Comparison of electrocardiographic criteria for diagnosis of left ventricular hypertrophy in hypertension: the MAVI study

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Key words:
Left ventricular hypertrophy; Electrocardiography; Echocardiography; Essential hypertension.

Background. **Standard electrocardiography (ECG) is a specific, but poorly sensitive tool for diagnosis of left ventricular (LV) hypertrophy. In a large population of subjects with hypertension we tested some standard ECG criteria in their sensitivity and specificity for LV hypertrophy. LV mass at echocardiography was the reference standard.**

Methods. **In the setting of the MAVI (MAssa Ventricolare sinistra nel soggetto Iperteso) study, the ECG and echocardiographic tracings of 947 hypertensive subjects were read blindly in a central office.**

Results. **Prevalence of LV hypertrophy at ECG was 0.6, 3.0, 4.8, 7.1, 11.1, 11.9 and 18.4%, respectively, using the following criteria: Wilson, typical strain, Romhilt-Estes score 5 points, Gubner-Ungerleider, Sokolow-Lyon, Cornell voltage ($S_{V3}+R_{aVL}$ > 2.8 mV in men or 2.0 mV in women) and Perugia score (positivity of at least one of the following: $S_{V3}+R_{aVL}$ > 2.4 mV in men or > 2.0 mV in women, a typical strain pattern, or a Romhilt-Estes point score 5). Prevalence of LV hypertrophy at echocardiography ranged from 27.2% (LV mass > 125 g/m^2) to 49.9% (LV mass > 51.0 g/m$^{2.7}$). Using the latter gold standard, sensitivity and specificity of the above ECG criteria were 0.8 and 99.6% (Wilson), 3.8 and 97.9% (strain), 5.9 and 96.4% (Romhilt-Estes), 9.7 and 95.6% (Gubner-Ungerleider), 11.2 and 91.1% (Sokolow-Lyon), 15.2 and 91.4% (Cornell), and 22.2 and 85.4% (Perugia score).**

Conclusions. **Sensitivity of traditional ECG criteria for LV hypertrophy in subjects with hypertension is poor. However, the combination of three highly specific criteria (Romhilt-Estes, LV strain and Cornell) in a cumulative score produces a rise in sensitivity without excessive deterioration of specificity, with a prevalence of LV hypertrophy at ECG of 18.4%. Traditional interpretation of ECG is valuable and should be reconsidered in the clinical work-up of subjects with hypertension.**

(Ital Heart J 2000; 1 (3): 207-215)

Presented in part at the 19th Congress of the European Society of Cardiology, Stockholm, Sweden, August 24-28, 1997. The study was partially supported by Pfizer SpA.

Received December 14, 1999; revision received March 1, 2000; accepted March 2, 2000.

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Introduction

The current guidelines for diagnosis and treatment of subjects with high blood pressure recommend standard 12-lead electrocardiography (ECG) as routine test for diagnosis of left ventricular (LV) hypertrophy[1,2]. Electrocardiographic LV hypertrophy is a powerful independent predictor of cardiovascular morbidity and mortality in different clinical settings including essential hypertension[3-9]. However, autoptic and echocardiographic investigations showed that the sensitivity of traditional ECG criteria of LV hypertrophy at high levels of specificity is quite poor[10-14]. Yet, because of its low cost and broad diffusion, ECG remains a potentially ideal method for diagnosis of LV hypertrophy in subjects with hypertension and any improvement in the diagnostic performance of ECG in this setting would be desirable from a clinical standpoint.

Recently, sophisticated analyses of ECG including the computer-assisted computation of the QRS time-voltage integral[15,16] and the computerized or manual calculation of the 12-lead voltage-duration product[17] have improved the accuracy of ECG for identification of LV hypertrophy[15-18]. Although these techniques are being increasingly used for research purposes[19], the traditional visual interpretation of 12-lead ECG continues to be the routine in most clinical settings.

Because comparative assessments of diagnostic performance of different standard

ECG criteria of LV hypertrophy are scanty, we planned an analysis of the MAVI (MAssa Ventricolare sinistra nel soggetto Iperteso) study, a multicenter ongoing investigation on the prognostic value of LV mass in essential hypertension[20]. We tested several ECG criteria for diagnosis of LV hypertrophy, none of which was dependent on computer-assisted analysis. Echocardiographic LV mass was used as the reference standard.

Methods

The MAVI study is a multicenter, prospective, observational study currently ongoing in 58 Hospital Centers in Italy. Details of the study have previously been published[20]. The pre-specified aim of the study[20] is the assessment of the independent prognostic value of LV mass at echocardiography in subjects with essential hypertension.

In brief, admission criteria to the MAVI study include clinic blood pressure in sitting position 140 mmHg systolic or 90 mmHg diastolic or current treatment for hypertension, no previous cardiovascular morbid events, age 50 years, and no pacemaker-induced rhythm. Both genders are included. Patients with cancer, other important disease or serum creatinine 2.0 mg/dl are excluded from the study. Patients under antihypertensive treatment are not required to withdraw their medications when they enter the study.

A two-dimensional-targeted M-mode echocardiographic study is carried out at the beginning of the study in the context of a complete diagnostic work-up including laboratory examinations, ECG and clinical examination. Working meetings among involved investigators are held periodically. Echocardiograms are recorded on tape and sent to a central laboratory for reading. Three expert readers examine tracings and allocation of tapes to readers is randomized. Furthermore, all three readers in blind conditions are examining a random sample of tapes, in order to check homogeneity between readers (results not yet available). All measurements are made on the screen using calipers. A long-axis parasternal approach is first examined to check perpendiculatory of the ultrasonic beam with respect to the septum. Then, the short-axis approach is used to take LV diastolic and systolic measurements (the average of three consecutive cycles on the best single reading set is considered). The original ECG tracings are also sent to a central laboratory for reading. ECG reading is manual, and performed by one expert reader. Readers for echocardiographic and ECG tracings are different, do not work in connection and are not aware of the clinical characteristics of patients.

Clinical data are stored on a computer using an *ad hoc* software for hypertension laboratories provided by ANMCO, and sent to the study headquarters in Florence (Italy). The main outcome events are death, myocardial infarction, stroke, coronary surgery, new-onset angina with concomitant ECG changes, severe heart failure requiring hospitalization, and severe renal failure requiring dialysis.

Sample size calculation assumed a prevalence of echocardiographic LV hypertrophy of 30% and a rate of events of 2 per 100 person-years in the absence vs 4 per 100 person-years in the presence of LV hypertrophy. On this basis, a sample size of 1811 subjects with an average follow-up time of 2 years per patient was judged suitable to detect a significant difference between the groups (two-tailed test) with a type I error of 5% and a type II error of 10%.

Electrocardiography. For the purpose of the present analysis, standard 12-lead ECGs were recorded at 25 mm/s and 1 mV/cm calibration. Subjects with complete bundle branch block, previous myocardial infarction, Wolff-Parkinson-White syndrome and atrial fibrillation were excluded from analysis.

The following ECG criteria for LV hypertrophy were tested: Sokolow-Lyon voltage (sum of the amplitudes of S wave in V_1 and R wave in V_5 or V_6 3.5 mV)[21]; Romhilt-Estes score 5 points[22]; sex-specific Cornell voltage (sum of the amplitudes of S wave in V_3 and R wave in aVL > 2.0 mV in women and > 2.8 mV in men)[13]; Gubner-Ungerleider voltage (sum of the amplitudes of R wave in I and S wave in III 2.5 mV)[23]; typical strain pattern in V_5-V_6[24] and Wilson (amplitude of the S wave in V_1 2.4 mV)[25]. We also tested the Perugia score, a recently developed[26] and prognostically validated[27] criterion which requires positivity of at least one of the following three criteria: $S_{V3}+R_{aVL}$ > 2.4 mV in men or > 2.0 mV in women, a typical strain pattern, or a Romhilt-Estes point score 5.

Echocardiography. The M-mode study was performed under two-dimensional control using commercially available instruments. End-diastolic and end-systolic measurements were taken with the patient in partial left lateral decubitus according to the American Society of Echocardiography recommendations[28]. Frames with optimal visualization of interfaces and showing simultaneous visualization of septum, LV internal diameter and posterior wall were used for reading. LV mass was calculated using the following formula introduced by Devereux et al.[29] on the basis of necropsy validation studies:

$$\text{LV mass (g)} = 0.80 \times \{1.04 \times [(\text{septal thickness} + \text{LV internal diameter} + \text{posterior wall thickness})^3 - (\text{LV internal diameter})^3]\} + 0.6 \text{ g}.$$

For definition of LV hypertrophy we considered a LV mass > 125 g/m^2, a partition point supported by ample prognostic evidence[30-33], and a LV mass > 51.0 g/m$^{2.7}$, in order to provide a more stringent allowance for obesity[34].

Statistical analysis. For measurements of sensitivity and specificity, echocardiographic LV hypertrophy was used as the reference standard against which the per-

formance of ECG criteria was compared in a standard analysis. Correlation between ECG variables and LV mass index was assessed by least square linear correlation. P values < 0.05 were considered statistically significant.

Results

Table I shows some clinical, echocardiographic and ECG characteristics of the 947 patients examined in the present study. Fifty-one per cent of patients were in hypertension grade I, 37.6% in grade II and 11.4% in grade III. Most patients (84.3%) were under antihypertensive therapy at inclusion. Diabetes mellitus was present in 7% of patients. An additional group of 466 subjects was excluded from the present analysis because echocardiographic tracings were not judged of good technical quality by the reading center. There were 547 subjects (57.8%) aged < 60, 322 (34.0%) aged 61-70, 73 (7.7%) aged 71-80 and 5 (0.5%) aged > 80.

Prevalence of LV hypertrophy at echocardiography was 27.2% using correction for body surface area, and 49.9% using the height$^{2.7}$ correction. Prevalence of LV hypertrophy at ECG varied markedly across the different criteria (Fig. 1), ranging from 0.6% (Wilson) to 18.4% (Perugia score). Results of sensitivity and specificity are reported in figure 2 (LV mass corrected by body surface area) and figure 3 (LV mass corrected by height$^{2.7}$). Sensitivity was < 30% for all tested criteria. In contrast, specificity of most criteria was quite high and > 90% with all criteria except the Perugia score. Regardless of the method used for LV mass indexization, the Perugia score yielded the highest sensitivity (29 and 22%, respectively, with correction of LV mass by body surface area or height$^{2.7}$), outweighed by a lesser specificity (85.1% with both corrections). Sensitivity of the Perugia score was marginally higher in women than in men (28.3 vs 27.2%), while its specificity was slightly higher in men (87.2 vs 84.1%).

Table I. Main characteristics of the study population.

N. patients	947
Age (years)	60 – 7
M/F	352/595
Weight (kg)	72 – 12
Height (cm)	163 – 8
Body mass index (kg/m^2)	26.9 – 3.7
Body surface area (m^2)	1.77 – 0.17
Diabetes mellitus (%)	7
Cigarette smoking (%)	
Current smokers	14
Ex-smokers	13.5
Never smokers	72.5
Antihypertensive treatment (%)	
Untreated	15.8
Current treatment	84.2
Clinic SBP/DBP (mmHg)	154 – 17/92 – 9
Interventricular septum (cm)	1.08 – 0.22
LV end-diastolic diameter (cm)	4.98 – 0.63
LV posterior wall (cm)	0.98 – 0.17
Shortening fraction (%)	38 – 7
LV mass	
g	196 – 71
g/m^2	111 – 38
g/m$^{2.7}$	53 – 19
Glucose (mg/dl)	103 – 29
Creatinine (mg/dl)	0.94 – 0.18
Uric acid (mg/dl)	5.09 – 1.3
Total cholesterol (mg/dl)	224 – 41
HDL cholesterol (mg/dl)	52 – 14
LDL cholesterol (mg/dl)	144 – 38
Triglycerides (mg/dl)	138 – 69
Sodium (mmol/l)	141 – 3
Potassium (mmol/l)	4.3 – 0.4

Data are expressed as mean – SD. DBP = diastolic blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; LV = left ventricular; SBP = systolic blood pressure.

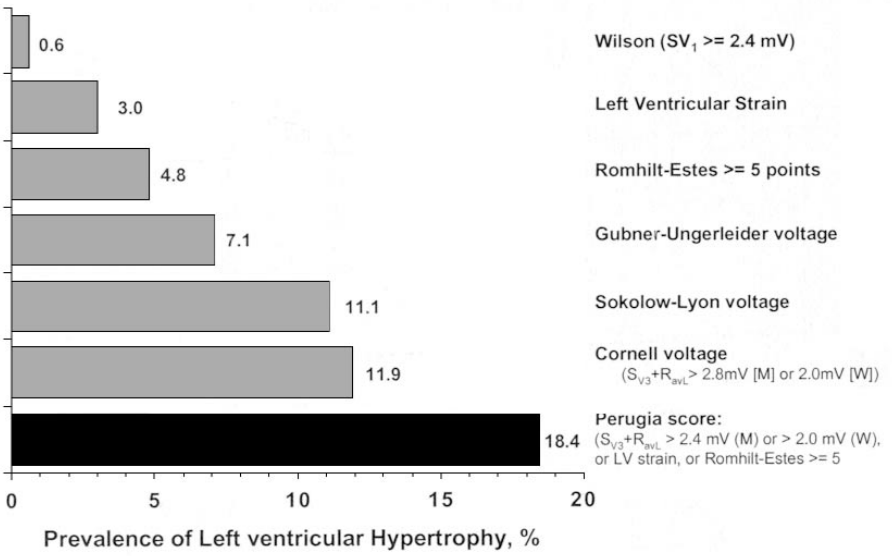

Figure 1. *Prevalence of left ventricular hypertrophy with the different electrocardiographic criteria.*

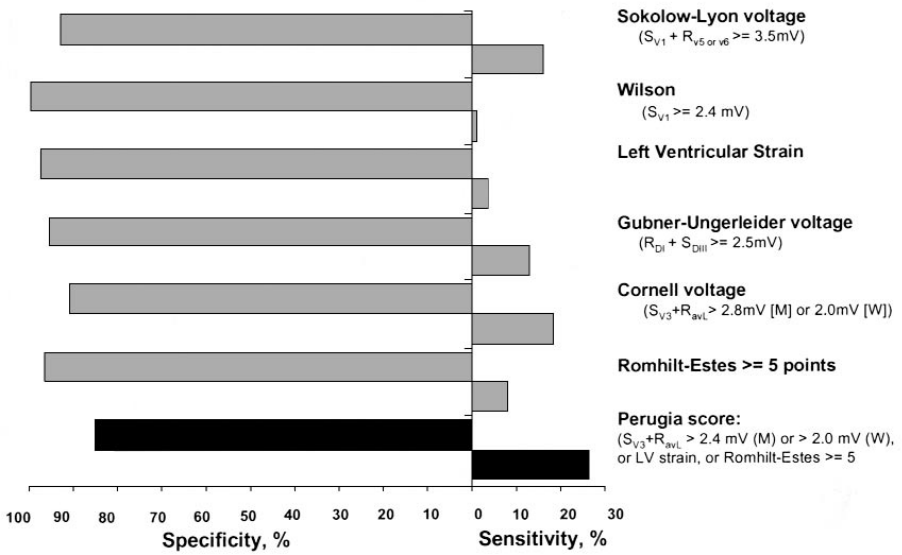

Figure 2. *Sensitivity and specificity of the different electrocardiographic criteria for left ventricular hypertrophy. An echocardiographic left ventricular mass > 125 g/m^2 was used as the reference standard.*

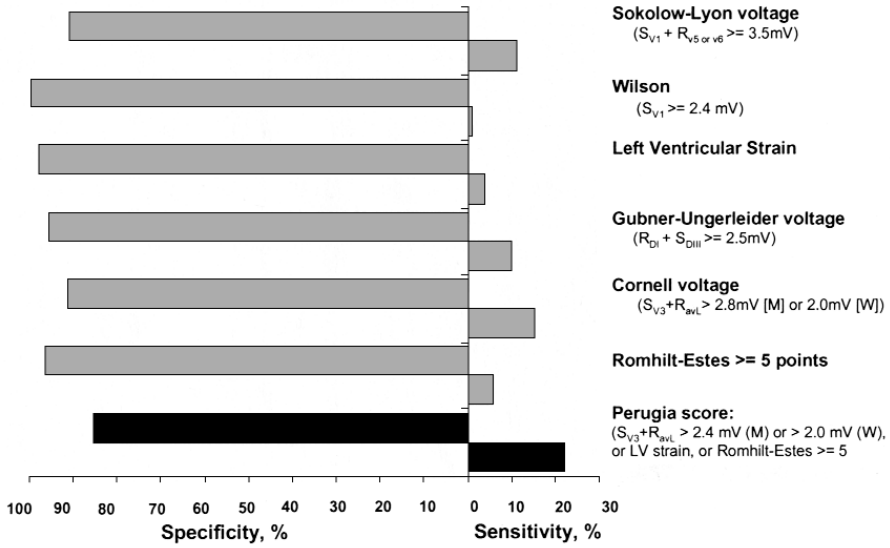

Figure 3. *Sensitivity and specificity of the different electrocardiographic criteria for left ventricular hypertrophy. An echocardiographic left ventricular mass > 51.0 g/m$^{2.7}$ was used as the reference standard.*

The correlations between echocardiographic LV mass index and ECG parameters (Table II) were generally weak. The closest association was achieved by the Cornell voltage (r = 0.245), which was more closely associated with LV mass index in women (r = 0.26) than it was in men (r = 0.20). Figure 4 shows the scatterplot of the association between LV mass index and the Cornell voltage in the two genders. As expected, LV mass was higher in the subjects with ECG evidence of LV hypertrophy than in those without hypertrophy (Table III). However, some of the comparisons did not achieve significance because of the small number of subjects with LV hypertrophy at ECG.

Discussion

This is the first comparative assessment of sensitivity and specificity of different ECG criteria for identification of LV hypertrophy in the setting of a large multicenter investigation. The blind central reading of ECG and echocardiographic tracings by different readers is an important methodological aspect of this study. Our findings confirm that ECG is a specific, but poorly sensitive tool for diagnosis of LV hypertrophy in subjects with essential hypertension. However, an increase in the diagnostic accuracy of standard ECG for detection of LV hypertrophy is achieved by the Perugia score, which incorporates three highly specific criteria (Cornell voltage, Romhilt-Estes, LV strain).

Table II. Correlation between echocardiographic left ventricular (LV) mass index and electrocardiographic (ECG) indexes of LV hypertrophy.

ECG index	Correlation coefficient			
	LV mass (g/m^2)	p	LV mass ($g/m^{2.7}$)	p
Cornell voltage	0.245	< 0.001	0.227	< 0.001
Sokolow-Lyon voltage	0.146	< 0.001	0.086	< 0.01
R_{aVL}	0.157	< 0.001	0.175	< 0.001
S_{V3}	0.190	< 0.001	0.154	< 0.001
Tallest R in V_5 or V_6	0.119	< 0.001	0.044	0.17
Romhilt-Estes point score	0.130	< 0.001	0.103	< 0.005

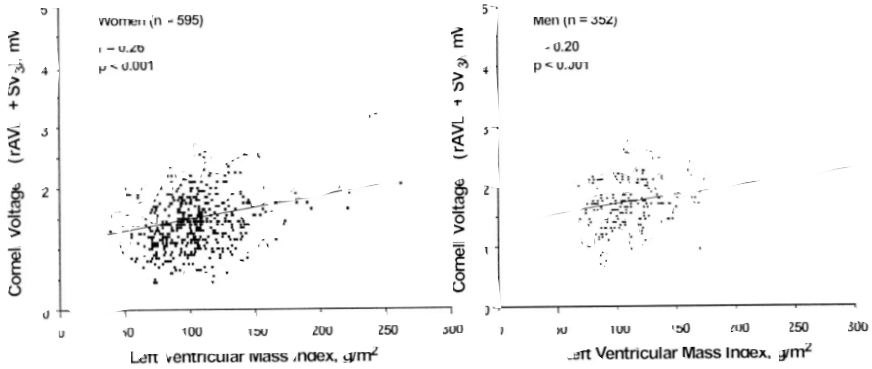

Figure 4. *Correlation between echocardiographic left ventricular mass and the Cornell voltage in women (*left*) and men (*right*).*

Table III. Left ventricular (LV) mass in subjects with and without electrocardiographic (ECG) evidence of LV hypertrophy.

ECG criterion	LV hypertrophy		LV hypertrophy	
	Absent LV mass (g/m^2)	Present LV mass (g/m^2)	Absent LV mass ($g/m^{2.7}$)	Present LV mass ($g/m^{2.7}$)
Cornell voltage	109 – 36	125 – 46*	52 – 18	60 – 23*
Wilson	111 – 38	114 – 40	53 – 18	57 – 20
LV strain	110 – 37	123 – 42	52 – 19	58 – 19
Sokolow-Lyon voltage	109 – 36	127 – 47*	52 – 18	58 – 22*
Romhilt-Estes point score	110 – 27	126 – 45*	52 – 19	59 – 21**
Perugia score	108 – 36	122 – 43*	51 – 18	58 – 21*

Data are expressed as mean – SD. * $p < 0.05$; ** $p < 0.01$.

A binary definition was used as the reference standard for echocardiographic LV hypertrophy, against which sensitivity and specificity of the different ECG criteria were tested. Such a procedure may be open to criticism since echocardiographic LV mass is normally distributed in the general population and hence any partition value between normal and abnormal values is arbitrary. However, the division line between normal and abnormal LV mass taken as reference in the present study provided an independent cardiovascular risk stratification in patients with hypertension[30-32]. There is also evidence that hypertensive subjects with LV hypertrophy whose LV mass regresses for effect of therapy are less likely to develop future cardiovascular events than those whose LV mass persists abnormal over time[33].

ECG for diagnosis of left ventricular hypertrophy. Several ECG criteria have been proposed for diagnosis of LV hypertrophy[3-9]. However, studies with autoptic or echocardiographic LV mass as reference have shown the low sensitivity of ECG[10-14]. It has been noted that the sensitivity of ECG improves with increasing severity of LV hypertrophy[26]. ECG has a sensitivity of 80% in malignant hypertension[35], and a sensitivity comparable[36] or

even superior[37] to that of echocardiography in some forms of familial hypertrophic cardiomyopathy.

In uncomplicated subjects with essential hypertension the prevalence of LV hypertrophy is generally low, and therefore a high test specificity, with limitation of false positives around 5-10% is required[38]. Unfortunately, the low prevalence of LV hypertrophy in the majority of studies in essential hypertension has limited the utility of traditional ECG for detection of LV hypertrophy.

The most widely used ECG criterion for diagnosis of LV hypertrophy is probably the Sokolow-Lyon voltage[21]. In a wide population of untreated and uncomplicated subjects with essential hypertension[26], the Sokolow-Lyon voltage showed both a low sensitivity (21%) and a low specificity (89%) and results of the present study confirm this. Overall, these findings appear to limit the clinical value of this classic criterion for detection of LV hypertrophy in hypertensive patients. In fact, if one assumes a true prevalence of LV hypertrophy in hypertension of about 34%[30-33], the predictive value of a positive Sokolow-Lyon test would be only 50%. In other words, of 2 subjects with positive Sokolow-Lyon criterion only 1 would have true LV hypertrophy. Some mechanisms may explain the poor diagnostic performance of this classic ECG criterion. Extracardiac factors including body size, adipose tissue, lung tissue, pericardial fluid and epicardial fat may attenuate the voltages recorded at the skin surface[39] and the Sokolow-Lyon voltage is strongly dependent on this limitation, it being the sum of two precordial voltages which are importantly affected by the distance between the left ventricle and skin.

The Cornell voltage (sum of R in aVL plus S in V_3) may be considered an improvement of the Sokolow-Lyon voltage because V_3 is the precordial lead most close to the heart surface and, hence, less likely to be affected by extracardiac factors. In addition, since the electrical forces tend to become more posterior[40] and horizontal[41] with development of LV hypertrophy, the S wave in V_3 and the R wave in aVL could be particularly suitable to reflect them. In the present study, sensitivity and specificity of the Cornell score were 20 and 91%, respectively, in agreement with most previous studies[39].

The Perugia score[26,27] is a combination of three highly specific standard ECG criteria. It requires the positivity of modified Cornell voltage, a typical LV strain, or a Romhilt-Estes score 5. The modified Cornell voltage consists in the sum of S_{V3} plus R_{aVL} > 2.4 mV in men and > 2.0 mV in women, that means a reduction of 0.4 mV in the standard Cornell voltage in men[11]. Such modification resulted from the application of a receiver operating characteristic curve analysis, aimed at yielding the highest sensitivity at high levels of specificity[26]. In a study[26], the Perugia score showed a sensitivity of 34% and a specificity of 93% in a large hypertensive population. In the present analysis of the MAVI population, the diagnostic performance of the Perugia score was slightly lesser in terms of sensitivity and specificity. However, sensitivity was the highest when compared with the other standard ECG criteria, and the resulting prevalence of LV hypertrophy in the overall hypertensive population was 18.4%. An explanation for the difference between these findings and those reported by Schillaci et al.[26] may be the multicenter nature of this study, with a high number of sonographers from different centers and consequent potential negative bearing on homogeneity. By contrast, only two sonographers were involved in the above-mentioned study[26]. On the other hand, specificity of the Perugia score was only slightly inferior in this study compared to that by Schillaci et al., despite the potential negative impact due to the different sonographers.

Some features of the Perugia score deserve comment. The first feature is shared by the other ECG criteria for LV hypertrophy, namely the possibility of being used in most patients with hypertension. In fact, only subjects with complete bundle branch block, previous myocardial infarction and Wolff-Parkinson-White syndrome are excluded from the ECG analysis for LV hypertrophy. By comparison, if we look at echocardiography, at least 10-20% of subjects must be excluded because of bad echocardiographic tracings[32,42] and, among the remaining patients, tracings may not be optimal in many. Second, owing to its higher sensitivity, the Perugia score allows diagnosis of LV hypertrophy in approximately 18% of all hypertensive patients (against < 12% with the other ECG criteria), including in this number the subjects with bad-quality echocardiographic tracings. Although this higher prevalence of LV hypertrophy was outweighed by a decrease in specificity, the frequency of false positives did not exceed 15%. When compared to the standard ECG criteria for LV hypertrophy, the Perugia score has thus the advantage of allowing a wider detection of true LV hypertrophy, at the expense of a limited increase of false positives.

When the rise in sensitivity achieved by a new diagnostic test to be used for risk stratification is outweighed by a decrease in specificity, only longitudinal prognostic studies will be able to clarify whether a wider detection of a disease-present status is outweighed, or not, by an increase in the false-positive diagnoses. In a study, the Perugia score carried the highest attributable risk for cardiovascular events, accounting for 16% of all cases and 37% of fatal cases[27]. The follow-up of the MAVI study will represent a suitable setting to verify these prognostic findings.

Limitations of the study. The findings of the present study cannot be extrapolated to blacks, who generally have a greater LV mass[43], a higher prevalence of LV hypertrophy at ECG[44] and a lower specificity of ECG[44] as compared with whites. Furthermore, we did not test more sophisticated analyses including the computer-assisted computation of the QRS time-voltage integral[15,16] and the computerized or manual calculation of the 12-lead volt-

age-duration product[17], which could improve the diagnostic performance of ECG. In a recent analysis of the Losartan Intervention for Endpoint Reduction (LIFE) study, the Perugia score performed similarly to the computer-assisted calculation of the QRS time-voltage product, and better than the Sokolow-Lyon criterion, for diagnosis of LV hypertrophy in overweight and obese hypertensives[45]. These findings suggest that LV strain, an important component of the Perugia score, may be considered a sensitive and reliable marker of LV hypertrophy, besides being a potential indicator of subendocardial ischemia and wall tension changes.

In conclusion, the present study confirms that sensitivity of standard electrocardiography for diagnosis of LV hypertrophy in hypertension is poor. However, the combination of three highly specific criteria (Romhilt-Estes, LV strain and Cornell) in a cumulative score (Perugia score) led to an increase in sensitivity without important deterioration of specificity. Using such a combination, prevalence of LV hypertrophy at ECG in a large sample of subjects with essential hypertension rose to 18.4%. These data suggest that standard ECG should be favorably re-evaluated in the clinical management of subjects with essential hypertension. Because of its potential advantage over standard ECG criteria for cardiovascular risk stratification, the Perugia score warrants further prognostic assessment.

Appendix

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