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Day-to-Day Variability of Voltage Measurements Used in Electrocardiographic Criteria for Left Ventricular Hypertrophy

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Although electrocardiographic (ECG) voltage can be used to estimate left ventricular mass, day-to-day variability of voltage combinations used for this purpose must be established before ECG changes are taken as evidence of progression or regression of hypertrophy. Accordingly, serial ECGs (mean 8 days apart), derived from 10 s samples digitized at 250 Hz, were examined in 78 patients with no intercurrent change in clinical status. The coefficient of variation was calculated as 1 SD of the difference between paired voltage measurements, divided by the average mean value.

Coefficient of variation for single leads was 22.3% for S_{V1}, 27.0% for R_{V5} or R_{V6}, 27.1% for R_{aVL} and 34.7% for S_{V3}. Coefficient of variation was lower for voltage combinations than for individual lead measurements: 18.5% for Sokolow-Lyon voltage (S_{V1} + R_{V5} or R_{V6}), 22.3% for Gubner-Ungerleider voltage (R_I + S_3) and 24.8% for Cornell voltage (R_{aVL} + S_{V3}). Serial reclassification due to variation above and below standard criteria for left ventricular hypertrophy occurred in only 3% of patients for Sokolow-Lyon voltage and 4% of patients for Cornell voltage in this group. Minute to minute reproducibility of voltage was assessed with electrodes in place in a separate group of 26 patients, and the coefficient of variation was 2.6% for Sokolow-Lyon voltage, 5.9% for Gubner-Ungerleider voltage and 2.9% for Cornell voltage.

These data indicate that serial variability of computer-measured ECG voltage combinations is high, due primarily to changes in lead placement and body position, but less than the variability of computer-measured voltage in individual leads.

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Left ventricular hypertrophy is associated with high cardiovascular risk in hypertensive patients and in the general population (1,2), but detection of hypertrophy and serial estimation of changes in left ventricular mass remain important diagnostic problems (3). Traditional electrocardiographic (ECG) criteria that are based on combined voltage partition values have poor sensitivity for left ventricular hypertrophy (4), and generally fail to identify patients with mild to moderate increases in ventricular mass (5,6). Although echocardiography can accurately measure left ventricular mass and has been used to predict cardiovascular risk in selected groups of patients (1,2), its use in large epidemiologic surveys is limited by cost and availability, as well as by occasional technical failure (7).

Combinations of ECG voltage and duration criteria that correlate as continuous variables with left ventricular mass have been proposed as practical methods for longitudinal evaluation of progression and regression of ventricular hypertrophy (8,9), and changing voltage has served as a marker for changing ventricular mass in previous studies (10–12). However, serial differences in voltage may reflect not only changes in generated signal amplitude and variations in performance among machines, but also the confounding effects of high frequency filtration and digital sampling error (13,14), variable lung and torso impedance (15) and, occasionally, large changes in patient position, the position of the heart in the chest and electrode location (16–19). As ECG methods for the assessment of left ventricular mass are utilized in epidemiologic studies and applied to serial comparison of tracings in clinical practice, the day-to-day variability of recorded ECG voltages must be established before changes in amplitude can be accepted as evidence for progression or regression of hypertrophy.

Therefore, the purpose of this study was to quantify the day-to-day variability of combined ECG voltages that have been correlated with left ventricular mass in patients without active cardiopulmonary disease. This analysis yields insights into sources of voltage variation between serial ECGs that bear on routine test interpretation and epidemiologic studies of ventricular hypertrophy.

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Methods

Study group. Consecutive ECGs from adult medical and surgical patients at The New York Hospital–Cornell Medical Center were selected for initial screening if the tracings fulfilled the following requirements: (1) two consecutive, technically satisfactory ECGs in nonpaced rhythm were obtained within 60 days of each other; (2) the ECGs were performed on a routine (nonemergency) basis; and (3) normal sinus rhythm without atrial or ventricular premature complexes was present. Patients were excluded if a chart review revealed evidence of active cardiac disease (such as ischemia or congestive heart failure), significant metabolic abnormalities or recent thoracic surgery. No attempt was made to specifically include or exclude patients on the basis of ECG evidence for left ventricular hypertrophy.

Serial measurements for analysis of day-to-day variability of combined voltage criteria were made from 78 pairs of ECGs (39 from men and 39 from women) separated by a mean interval of 8 days. The mean age of the study group was 59 years. After analysis of the data was complete, it was noted that two pairs of ECGs were from separate intervals in the same woman; accordingly, the 39 paired measurements in women represent data from 38 patients.

Serial measurements for analysis of immediate variability of combined voltage criteria were also made from an additional 26 paired ECGs in a separate group of clinically stable patients, including 14 men and 12 women, whose mean age was 58 years. These ECGs were taken within 1 min of each other for the purpose of this part of the study, without removing the recording electrodes or changing patient position between tracings. All of these patients also had normal sinus rhythm, and were also selected without regard to the magnitude of ECG voltage.

Electrocardiography. All ECGs were acquired by laboratory technicians using Marquette Electronics, Inc. MAC-2 carts and a MUSE central system, from which computer-based measurements were derived from the median complexes formed by 10 s sampling of 12 simultaneous leads digitized at 250 Hz. Median complexes are formed from the median voltage measured by computer for each 4 ms of digitally sampled data from successive complexes analyzed during the 10 s recording interval. Amplitudes are reported in microvolts (μV), and in each case, visual confirmation of the measurement was performed by comparison with the raw ECG tracing.

Combined voltage criteria were derived by addition of computer-measured amplitudes, according to the following definitions: 1) Sokolow-Lyon voltage: S_{V1} + the greater of R_{V5} or R_{V6} (20); 2) the limb lead voltage of Gubner and Ungerleider: $R_I + S_3$ (21); and 3) Cornell voltage: $R_{aVL} + S_{V3}$ (22). Paired measurements were also examined for computer-derived heart rate and QRS width (in ms), both of which were also subject to visual confirmation.

The paired studies used for evaluation of day-to-day variability were all done as clinically indicated, routine tracings, and all were selected randomly and retrospectively for screening, as outlined. Accordingly, technicians were not aware that these tracings were to be compared, there was no attempt to provide the same technician for each study and no marking of previous electrode placement was used. All paired studies used for evaluation of immediate reproducibility of ECG measurements were performed by a single technician who was aware of the purpose of the sequential recordings.

Statistical methods. Variability of serial measurements was expressed according to several methods. The coefficient of variability, in percent, was taken as the standard deviation (SD) of the difference between paired measurements divided by the average value of the means for each set of serial measurements. In addition, the coefficient of reproducibility, in μV, was calculated as 2 SD of the difference between paired measurements.

Each term provides different, but related, information. The coefficient of variability estimates 1 SD of variation as a percent of the measurement of interest, and it is, therefore, dependent in part on the magnitude of the underlying measurement. The coefficient of reproducibility estimates 95% confidence limits for the variability of voltage in absolute measurement units, taken as 2 SD of variation (rather than the 1 SD used in the numerator of the coefficient of variability). As a result of differences in magnitude for the various voltages that were examined, the coefficient of variability may be proportionally larger or smaller than would be suggested by the coefficient of reproducibility alone.

For each pair of measurements, the standard coefficient of correlation (r) derived from linear regression analysis was also calculated, despite its recognized limitations (23); the standard error of the estimate is equivalent to one half of the coefficient of reproducibility.

Results

Day-to-day variability of ECG voltage. Day-to-day variability of individual ECG voltage measurements and combined voltage criteria for left ventricular hypertrophy are described by the coefficients of reproducibility and coefficients of variability in Table 1. Coefficients of variability for amplitude measurements in individual leads ranged from 18% for R_I to 39% for S_3, and day-to-day variability for each of the combined voltage criteria for left ventricular hypertrophy was also large (18.5% for Sokolow-Lyon voltage, 22.3% for Gubner-Ungerleider voltage, and 24.8% for Cornell voltage). In each case, the coefficient of variability of combined voltage was smaller than the variability in component single leads. Day-to-day variability of individual lead and combined voltages was similar when men and women

Table 1. Day-to-Day Variability of ECG Voltage Measurement in 78 Patients

Measurement	Coefficient Correlation (r)	Average Value (μV)	Coefficient of Reproducibility (μV)	Coefficient of Variability (%)
S_{V1}	0.892	994	443	22.3
$R_{V5\text{ or }6}$	0.884	1,569	846	27.0
SLV	0.911	2,562	945	18.5
R_I	0.884	838	307	18.3
S_3	0.934	351	274	39.0
R_IS_3	0.909	1,189	530	22.3
R_{aVL}	0.905	538	292	27.1
S_{V3}	0.846	958	665	34.7
CV	0.863	1,496	743	24.8

CV = Cornell voltage (sum of R_{aVL} plus S_{V3}); BCG = electrocardiographic; R_I = R amplitude in standard lead I; R_IS_3 = Gubner-Ungerleider voltage (sum of R_I plus S_3); R_{aVL} = R amplitude in standard lead aVL; $R_{V5\text{ or }6}$ = R amplitude in V_5 or V_6, whichever is larger; SLV = Sokolow-Lyon voltage (sum of S_{V1} plus $R_{V5\text{ or }6}$); S_3 = S amplitude in lead III; S_{V1} = S amplitude in lead V1; S_{V3} = S amplitude in lead V3.

were examined separately (Table 2). For the entire group, the day-to-day variability of measured heart rate was 15.9% (coefficient of reproducibility 26 beats/min), and variability for QRS duration was 5.6% (coefficient of reproducibility 10 ms).

The relation of the coefficients of variability and reproducibility to the absolute magnitude of measured voltage was further explored by calculation of these coefficients for subsets of patients partitioned at the mean values of Sokolow-Lyon voltage and Cornell voltage within the total population (Table 3). Variability of Sokolow-Lyon voltage increased with higher voltage (>2,600 μV, the population mean value). In contrast, the coefficient of reproducibility of Cornell voltage was less dependent on the absolute magnitude of combined voltage, so that percent variability was actually less at higher (>1,500 μV) than at lower measured amplitudes.

Table 2. Reproducibility and Variability of ECG Voltage Measurement, According to Gender in 78 Patients

Measurement	Coefficient of Reproducibility (μV)		Coefficient of Variability (%)	
	Men (n = 39)	Women (n = 39)	Men (n = 39)	Women (n = 39)
S_{V1}	377	505	21.2	22.3
$R_{V5\text{ or }6}$	895	776	27.2	26.0
SLV	1,026	846	20.2	16.3
R_I	276	336	17.9	18.6
S_3	233	312	37.9	39.5
R_IS_3	446	606	20.1	23.3
R_{aVL}	253	325	25.4	28.1
S_{V3}	703	618	35.4	33.5
CV	718	752	24.1	25.0

Definitions and abbreviations as in Table 1.

Table 3. Effect of Voltage Magnitude on Reproducibility and Variability

Measurement	Coefficient of Reproducibility (μV)	Coefficient of Variability (%)
SLV <2,600 μV	563	14.4
SLV >2,600 μV	1,373	19.2
CV <1,500 μV	619	28.0
CV >1,500 μV	810	19.7

Definitions and abbreviations as in Table 1.

Serial reclassification. Despite the large day-to-day variability of combined voltage measurements, diagnostic reclassification of individual patients between studies because of voltage variation above and below established partition-based criteria for left ventricular hypertrophy was uncommon in this population. Only 2 (3%) of 78 patients fulfilled Sokolow-Lyon criteria (>3,500 μV [3.5 mV]) and only 3 (4%) fulfilled gender-adjusted Cornell voltage criteria (>2,800 μV for men, >2,000 μV for women) for hypertrophy on one, but not the other, of the paired studies. This may be a consequence of the wide range of normal voltages and the smaller number of higher voltages present in our patients. Only 10 patients had Sokolow-Lyon voltage and only 28 patients had Cornell voltage that was within 500 μV (±0.5 mV) of the amplitudes routinely used for the diagnosis of hypertrophy.

Immediate variability of ECG voltage. Immediate variability of individual and combined voltages, with electrodes in place, is shown in Table 4. Minute to minute coefficients of variability for individual amplitudes ranged from 4.3% for S_{V1} to 9.0% for S_3, and variability of each combined voltage criterion was lower than that of its component parts (2.6%

Table 4. Immediate Reproducibility of ECG Voltage Measurement in 26 Patients

Measurement	Coefficient of Correlation (r)	Average Value (μV)	Coefficient of Reproducibility (μV)	Coefficient of Variability (%)
S_{V1}	0.994	934	80	4.3
$R_{V5\text{ or }6}$	0.994	1,416	144	5.1
SLV	0.997	2,350	124	2.6
R_I	0.992	715	71	4.9
S_3	0.997	370	66	9.0
R_IS_3	0.996	1,084	127	5.9
R_{aVL}	0.995	477	78	8.2
S_{V3}	0.999	984	90	4.5
CV	0.998	1,461	128	2.9

Definitions and abbreviations as in Table 1.

for Sokolow-Lyon voltage, 2.9% for Cornell voltage and 5.9% for Gubner-Ungerleider voltage). Immediate variability of heart rate was 3.8% (coefficient of reproducibility 6 beats/min), and variability for QRS duration was 4.7% (coefficient of reproducibility 8 ms).

Discussion

These data demonstrate large day-to-day variability of single and combined ECG voltages in a group of hospitalized patients in stable condition. With respect to intraindividual variability of single leads, our findings are similar in magnitude to previously reported data (17,24,25), but also demonstrate and quantify the variability of more clinically relevant combined lead voltages used as criteria for the detection of left ventricular hypertrophy and for the estimation of left ventricular mass (20–22).

Variability of individual voltage measurements was substantially reduced when serial tracings were taken without removing the recording electrodes and without changing patient position, as also noted in previous studies (17,24–26) in which electrodes were left in place between tracings or specific attention was paid to constant lead placement by marking of the skin. However, this method of assuring reproducibility of electrode location is not practical in studies examining serial changes that occur over periods of months to years, and cannot be assumed in retrospective analysis of established data bases.

Previous studies. Few data are available regarding the effect of day-to-day measurement variability on the diagnostic performance of commonly used voltage criteria for left ventricular hypertrophy. Larkin and Hunyor (26) measured intertest variability of combined precordial voltage determined by the sum of the largest individual R and S waves in a small group of normal subjects over 4 consecutive days. When electrodes were removed between recordings, the coefficient of variation (estimated from their data according to our methods) was approximately 12%, with a coefficient of reproducibility of approximately 720 μV. These values are comparable with our findings for more widely used voltage combinations. In the Multiple Risk Factor Intervention Trial (27), only 2% of patients had a significant worsening of Minnesota code criteria for left ventricular hypertrophy between serial ECGs taken 2 weeks apart. This intertest reclassification rate is similar to the findings in our patients.

Sources of QRS voltage variability. Serial differences in voltage may be caused by biologic, temporal or measurement variability. Sources of variation include a true change in generated signal amplitude, which, in addition to changing cardiac mass or geometry, might also reflect changing metabolic conditions on a beat-to-beat or minute-to-minute basis. Variability of measured voltage might also result from changing transthoracic impedance due to effects of respiration (15), torso geometry (28) or electrode conductivity. Most important, variability can reflect changes in relative cardiac orientation within the chest due to altered body position or different phase of respiration during recording, or, of course, to a change in electrode placement between tracings.

In addition to simple measurement error and the error due to differences among recording units, variability of amplitude determination in digitally acquired ECGs can result from sampling error that is inherent to the digitizing process itself (13). When ECG waveforms are sampled every 4 ms, it may be difficult to accurately quantify high frequency amplitudes that can peak between samples; however, comparable error in amplitude measurement can also affect analog ECG signals when standard high frequency filtration is used (14). Although the digital sampling problem may be minimized by signal processing that can effectively average acquired data during generation of a median complex, the potential error involved in digital-based measurement of R wave amplitude has been estimated by Zywietz (13) to approximately 5% to 10% for adult tracings sampled at 250 Hz.

Immediate and day-to-day variability of voltage. If it is assumed that computer measurement error is negligible, the relatively small changes in minute to minute voltage found when serial tracings were obtained with electrodes in place should represent variability due to the combined effects of digital sampling error and phasic respiration. In each case, the coefficient of variability for combined voltage criteria was less than the variability in component single leads. This is most likely explained by the somewhat orthogonal orientation of leads from which combined voltages are derived, which may partially offset the effect of respiration on amplitude variation in any one lead with an opposite variation in the second. The data of Table 4 suggest that voltage variability due to digital sampling error under our recording conditions is unlikely to exceed 2% to 3%, whereas variability in individual leads due to respiration under these conditions approximates 5% to 9%. It is likely that variability due to phasic change in respiration is also minimized by our recording methods because measurements were made from signal-averaged median complexes obtained during 10 s of data acquisition in each lead.

Smaller variability for combined voltages than for individual lead voltages was also found in our day-to-day studies. The greater magnitude of day-to-day than of immediate variability in our patients is most reasonably explained by the additional combined effects of inconstant patient position and electrode placement. This variability was similar in men and women, a finding also noted by Michaels and Cadoret (25). The separate effects of patient position and variable electrode placement might have been distinguished

by marking lead locations in a subset of subjects studied on different days. This was not examined in the present study group which, instead, can be considered to be representative of patients receiving routine serial ECG evaluation with all technical inconsistencies preserved (27).

Clinical implications. The large day-to-day variability of commonly used voltage criteria for left ventricular hypertrophy suggests that these measurements alone may be poor markers for modest progression and regression of left ventricular mass. By way of example, examination of Table 1 reveals that repeat measurements of Sokolow-Lyon voltage (S_{V1} + R_{V5} or R_{V6}) can differ by as much as ±37% of the original amplitude, with a corresponding difference in absolute voltage as much as ±945 μV, before the change exceeds 95% of the variability found in routine day-to-day examination of subjects in stable condition. Similarly, serial measurements of Cornell voltage (R_{aVL} + S_{V3}) may differ by as much as ±50% before the change exceeds 95% of expected variability, with the smaller corresponding difference in absolute voltage of ±743 μV explained by the smaller mean amplitude for this combined criterion. Thus, changes of combined voltage that occur within these limits may represent measurement variability and not a clinically relevant difference in ventricular structure.

In addition, our findings bear directly on the interpretation of standard ECG criteria for left ventricular hypertrophy and have particular relevance to the serial comparison of tracings. For example, with reference to Sokolow-Lyon voltage, it is clear that combined precordial measurements of 33 mm (3.3 mV) and 40 mm during serial studies are entirely within the expected range of day-to-day variability predicted by our data. Yet one tracing would be considered normal, although the other might be interpreted as indicative of left ventricular hypertrophy. More important, literal comparison of the two tracings presents the suggestion that ventricular hypertrophy has developed between examinations, or in the equally likely reverse sequence, that it has resolved. These conclusions are not justified by our findings, which, instead, argue for incorporating the range of expected measurement variability in both single and comparative diagnostic statements.

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