figs 2 and 3. For both 12-lead sum and Sokolow-Lyon criteria, there was a stepwise increase in sensitivity and overall performance from simple voltage criteria to voltage-duration product criteria and finally to time-voltage area criteria. Using gender-specific partitions with matched specificities of 98%, the 76% sensitivity of the 12-lead sum area was significantly greater than the 54% sensitivity of the 12-lead voltage-duration product (P<.001) and the 46% sensitivity of the 12-lead sum of voltage (P<.001). Similarly, the 65% sensitivity of Sokolow-Lyon area criteria was significantly greater than the 54% sensitivity of the Sokolow-Lyon product (P=.021) and the 43% sensitivity of simple Sokolow-Lyon voltage criteria (P<.001). Comparison of ROC curves confirmed the superior overall performance of each time-voltage area method compared with both the approximation of the area provided by the voltage-duration product and with simple voltage criteria (Figs 2 and 3). Because sensitivity of ECG criteria for LVH will be higher in patients with more severe LVH, we separately examined sensitivity of the 12-lead sum criteria in the 37 subjects with LVH who had an indexed LV mass less than the median value of 148 g/m². In these subjects, the 65% (24/37) sensitivity of the 12-lead sum area remained significantly greater than the 41% (15/37) sensitivity of the 12-lead voltage-duration product (P=.004) and the 35% (13/37) sensitivity of the 12-lead sum of voltage (P<.001).

Sensitivity and overall performance of Sokolow-Lyon area, the 12-lead sum area, and the time-voltage area of the horizontal plane vector integral from the signal-averaged ECG are compared in Figs 4 and 5. At matched specificity of 98%, the 76% sensitivity of the 12-lead sum area was significantly greater than the 65% sensitivity of Sokolow-Lyon area (P<.05) and was similar to the 74% sensitivity of the horizontal plane vector integral (Fig 4). The difference in sensitivity between Sokolow-Lyon area and the horizontal plane integral did not achieve statistical significance. However, comparison of ROC curves (Fig 5) revealed that overall test performance of the 12-lead sum area was significantly greater than the overall performance of either the horizontal plane vector integral or the Sokolow-Lyon area and confirmed that there was no significant difference in test performance between the horizontal plane integral and Sokolow-Lyon area.

Discussion
This study demonstrates for the first time that time-voltage area measurements derived from a standard digitally acquired 12-lead ECG using commercially available equipment signif-

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<th>TABLE 1. ECG Measurements According to Gender and Presence or Absence of LVH</th>
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<td>QRS duration, ms</td>
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<td>Sokolow-Lyon voltage, μV</td>
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<td>12-Lead sum of voltage, μV</td>
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<td>12-Lead sum area, μV² · s</td>
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<td>Criteria</td>
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*Partitions used for each criterion with matched specificity of 98% were Sokolow-Lyon voltage: women >3358 μV, men >3808 μV. Sokolow-Lyon product: women >322.4 μV · s, men >367.4 μV · s; Sokolow-Lyon area: women >372.6 μV · s, men >483.9 μV · s; 12-lead sum of voltage: women >18 490 μV, men >19 530 μV; 12-lead sum product: women >1683.8 μV · s, men >1957.9 μV · s; 12-lead sum area: women >1960.7 μV · s, men >2348.8 μV · s.
The time-voltage area of the QRS significantly improved the ECG identification of LVH beyond that available from criteria based on standard QRS voltage and duration measurements. Moreover, overall test accuracy provided by the 12-lead sum area was significantly greater than test performance of either simple voltage criteria or of the approximation of the time-voltage area provided by the voltage-duration product. \(P < .05\) vs the 12-lead sum area.

Previous observations that the time-voltage integral of the vectorcardiographic QRS complex improves ECG correlation with LV mass\(^1\) suggest that increases in LV mass may be paralleled by subtle increases in both QRS voltage and duration that together produce a proportionally greater increase in the area under the QRS complex than in either QRS duration or maximal amplitude alone. Indeed, use of the simple product of QRS duration and voltages, as an approximation of the time-voltage area, has been found to improve the accuracy of the ECG for the identification of LVH relative to criteria based on QRS voltages or duration alone, or in combinations of linear weighted sums.\(^{15,16}\) Previous studies from our laboratory\(^{17,18}\) have demonstrated that measurement of true time-voltage area of the QRS using the orthogonal-lead signal-averaged ECG significantly improved the identification of echocardiographic LVH beyond the increase in test performance provided by voltage-duration products. However, the clinical applicability of this approach is limited by the lack of widespread use of orthogonal lead vectorcardiography.

Figure 2. ROC curves comparing overall performance of the 12-lead sum of QRS voltage, the 12-lead voltage-duration product, and the 12-lead sum area for the identification of LVH. Overall accuracy of the 12-lead sum area was significantly greater than test performance of either simple voltage criteria or of the approximation of the time-voltage area provided by the voltage-duration product. \(P < .05\) vs the 12-lead sum area.

Figure 3. ROC curves comparing overall performance of Sokolow-Lyon voltage, the Sokolow-Lyon voltage-product, and the Sokolow-Lyon area for the identification of LVH. Overall accuracy of the Sokolow-Lyon area was significantly greater than test performance of either simple voltage criteria or of the approximation of the time-voltage area provided by the voltage-duration product. \(P < .05\) vs Sokolow-Lyon area.

Figure 4. Comparison of sensitivity of the 12-lead sum area, Sokolow-Lyon area, and the horizontal plane vector integral for the identification of LVH using partitions with matched specificities of 98%. \(P < .05\) vs Sokolow-Lyon area.

Figure 5. ROC curves comparing overall performance of the 12-lead sum area, Sokolow-Lyon area, and the horizontal plane voltage integral for the identification of LVH. Overall test accuracy of the 12-lead sum area was significantly greater than test performance of either Sokolow-Lyon area or the horizontal plane vector integral; there was no significant difference in overall accuracy between the horizontal plane integral and Sokolow-Lyon area. \(P < .05\) vs the 12-lead sum area.
The present study extends these observations to time-voltage area criteria derived from the standard 12-lead ECG. For both the Sokolow-Lyon and 12-lead sum approaches to analysis of the ECG, true time-voltage area criteria had higher sensitivity and overall accuracy than either the approximation of area provided by each voltage-duration product or the underlying voltage combinations. Additionally, accuracy of the voltage-duration product criteria was intermediate between the lower performance of voltage criteria alone and the higher accuracy of the time-voltage area criteria. Although sensitivity of the 12-lead sum area remains imperfect at 76% in the present study, this represents a large increase in sensitivity at the high level of specificity used. Moreover, the 24% of patients with false-negative 12-lead sum-time-voltage area criteria had significantly lower indexed LV mass than the 76% of patients correctly identified by this method (138±19 g/m² versus 163±35 g/m², P<.004), suggesting that these patients may be at lower risk of subsequent morbid events. 15,16,27,34–36 In addition, sensitivity of the 12-lead sum area remained higher than that of the 12-lead voltage-duration product and simple sum of voltage in the 37 subjects with milder LVH (indexed LV mass less than the median value of 148 g/m²), suggesting that this approach will improve the detection of LVH even in populations with less severe LVH.

Additional work is necessary to determine the applicability of this approach in clinically more heterogeneous populations with different geometric patterns of LVH and to identify optimal criteria for the time-voltage area method. The criteria used in the present study were chosen to reflect two commonly used voltage criteria for which the approximation of time-voltage area using the product of voltage and QRS duration have been shown to improve sensitivity for LVH. 14,15 However, these criteria do not necessarily represent the optimal combination of Q, R, and S wave areas for the detection of LVH. Assessment of the accuracy of time-voltage area criteria in relation to gender and to body habitus will be also be required. The similar performance of the horizontal plane vector integral in men and women and in lean, normal-weight, and obese individuals, 38 in contrast to the lower sensitivity of standard voltage criteria in women 39 and among obese subjects, 40 suggests that performance of 12-lead time-voltage area criteria may also be independent of gender and body habitus.

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*Hypertension*. 1998;31:937-942
doi: 10.1161/01.HYP.31.4.937

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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