

Diagnostic value of different electrocardiographic voltage criteria for hypertrophic cardiomyopathy in young people

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Differences in the diagnostic value of various electrocardiographic (ECG) voltage indices for hypertrophic cardiomyopathy (HCM) are yet to be elucidated. The objective of this study was to examine the strongest predictor within ECG voltage criteria for left ventricular hypertrophy (LVH) in HCM to be applied in cardiovascular examination of young people. The electrocardiograms of 36 healthy individuals with high voltages, mimicking HCM (i.e., false-positive), were statistically compared with those of 30 subjects with an ECG diagnosis of HCM. The most striking ECG voltages observed in HCM patients were those included in leads DI, aVL (R wave) and V3 (S wave) ($P < 0.001$), typically present in the Cornell, Gubner and Lewis voltage criteria.

In a stepwise logistic regression analysis model, these indices were the most significant predictors of HCM ($P < 0.001$, $P < 0.027$ and $P < 0.006$, respectively). The combination of Cornell ($RaVL + SV3 > 2.8$ mV in men and > 2.0 mV in women) with Lewis ($RI + SIII - RIII - SI > 1.7$ mV) or Gubner–Ungerleider ($RI + SIII > 2.5$ mV) indices displayed the highest net sensitivity (80.0% and 76.7%, respectively) while retaining excellent specificity (88.9% and 91.6%, respectively). In conclusion, the combination of the Cornell and the Lewis or Gubner voltage criteria showed the greatest net sensitivity and specificity for the LVH diagnosis of HCM in a cardiovascular examination conducted in young people.

The association between strenuous exercise and sudden death is well recognized (Maron et al., 2003; Corrado et al., 2005, 2006). In individuals under the age of 35, cardiac arrest is generally due to several unsuspected congenital and inherited cardiovascular disorders, hypertrophic cardiomyopathy (HCM) being the most frequent abnormality, accounting for about one-third of cases in the United States (Maron et al., 2003). Different experiences have shown that a systematic cardiovascular evaluation of young people, athletes or non-athletes, including a 12-lead electrocardiogram, is effective in identifying HCM and in preventing sudden death (Corrado et al., 1998; Nistri et al., 2003; Tanaka et al., 2006). However, the cost-effectiveness of this strategy remains controversial (Fuller, 2000; Corrado et al., 2005; Maron et al., 2005b; Kjaer, 2006; Tanaka et al., 2006) because the specificity of the electrocardiogram in cardiovascular screening in young people is felt to be relatively low (Nistri et al., 2003; Maron et al., 2005b). Indeed, the main drawback to the use of electrocardiograms in screening is the high rate of abnormal electrocardiographic (ECG) voltage findings (i.e., false-positive) associated with a physiolo-

gical elevation of the voltages commonly observed in young people (The Criteria Committee of the New York Heart Association, 1994) and/or with the normal physiological adaptations of an athlete's heart to training [i.e., physiologic left ventricular hypertrophy (LVH) suggestive of HCM] (Pelliccia et al., 2000; Sharma et al., 2002).

Nevertheless, the conventional ECG voltage criteria of LVH typically used to assess HCM (i.e., Sokolow–Lyon or Romhilt–Estes scores) are being applied in cardiovascular examinations (Corrado et al., 1998, 2005; Sharma et al., 2002; Nistri et al., 2003; Pelliccia et al., 2007) despite the fact that differences in the diagnostic value of several voltage indices have not yet been clarified for HCM (Charon et al., 1998; Konno et al., 2005; Montgomery et al., 2005).

Previous studies have shown that structural and functional differences exist between pathological and physiological LVH (Douglas et al., 1988; Richey & Brown, 1998; Vinereanu et al., 2001) and that an ECG recording may differentiate a pathologic from a physiologic LVH (Kohsaka et al., 2005). Recently, Kohsaka et al. (2005) reported that a significant

association exists between LVH defined by Cornell voltage criterion and ischemic stroke. A previous study of Panza and Maron (1989) also showed that in some patients with HCM and marked LVH, the most striking voltages were confined to the mid-precordial leads (V_3 – V_4). Thus, we hypothesized that LVH in HCM might reveal certain particular ECG voltage criteria. In this context, the first goal of this study was to determine the most sensitive and specific diagnostic definition of ECG voltage criteria of HCM for application in a cardiovascular examination of young individuals. To reach this objective, a comparative study was performed between ECG recordings of healthy young subjects with elevated voltages, mimicking HCM (i.e., false-positive) and those of young patients with an echocardiographic diagnosis of HCM.

Methods

Selection of patients with HCM

The patients with HCM were selected after an echocardiographic diagnosis at two local hospitals. Owing to the low prevalence of HCM in people under 20 years of age (Miura et al., 2002), the patient sample size included patients outside of our initial community of study. After enrollment of 31 patients, one subject was excluded because of pre-excitation. Therefore, 30 patients were included in the final study HCM group. All patients were Caucasian with a mean age of 13.1 ± 5.1 years (range: 4–21 years), and the male/female ratio was 17/13 (56.7% and 43.3%, respectively). Fourteen patients (47.8%) were studied because of heart murmur, 12 (39.1%) were studied due to a family history of HCM, three (8.7%) had cardiovascular symptoms and one because he had ECG abnormalities after a routine health examination.

None of these subjects presented any congenital malformation or syndromes (Noonan's syndrome, Wolff–Parkinson–White syndrome with HCM phenotype, Friedrich's ataxia). Each subject had normal blood pressure ($\leq 140/90$ mmHg). The 30 12-lead electrocardiograms obtained at or nearest to the time of the initial diagnostic echocardiographic study were analyzed.

Electrocardiography

The 12-lead electrocardiogram (standard calibration 10 mm/1 mV) was performed in a routine fashion in the supine position during quiet respiration and recorded at 25 mm/s. In each lead, the height or the depth of the standard and precordial voltages was measured manually with callipers by a single blinded observer (B. E.). The classic ECG voltage criteria were defined as follows on the basis of previous studies: (1) Sokolow–Lyon voltage criterion: $SV_1 + RV_5$ or RV_6 , whichever is >3.5 mV (Sokolow & Lyon, 1949); (2) Romhilt–Estes voltage criterion: amplitude of R or S wave in a standard lead ≥ 2 mV, S wave in lead V_1 or $V_2 \geq 3$ mV or R wave in lead V_5 – $V_6 \geq 3$ mV (Romhilt & Estes, 1968); (3) Cornell voltage criterion: $RaVL + SV_3$, with 0.8 mV added in women, >2.8 mV (Casale et al., 1987); (4) Gubner–Ungerleider voltage criterion: amplitude of R wave in lead DI minus amplitude of R wave in lead DIII ≥ 2.5 mV (Gubner & Ungerleider, 1943); (5) Lewis voltage criterion: amplitude of R wave in lead DI minus amplitude of R wave in

lead DIII plus amplitude of S wave in lead DIII minus S wave in lead DI ≥ 1.7 mV (Lewis, 1914); and (6) Sum of QRS voltages in all 12 leads >17.5 mV (Dollar & Roberts, 1989).

Echocardiography

Two-dimensional echocardiographic studies were performed with a commercially available Philips Sonos 5500 series instrument, using a 2.5-MHz transducer. The magnitude and distribution of LVH were assessed prospectively according to previously published criteria (Klues et al., 1995). HCM was defined by two-dimensional echocardiographic identification of a hypertrophied, non-dilated left ventricular wall thickness of 15 mm or more (in children, two or more standard deviations from the mean relative to body surface area; z-score of 2 or more) in the absence of another cardiac or systemic disease capable of producing a comparable magnitude of LVH (Maron et al., 2005a). Echocardiograms were analyzed without knowledge of the ECG findings. The maximum left ventricular wall thickness (29 patients, 97%, in the anterior ventricular septum) was 13 to 31 mm (mean 18.9 ± 6.0) and was ≥ 30 mm in two of 30 patients (6.7%). The posterior wall thickness was 3–16 mm (mean 10.9 ± 3.1), and left ventricular mass was 86–417 g (mean 221.8 ± 92.4). The basal left ventricular outflow obstruction (gradient ≥ 30 mmHg), as estimated by continuous-wave Doppler echocardiography, was present in six patients (20%).

Healthy subjects (false-positives)

The healthy subjects were selected from cardiovascular screening among 471 voluntary young subjects, athletes and non-athletes (91% of the subjects between 12 and 19 years of age) of a Public Health Centre in a community of approximately 8000 people. Subjects were invited to undergo a pre-participation screening. In brief, these subjects were submitted to a standard protocol with a clinical history and a physical examination including blood pressure and a standard 12-lead electrocardiogram [according to the European Society of Cardiology (ESC) recommendations (Corrado et al., 2005)].

Of the 471 young people screened, 53 (11.3%) had screening abnormalities [LVH voltage criteria in 36 (7.6%)]. Of those 53 subjects none was found to have HCM. It is worth emphasizing that the cardiovascular screening, including a 12-lead electrocardiogram, was effective in identifying three subjects with cardiovascular diseases, which increases the risk of sudden death or disease progression in the presence of intense physical exertion (Pelliccia et al., 2005; Maron et al., 2005b): a WPW syndrome, a long QT syndrome and a stage 2 hypertension (160/100 mmHg).

Individuals were selected on the basis of the electrocardiogram, when one of the conventional ECG voltage criteria of LVH proposed in this study was present, and after an echocardiographic discard of HCM (i.e., false-positive). Therefore, the 36 young individuals constituted the definitive healthy subjects group (15.9 ± 2.5 years; range 12–20 years), with a male/female ratio of 29/7 (80.6% and 19.4%, respectively). Among these 36 individuals, a family history of HCM was ruled out. All subjects had normal blood pressure ($\leq 140/90$ mmHg). None presented any cardiovascular symptom. In these healthy subjects, the maximum left ventricular wall thickness was 6–12 mm (mean 8.6 ± 1.3), the posterior wall thickness was 7–11 mm (mean 8.7 ± 1.0) and left ventricular mass was 71–213 g (mean 148.6 ± 35.6).

Statistical analysis

Data were expressed as mean \pm SD. An unpaired Student's *t*-test was used to compare normally distributed data between individuals with and without HCM. The results observed in the Student *t*-test analysis were similar to those observed in a comparative odds ratio study, even after adjusting for age and sex. The χ^2 test was used to compare non-continuous variables. Multivariate analyses were performed with HCM as the dependent variable, using a stepwise forward logistic regression model in which each variable with a *P* value of ≤ 0.05 (based on univariate analysis) was entered into the model. Results were presented as odds ratios with their 95% confidence interval. A two-tailed $P < 0.05$ was considered to be statistically significant. Calculations were performed with SPSS 11.0 software. Sensitivity was defined in percentages as true-positives/(true-positives+false-negatives) $\times 100$; specificity as true-negatives/(true-negatives+false-positives) $\times 100$; positive predictive value as true-positive/(true-positive+false-positive) $\times 100$; and negative predictive value as true-negative/(true-negative+false-negative) $\times 100$ (Grimes & Schulz, 2002). Taking into account the difficulty of finding patients with an HCM, due to the low prevalence in people under 20 years of age (Miura et al., 2002), patients were selected outside of our initial community of study. In this regard, the sensitivity and specificity were calculated through a direct deduction of the study, and the predictive values were calculated according to the Bayes theorem, taking into account the prevalence of HCM in the population: 1/500 (Maron et al., 2005a).

Results

Healthy subjects (false-positives)

The analysis of the ECG recordings showed that the Romhilt–Estes voltage criteria were observed in 30 of the 36 (83%) healthy subjects, and the Sokolow–Lyon in 23 of the 36 (64%). Curiously, none presented high voltages of the R wave in DI (> 2.0 mV), S wave in precordial V₃ (> 3.0 mV) or R wave in standard aVL (≥ 1.3 mV) leads, and as a result the Cornell criterion (RaVL+SV₃ > 2.8 mV in males and > 2.0 mV in females) and the Lewis criterion ((RI+SIII – (SI+RIII) ≥ 1.7 mV) were only present in three and one out of 36 (8.3% and 2.8%, respectively) ECG recordings. Moreover, none of these 36 ECG recordings showed the Gubner–Ungerleider criterion (RI+SIII ≥ 2.5 mV).

In the present study, other ECG patterns associated with HCM such as abnormal Q waves (Q waves ≥ 0.04 s in duration or $\geq 25\%$ of the height of the subsequent R wave or QS pattern in two or more leads), repolarization alterations (ST-segment depression or T-wave flattening or inversion in two or more leads) and a deviation of $\leq 30^\circ$ in the QRS axis (Corrado et al., 2005) were not observed.

HCM patients

In our study, the commonly used ECG criteria were infrequently indicative of HCM: the Romhilt–Estes voltage criterion was present in only 16 out of 30 (53%) HCM patients and the Sokolow–Lyon criterion

in only 10 out of 30 (33%). Moreover, contrary to what was observed in our healthy subjects, five out of 30 (17%) HCM patients had increased the voltage in R wave in the standard aVL lead (≥ 1.3 mV) and 14 out of 30 (47%) had elevated the voltages in the V₃ lead (S wave) (≥ 3.0 mV). These leads are typically present in the Cornell criterion. Indeed, this score was present in 23 (76.7%) HCM patients. Moreover, the Lewis criterion was present in 12 (40%) and the Gubner–Ungerleider criterion in 4 (13%) out of 30 HCM patients.

Comparative analysis of the ECG voltages between healthy (false-positive) subjects and HCM patients

In the Student *t*-test analysis, the HCM patients showed significantly higher voltages of R wave in DI ($P = 0.013$), aVL ($P < 0.001$) and of S wave in DIII and V₃ ($P < 0.001$). Moreover, this group of patients showed significantly higher voltages in the Cornell, Lewis, Gubner–Ungerleider ($P < 0.001$) and the sum of QRS voltages in all 12-lead scores ($P = 0.039$) with regard to the healthy group (Table 1). Surprisingly, in the healthy group, the Sokolow–Lyon criterion (SV₁+RV₅₋₆) was 3.86 ± 0.99 mV, while it was 2.98 ± 1.63 mV ($P = 0.012$) in the HCM group.

The results observed in the Student *t*-test analysis were similar to those observed in a univariate logistic regression analysis, even after adjustment for age and sex.

The stepwise logistic regression analysis showed that the strongest independent predictor of HCM disease was the Cornell score ($P < 0.001$), followed by the Gubner–Ungerleider criterion ($P = 0.027$) (Table 2). When variables were categorized at previously well-defined abnormal values, the strongest predictor was also the Cornell criterion ($P < 0.001$), followed by the Lewis index ($P = 0.006$) (Table 3).

Diagnostic value of various ECG voltage criteria

Table 4 lists the diagnostic value of the various ECG voltage criteria for patients with HCM. Ultimately, the combination of the Cornell and the Lewis criterion (considered as positive when at least one of them is positive) showed the highest sensitivity and specificity. Indeed, when the Cornell and Lewis criteria were combined, 24 patients out of 30 were detected (net sensitivity = 80.0%) and only four false-positive individuals out of 36 fulfilled some of those criteria (net specificity = 88.8%). In contrast, with the other classical voltage criteria (Sokolow–Lyon, Romhilt–Estes voltage criterion), the sensitivity was 33.3% and 53.3%, respectively, with also a low specificity (36.1% and 16.6%, respectively). The sum of QRS voltages in all 12-lead criteria (> 17.5 mV according to Dollar & Roberts, 1989, and > 23.5 mV according to Konno et al., 2005) showed high sensitivity

ECG voltage criteria in the diagnosis of HCM

Table 1. Comparative analysis of mean ECG voltages between healthy false-positive subjects and HCM patients

| Variables | False-positive subjects (<i>N</i> = 36) X (mm) ± SD | HCM patients (<i>N</i> = 30) X (mm) ± SD | <i>t</i> | 95% CI | <i>P</i> |
|----------------------------------|--|---|----------|--------------|----------|
| RI | 6.6 ± 3.8 | 9.6 ± 5.2 | -2.56 | -5.2; -0.6 | 0.013 |
| SI | 1.2 ± 1.3 | 2.1 ± 2.4 | -1.67 | -1.8; 0.2 | 0.102 |
| RII | 17.4 ± 5.0 | 11.1 ± 9.0 | 3.41 | 2.6; 910.0 | 0.001 |
| RIII | 12.2 ± 7.2 | 6.6 ± 7.8 | 3.04 | 1.9; 9.3 | 0.003 |
| SIII | 1.1 ± 1.9 | 6.8 ± 6.5 | -4.67 | -8.2; -3.2 | <0.001 |
| RaVL | 2.4 ± 2.5 | 7.5 ± 4.5 | -5.49 | -6.9; -3.2 | <0.001 |
| RaVF | 14.7 ± 5.8 | 8.0 ± 8.0 | 3.95 | 3.3; 10.1 | <0.001 |
| RV ₅ | 22.2 ± 8.2 | 16.1 ± 10.7 | 2.57 | 1.3; 10.6 | 0.012 |
| RV ₆ | 15.5 ± 5.8 | 13.7 ± 8.6 | 0.99 | -1.8; 5.3 | 0.321 |
| SV ₁ | 16.5 ± 5.7 | 13.6 ± 8.6 | 1.59 | -0.8; 6.6 | 0.118 |
| SV ₂ | 25.6 ± 9.7 | 23.8 ± 15.0 | 0.57 | -4.6; 8.2 | 0.571 |
| SV ₃ | 13.7 ± 7.9 | 28.4 ± 15.7 | -4.64 | -21.1; -8.3 | <0.001 |
| SV ₁ +RV ₅ | 38.6 ± 9.9 | 29.8 ± 16.3 | 2.60 | 2.0; 15.7 | 0.012 |
| SV ₁ +RV ₆ | 32.0 ± 7.8 | 27.3 ± 15.0 | 1.55 | -1.4; 10.8 | 0.128 |
| SV ₂ +RV ₅ | 47.8 ± 12.8 | 40.0 ± 18.4 | 2.03 | 0.2; 15.3 | 0.049 |
| SV ₂ +RV ₆ | 41.1 ± 9.4 | 37.5 ± 17.6 | 1.00 | -3.6; 10.8 | 0.321 |
| Cornell | 16.1 ± 7.7 | 35.9 ± 16.8 | -5.95 | -26.5; -13.0 | <0.001 |
| RI+SIII | 7.7 ± 4.8 | 16.4 ± 9.5 | -4.55 | -12.6; -4.9 | <0.001 |
| Lewis | -5.9 ± 12.0 | 7.7 ± 16.1 | -3.90 | -20.5; -6.6 | <0.001 |
| Sum of QRS in all 12-lead | 222.7 ± 36.3 | 259.0 ± 86.9 | -2.14 | -70.7; -1.9 | 0.039 |

Data are expressed as mean (mm) ± SD, with 1 mm = 0.1 mV; CI, confidence interval; ECG, electrocardiographic; HCM, hypertrophic cardiomyopathy; Cornell: Cornell criterion (RaVL+SV₃); (Casale et al., 1987) Lewis: Lewis index [RI+SIII - (SI+RIII)]; (Lewis 1914).

Table 2. Electrocardiographic predictors of HCM. Multivariate logistic regression analysis

| | Criterion | OR | OR (95% CI) | <i>P</i> |
|--------|-----------|-------|-------------|----------|
| Step 2 | Cornell | 1.149 | 1.05-1.26 | <0.001 |
| | Gubner | 1.131 | 1.00-1.27 | 0.027 |

CI, confidence interval; HCM, hypertrophic cardiomyopathy; OR, odds ratio; Cornell criterion: RaVL+SV₃; Gubner-Ungerleider criterion: RI+SIII.

(80.0% and 56.7%, respectively) but the numbers of false-positives were 29 and 12 (a specificity of 19.4% and 66.7%, respectively). If these criteria are applied to the initial sample (the 471 initially screened), the sensitivity of the test is the same, but the specificity increases for all criteria (Table 5).

Other ECG abnormalities associated with HCM

When other ECG patterns associated with HCM were studied, such as abnormal Q waves or repolarization alterations, 16 of the 30 patients (53.3%) showed repolarization alterations and 14 (46.7%) abnormal Q waves. Interestingly, six out of eight patients not presenting any of these ECG patterns showed high ECG voltages according to the Cornell (*n* = 5) or Lewis (*n* = 1) criteria.

Discussion

The results of this study offer new insights into the ECG diagnosis of HCM in cardiovascular screening

Table 3. Electrocardiographic predictors of HCM, with variables categorised. Multivariate logistic regression analysis

| | Criterion | OR | OR (95% CI) | <i>P</i> |
|--------|--------------------|-------|-------------|----------|
| Step 2 | Cornell* | 20.97 | 3.73-118.1 | <0.001 |
| | Lewis [†] | 24.63 | 1.87-324.97 | 0.006 |

CI, confidence interval; HCM, hypertrophic cardiomyopathy; OR, odds ratio; Cornell criterion: RaVL+SV₃; Lewis criterion: RI+SIII - (SI+RIII). *Categorized Cornell criterion: ≥ 2.8 mV and >2.8 mV (2.0 mV in women).

[†]Categorized Lewis criterion: <1.7 mV and ≥ 1.7 mV.

of young people, the combination of the Cornell and either the Lewis or the Gubner voltage criteria showing greater net sensitivity and excellent specificity.

Recently, the European Society of Cardiology (ESC) (Corrado et al., 2005) and the Medical Commission of the International Olympic Committee (Bille et al., 2006) recommended a baseline 12-lead electrocardiogram as part of pre-participation screening to identify young competitive athletes at risk for sudden death. However, the classic limits in the standard and precordial (SV₁₋₂ and RV₅₋₆) leads proposed by the ESC (Romhilt-Estes voltage criterion) as the valid criterion for detecting LVH associated with HCM have been shown to have low specificity in young people (The Criteria Committee of the New York Heart Association, 1994) and appear to account for an excessive number of ECG false-positives in athletes (Pelliccia et al., 2000; Sharma et al., 2002). Such unavoidable facts also

Table 4. Diagnostic value of classic ECG voltage criteria for detecting HCM disease in young people. Based on the 66 individuals of the study sample

| Criterion | HCM subjects <i>N</i> = 30 | False-positive Subjects <i>N</i> = 36 | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|-------------------------------|---|--------------------|--------------------|------------|------------|
| 1. Sokolov–Lyon | 10 | 23 | 33.3 | 36.1 | 0.1 | 96.4 |
| 2. Romhilt–Estes voltage criterion | 16 | 30 | 53.3 | 16.6 | 0.1 | 94.7 |
| 3. Cornell | 23 | 3 | 76.7 | 91.6 | 1.8 | 99.5 |
| 4. Gubner–Ungerleider | 4 | 0 | 13.3 | 100 | 100 | 98.3 |
| 5. Lewis | 12 | 1 | 40.0 | 97 | 2.6 | 98.8 |
| 6. Sum of QRS voltages in all 12-leads > 17.5 mV | 24 | 29 | 80.0 | 19.4 | 0.2 | 97.9 |
| 7. Cornell+Gubner | 23 | 3 | 76.7 | 91.6 | 1.8 | 99.5 |
| 8. Cornell+Lewis | 24 | 4 | 80.0 | 88.8 | 1.4 | 99.6 |

ECG, electrocardiographic; HCM, hipertrophic cardiomyopathy; NPV, negative predictive value; PPV, positive predictive value.

Sokolov–Lyon index: $SV_1 + RV_{5-6} > 3.5$ mV. Romhilt–Estes voltage criterion: amplitude of R or S wave in a standard lead ≥ 2.0 mV, S wave in lead $V_{1-2} \geq 3.0$ mV or R wave in lead $V_{5-6} \geq 3.0$ mV; Cornell criterion: $RaVL + SV_3 > 2.8$ mV in males and > 2.0 mV in females; Gubner–Ungerleider criterion: $(RI + SIII) - (RIII + SI) \geq 2.5$ mV; Lewis criterion: $(RI + SIII) - (RIII + SI) \geq 1.7$ mV. Cornell+Gubner and Cornell+Lewis criteria: considered as positive when at least on of them is positive.

Table 5. Diagnostic value of classic ECG voltage criteria for detecting HCM disease in young people. Based on the 471 individuals initially screened

| Criterion | HCM subjects <i>N</i> = 30 | Subjects screened <i>N</i> = 471 | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|-------------------------------|-------------------------------------|--------------------|--------------------|------------|------------|
| 1. Sokolov–Lyon | 10 | 23 | 33.3 | 95.1 | 1.3 | 98.6 |
| 2. Romhilt–Estes voltage criterion | 16 | 30 | 53.3 | 93.6 | 1.6 | 99.0 |
| 3. Cornell | 23 | 3 | 76.7 | 99.4 | 20.4 | 99.5 |
| 4. Gubner–Ungerleider | 4 | 0 | 13.3 | 100 | 100 | 98.3 |
| 5. Lewis | 12 | 1 | 40.0 | 99.8 | 28.6 | 98.8 |
| 6. Sum of QRS voltages in all 12-leads > 17.5 mV | 24 | 29 | 80.0 | 93.8 | 2.5 | 99.6 |
| 7. Cornell+Gubner | 23 | 3 | 76.7 | 99.4 | 20.4 | 99.5 |
| 8. Cornell+Lewis | 24 | 4 | 80.0 | 99.2 | 16.7 | 99.6 |

ECG, electrocardiographic; HCM, hipertrophic cardiomyopathy; NPV, negative predictive value; PPV, positive predictive value.

Sokolov–Lyon index, $SV_1 + RV_{5-6} > 3.5$ mV. Romhilt–Estes voltage criterion: amplitude of R or S wave in a standard lead ≥ 2.0 mV, S wave in lead $V_{1-2} \geq 3.0$ mV or R wave in lead $V_{5-6} \geq 3.0$ mV; Cornell criterion: $RaVL + SV_3 > 2.8$ mV in males and > 2.0 mV in females; Gubner–Ungerleider criterion: $(RI + SIII) - (RIII + SI) \geq 2.5$ mV; Lewis Criterion: $(RI + SIII) - (RIII + SI) \geq 1.7$ mV. Cornell+Gubner and Cornell+Lewis criteria: considered as positive when at least on of them is positive.

raise the differential diagnosis with structural cardiac diseases such as HCM, and represent a potential limitation to routine ECG testing as part of pre-participation screening (Maron et al., 2005b).

Low specificity of the traditional ECG voltage criteria in young people

In a recent study, Pelliccia et al. (2000) showed increased R or S wave voltages in precordial leads (≥ 30 mm) (Romhilt–Estes voltage criterion) in 233 of the 1005 (23%) examined trained health athletes (i.e., false-positive), mimicking HCM. Previously, Bjornstad et al. (1991) observed that the Sokolov–Lyon index was significantly higher in athlete students compared with sedentary controls, and Sharma et al. (1999) reported that the Sokolov–Lyon and Romhilt–Estes voltage criteria for left LVH were more common in adolescent athletes than in the relatively sedentary-lifestyle students ($P < 0.0001$).

However, although the Sokolov–Lyon voltage criterion was significantly more common in athletes, it was also present in 23% of non-athletes, indicating that it is probably a poor indicator of LVH in the young.

In line with these studies, the present investigation found that 36 of the initially 471 (7.6%) examined young people, athletes and non-athletes, had presented at least one voltage criterion for LVH: for example, 30 out of 471 (6.4%) showed the Romhilt–Estes (ESC proposed) voltage criterion, and 23 out of 471 (4.9%) showed the Sokolov–Lyon index, but any disease was finally discarded in these subjects (i.e., false-positive).

ECG voltage criteria in HCM disease

The high voltages in HCM patients that differentiate significantly from healthy subjects were located in four specific leads: the magnitude of the R wave in

both DI and aVL, and the magnitude of the S wave in both DIII and V3. Subsequently, the Cornell voltage criterion ($R_{aVL} + SV_3$) and the Lewis and Gubner indexes were the best to discriminate both groups. Indeed, 23 of the 30 (76.7%) patients with HCM showed the Cornell voltage criterion (higher sensitivity), and only three of the 36 healthy individuals (and also only three of the 471 initially screened) presented this criterion, the Lewis index being observed in only one, and no subject showed the Gubner index (higher specificity). This is in line with the findings of Panza and Maron (1989), who observed that in some patients with HCM and marked LVH the most striking voltages may be confined to the mid-precordial leads (that is, V3 and V4) and with Montgomery's et al. (2005) results, who reported that 41% of enrolled patients with HCM had criteria for LVH with the Cornell voltage score. Interestingly, these findings recall those of Norman and Levy (1995), who showed that the criteria of Cornell, Gubner–Ungerleider, Lewis and the R wave in aVL are the most highly correlated with left ventricular mass for detecting a pathologic LVH. Likewise, the presence of LVH Cornell voltage has been associated with an increased risk of ischemic stroke, indicating that it may detect electrical abnormalities induced by the hypertrophic process that are not detectable by echocardiography (Kohsaka et al., 2005). To sum up, these criteria may be helpful to differentiate this pathologic LVH from physiologic compensatory anatomical LV adaptation.

In relation to the specificity of the particular Cornell, Gubner–Ungerleider and Lewis criteria found in the present study, Bjornstad et al. (1991) showed that while the Sokolow–Lyon index was significantly higher in a group of athletes, the Gubner index (which detects primarily LVH in subjects with a horizontal heart position) were not observed in athletes. Douglas et al. (1988) also reported that only 8% of their healthy athletes presented the Cornell voltage index, and Kinoshita et al. (2003) also found that only one person among 890 professional sumo wrestlers showed LVH based on the Cornell voltage (> 35 mm alone).

At present, there is a paucity of information regarding the differences in the diagnostic value of various voltage scores for HCM. Furthermore, as far as we know, only a few studies have considered the Cornell index as a voltage criterion in the study of LVH in HCM. Hence, Charron et al. (1998), who analyzed the diagnostic value of electrocardiography for familial HCM in genotyped children, only included the voltage criterion defined with the sum of the S wave in V_1 and R wave in V_6 in the comparative study [and observed a low sensitivity (25%)]. Dollar and Roberts (1989) reported that a total 12-lead QRS amplitude higher than 17.5 mV is a useful indicator

of LVH and, among patients with HCM studied at necropsy (predominantly adults), it is more sensitive (53%) than other more commonly used criteria such as the Sokolow–Lyon index or the Romhilt–Estes voltage criteria. However, they did not include the Cornell criterion in their study. More recently, Konno et al. (2005) demonstrated that in their younger subjects (< 35 years), the 12-lead QRS voltage criterion (> 17.5 mV) showed the greatest sensitivity (78%) but a low specificity (68%) for the diagnosis of HCM carriers. When the cut-off point was set at 23.5 mV, the specificity increased to 91% but the sensitivity was only 37%, although this level was higher than that shown by the Cornell and Sokolow–Lyon criteria (25% and 14%, respectively). In this respect, the present study shows that the specificity of the 12-lead QRS voltage criterion, using 17.5 mV as the cut-off point, was 19.4% (if we analyze the 471 screened individuals, the value increases to 93.8%), but even when the cut-off point was > 23.5 mV the specificity was also poor (66.7%, and 97.4% if we analyze all of the subjects screened). The reason for the conflicting findings may be related to the fact that some of the participants in the Konno study were only carriers of the disease, and also due to the different ages of the study samples. When values are related to those of the 471 young people screened initially, we assume a minimal error. Indeed, among the 471 individuals, only those with some positive result in the initial screening (a total of 60 subjects) were subjected to an echocardiographic study to discard an HCM. Owing to the relatively low prevalence of this disease in the general population (1:500) (Maron et al., 2005a) and because a 12-lead ECG is abnormal in up to 95% of patients with HCM (Maron 2002), the possibility that other individuals among those 411 (471 – 60) suffer from the disease is minimal.

Finally, the other ECG patterns associated commonly with HCM, such as abnormal Q waves or alterations in repolarization, were noted in 22 out of 30 patients (73.3%). It is striking that the combination of the Cornell and Lewis criteria was of significant diagnostic value for HCM in patients not presenting these other ECG abnormalities. Indeed, six out of eight remaining patients showed high ECG voltages as per the Cornell ($n = 5$) or the Lewis ($n = 1$) criteria.

Study limitation

The present study has several limitations. First, the number of subject cases was limited because of the low prevalence of HCM disease in hospital-based young patients (Miura et al., 2002). However, the study is unique in comparing the ECG recordings of young people with electrocardiograms strongly sug-

gestive of HCM with those having HCM, thereby demonstrating that ECG voltage criteria exist that are different from the conventional ones that increase ECG specificity. Second, although we did not have a genetic study to avoid false-negatives in the youngest subjects, when HCM may be in an echocardiographically prehypertrophic phase (Maron et al., 2003), a posterior evaluation at the age of 15 years demonstrated that none of these subjects presented any finding suggestive of HCM. Finally, further studies on different populations are an obvious next step for confirming the role of the combination of ECG voltage criteria giving the highest precision in the present study.

Perspectives

These observations taken together suggest that when the Cornell and Lewis or Gubner voltage criteria

are applied to the LVH detection of HCM in a cardiovascular evaluation conducted in young people (athletes and non athletes), the 12-lead electrocardiogram is not only a convenient, accessible and relatively inexpensive tool in clinical practice but also a sensitive and specific test to identify people at risk.

Key words: cardiovascular examination, hypertrophic cardiomyopathy, left ventricular hypertrophy, false-positive, sudden death, Cornell criterion, Lewis criterion, Gubner–Ungerleider criterion.

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