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Assessment of a new electrocardiographic criterion for the diagnosis of left ventricle hypertrophy: a validation study

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ABSTRACT

OBJECTIVE: Numerous criteria have been developed to predict left ventricular hypertrophy using electrocardiogram (ECG). However, one major common limitation of all has been their low sensitivity. Based on that, recently, a novel criterion has been proposed which is believed to have higher sensitivity without a compromise in specificity. Therefore, in our study, we aimed to test this novel ECG criterion prospectively, in a large unselected cardiac patients.

METHODS: Patients who were referred to our echocardiography laboratory due to various etiologies were prospectively enrolled. The novel Peguero-Lo Presti criterion was assessed along with other established ECG criteria. Left ventricular mass index was calculated using echocardiography. Performance of each index was evaluated.

RESULTS: Overall 767 patients were enrolled in the study. The sensitivity and specificity of Peguero-Lo Presti criterion were 17.5% and 94.5% respectively. Although the highest sensitivity belonged to Peguero-Lo Presti criterion, in ROC analysis it showed modest predictive capability which was similar to the established Cornell voltage criterion (AUC=0.64 [0.56-0.68 95% CI], p<0.01).

CONCLUSION: Although this novel criterion had higher sensitivity, the overall performance was similar to the current indices. Further adjustments particularly based on age and body mass index might yield better results.

Keywords: Electrocardiogram; hypertrophy; left ventricular mass.

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Electrocardiogram (ECG) is still the most widely used tool for screening cardiac abnormalities, in particular, left ventricular hypertrophy (LVH) which is closely related to morbidity and mortality [1, 2]. Despite its low cost and widespread availability, ECG has many limitations with respect to LVH assessment leading to the development of more than 30 different criteria most of which have only modest sensitivities [3]. However, recently a new criterion has been proposed by Peguero et al to identify LVH on ECG [4]. Contrary to the previously described measurements, in which fixed leads are chosen for calculation, this new method incorporates the sum of S wave amplitude in lead V4 and the greatest S wave in any lead. It is believed that selective measurement of the S wave of the QRS complex combined with the flexible lead selection improves sensitivity without hampering specificity.

On the other hand, this new criterion has only been tested in a small number of patients and thus it is hard to implement it into clinical practice without validation.

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Therefore, in our study, we wanted to assess the sensitivity and the specificity of this newly proposed criterion in a larger, unselected, real-world population and compare results with previously established Sokolow-Lyon and Cornell criteria.

MATERIALS AND METHODS

Patients

We prospectively enrolled patients who were referred to our echocardiography laboratory due to a wide range of diagnosis. Patients with inadequate acoustic window, pace-maker rhythm, and complete bundle branch block were excluded from the study. Ethical board approval was obtained from the institutional review board (Approval number: 2092, Date: 28/08/2018).

Echocardiographic measurements

Echocardiography was used to calculate left ventricle (LV) mass using the Devereux formula according to which LVH was described as left ventricular mass index greater than 115 g/m^2 in male and 95 g/m^2 in female subjects. Devereux formula for left ventricular mass (g): 0.80 x {1.04 x [(septal thickness + internal diameter + posterior wall thickness) 3 – (internal diameter)3]} + 0.6 g [5]. The left ventricular mass was indexed according to body surface area. All echocardiographic measurements were performed by two physicians who had at least 10-year-experience in cardiology and echocardiography, in accordance with the recommendations of American Society of Echocardiography [6]. All measurements were recorded in a standardized manner using a Philips iE33 echocardiography machine (Philips, the Netherlands), with a 3 MHz transducer. Frames showing left ventricular end-diastolic diameter, septum, and posterior wall simultaneously were chosen for measurements.

ECG interpretation

An electrocardiogram was obtained from each patient on the same day echocardiogram was performed. Standard 12-lead ECGs were recorded in all patients at 1 mV/10 mm and 25 mm/sec. calibration and evaluated by two different cardiologists who were blinded to the echocardiographic findings. When assessing newly proposed Peguero-Lo Presti criterion the amplitude of the deepest S wave in any lead was added to the amplitude of the S wave in lead V4. Cut-off values for hypertrophy were 2.3 mV for women and 2.8 mV for men respectively. In order to compare the sensitivity and specificity of this newly proposed method, we also assessed LVH according to Sokolow-Lyon and Cornell criteria. The Sokolow-Lyon voltage criterion was calculated by adding the amplitude of S wave in lead V1 and the amplitude of R wave in lead V5 or V6 and values greater than 3.5 mV were considered as LVH [3]. In the limb lead voltage criteria, amplitude of R wave in aVL greater than 1.1 mV and amplitude of R wave in lead D1 greater than 1.4 mV were also considered as LVH. When calculating LVH according to Cornell criteria sex-specific cut-off values were applied in which the amplitude of R wave in lead aVL plus the amplitude of S or QS complex in lead V3 greater than 2.8 mV in men and 2.0 mV in women were considered as LVH [3].

Statistical analysis

Distribution of data was evaluated using Kolmogorov-Smirnov test. Continuous variables were reported as means±standard deviation and categorical data were reported as numbers and percentages. Receiver operator characteristics (ROC) analysis was performed to estimate the performance of selected indices and the newly proposed Peguero-Lo Presti criterion. Mc Nemar test was used to evaluate the agreement between the ECG criteria and the left ventricular mass index. Also, Pearson correlation analysis was performed to assess the relationship between LV mass index and ECG voltage amplitude. All statistical analysis was performed using SPSS software, version 20.

RESULTS

Overall 767 patients were included in the final analysis. Mean age was 51.1±16.2 (18–93) and 405 (52.8%) of them were female. The main indications for echocardiography referral included hypertension (n=169, 22%), ischemic heart disease (n=238, 31%), valvular heart disease (n=122, 16%), evaluation of chest pain (n=191, 25%) and other etiologies (n=46, 6%). The clinical characteristics and echocardiographic findings are presented in Table 1. The definition of left ventricular hypertrophy was based on the left ventricular mass index calculated based on Devereux formula derived from echocardiographic measurements. Patients with LVH were older (61.0±12.1 vs 48.9±16.2 $p<0.01$) and mostly female (n=96 [62.3%] vs n=309 [50.4%] $p<0.01$). Also, comorbidities including hypertension, diabetes mellitus, chronic renal insufficiency, ischemic heart disease were

TABLE 1. Clinical characteristics and echocardiographic findings of the study patients

	No hypertrophy (n=613, 79.9%) Mean (SD)	Hypertrophy* (n=154, 20.1%) Mean (SD)	p
Age (years)	48.9 (16.2)	61.0 (12.1)	<0.01
Gender (female)	309 (50.4)	96 (62.3)	<0.01
Height (cm)	166.7 (9.0)	162.2 (8.4)	<0.01
Weight (kg)	74.5 (14.2)	76.9 (15.1)	0.06
Body mass index	26.8 (5.0)	29.3 (5.9)	<0.01
Body surface area	1.82 (0.18)	1.81 (0.18)	0.4
Hypertension	211 (34.4)	99 (64.3)	<0.01
Diabetes mellitus	131 (21.5)	58 (37.7)	<0.01
Chronic kidney disease	22 (3.6)	20 (12.9)	<0.01
Ischemic heart disease	83 (13.6)	49 (31.8)	<0.01
Stroke	27 (4.4)	9 (5.9)	0.4
Chronic obstructive pulmonary disease	57 (9.4)	21 (13.9)	0.1
Left ventricular end-diastolic diameter, mm	45.2 (4.4)	49.9 (5.5)	<0.01
Left ventricular end-systolic diameter, cm	31.1 (2.1)	33.2 (1.9)	<0.01
Ejection fraction, %	59.5 (3.5)	57.7 (6.7)	<0.01
Interventricular septum diameter, mm	9.6 (1.3)	12.0 (1.5)	<0.01
Posterior wall diameter, mm	9.1 (1.1)	11.1 (1.1)	<0.01
Left ventricular mass, g	144.6 (34.5)	224.4 (44.7)	<0.01
Left ventricular mass index g/m^2	78.9 (15.8)	123.9 (22.6)	<0.01
Eccentric hypertrophy	–	60 (39.0)	N/A
LV dysfunction (EF<45%)	12 (2.0)	12 (7.8)	<0.01

SD: Standard deviation; LV: Left ventricle; *The definition of left ventricular hypertrophy was based on the left ventricular mass index which was calculated based on Devereux formula derived from echocardiographic measurements.

more frequent in patients with left ventricular hypertrophy. In terms of echocardiographic findings, LV mass and LV mass index were significantly higher in patients with hypertrophy (224.4±44.7 gr vs 144.6±34.5 gr p<0.01 and 123.9±22.6 gr/m^2 vs 78.9±15.8 gr/m^2 p<0.01 respectively). Mean LV ejection fraction was similar in both groups despite having a statistical significance (57.7±6.7% vs 59.5±3.5%, p<0.01). LV systolic dysfunction which was defined as LVEF <45% was more common in patients with LV hypertrophy (n=12 [7.8%] vs n=12 [2.0%], p<0.01)

Sensitivity and specificity of different criteria based on Mc Nemar test are presented in Table 2. In particular, the sensitivity and specificity of Peguero-Lo Presti criterion were 17.5% and 94.5% respectively. Among different criteria, while the highest sensitivity belonged to Peguero-Lo Presti criterion, the highest specificity was seen in RL1 (98.5%). These analyses were also performed including only hypertensive patients. The results are presented in Table 3. In general, the sensitivities of all criteria increased with accompanying a slight decrease in the specificity. Again, the highest sensitivity and the lowest specificity were seen in Peguero-Lo Presti criterion (19.2% and 93.8% respectively).

TABLE 2. Sensitivity and specificity of each criterion in the entire cohort

	Sensitivity (95% CI)	Specificity (95% CI)	p
RL1	5.2	98.5	<0.01
RaVL	6.5	98.4	<0.01
Sokolow-Lyon voltage	3.9	97.6	<0.01
Cornell voltage	9.7	98.2	<0.01
SD+SV4 (Peguero–Lo Presti)	17.5	94.5	<0.01

CI: Confidence intervals.

Table 3. Sensitivity and specificity of each criterion in hypertensive patients

n=310	Sensitivity (95% CI)	Specificity (95% CI)	p
RL1	6.1	97.6	<0.01
RaVL	7.1	96.7	<0.01
Sokolow-Lyon voltage	5.1	99.5	<0.01
Cornell voltage	12.1	94.8	<0.01
SD+SV4 (Peguero–Lo Presti)	19.2	93.8	<0.01

CI: Confidence intervals.

Table 4. Area under curve values of all indices

	AUC value	95% CI	p
RL1	0.63	0.58–0.68	<0.01
RaVL	0.68	0.63–0.72	<0.01
Sokolow-Lyon voltage	0.52	0.47–0.57	0.3
Cornell voltage	0.67	0.63–0.72	<0.01
SD+SV4 (Peguero–Lo Presti)	0.64	0.59–0.68	<0.01

AUC: Area under curve; CI: Confidence intervals.

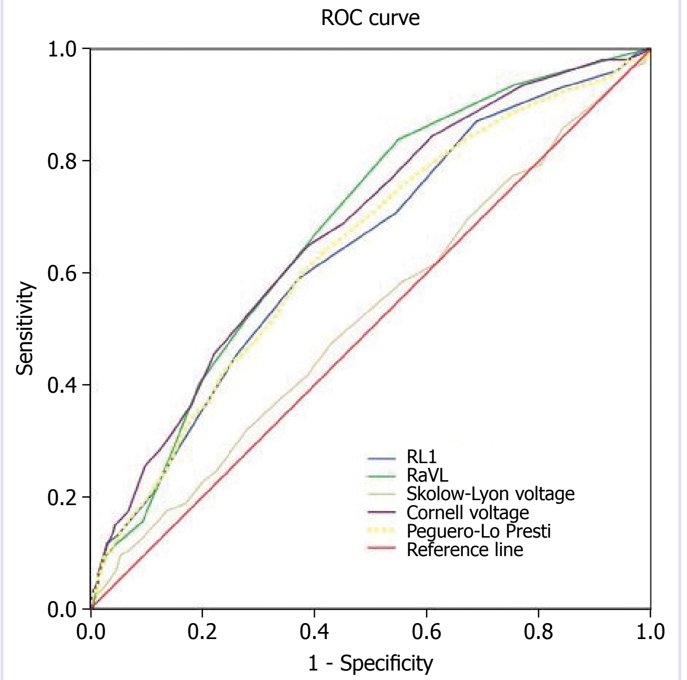

Figure 1. ROC analysis showing area under curve values of each index including the novel Peguero-Lo Presti criterion. ROC: receiver operating characteristics.

ROC analysis was also performed and the results are demonstrated in Table 4 and Figure 1. Peguero-Lo Presti criterion's area under curve (AUC) value was 0.64 (0.56–0.68 95% CI, p<0.01). While the highest AUC value was seen in RaVL criterion (AUC=0.68, [0.63–0.72 95% CI], p<0.01), Sokolow-Lyon voltage criterion did not reach a statistical significance (AUC=0.52, [0.47–0.57 95% CI], p=0.3). Pearson correlation analysis showed a weak correlation between LV mass index and Peguero-Lo Presti measurements (r=0.3, p<0.01).

DISCUSSION

In our study, although the sensitivity of the novel Peguero–Lo Presti criterion was higher compared to other indices, the overall predictive performance was modest and similar to that of Cornell voltage criterion. There was also a weak correlation between LV mass index and ECG voltage amplitude. On the other hand, Sokolow-Lyon voltage criterion showed the worst sensitivity and specificity based on ROC analysis.

This novel ECG criterion emerged based two distinct premises: improvement in the overall accuracy of LVH prediction due to the flexibility of any lead selection since fixed lead selection overlooks the position of the heart within the thorax and adjacent structures. Alterations in the distance of left ventricular cavity to the electrode, the position of the surface electrode, and anthropometric differences are all considered as the major limitations of fixed lead selection [7]. The other hypothesis was based on the temporal multiple wave front changes within the left ventricle during depolarization in which myocardial and epicardial LV free wall activation occur after the first 50 msec and thus better represented with the S wave of the QRS complex [4].

Despite these two promising hypotheses, we did not find superiority of this new index compared to standard indices. First of all, the low sensitivity of ECG has long been acknowledged in the literature [8]. For example, in the Framingham Heart Study, the sensitivity of the gender-specific Cornell voltage criterion was only 10% in men and 22% in women and in PIUMA study it was 12% in men and 19% in women respectively [9, 10]. Likewise, the prevalence of LVH detected by ECG using the Framingham method (voltage criteria with "strain pattern") was only 2% in the general population [11]. The inherent limitation of ECG to detect LVH accurately is related to many factors. First; it relies on the electrical activity of the myocardium; however alterations in the interstitium such as fibrosis and deposition of other materials lower the voltage expression which limits the ECG to detect LVH [12]. Second; when measuring voltage changes, several confounding factors such as age, sex, body habitus, and race, affect the reliability of these measurements which are not truly addressed in the ECG indices [13].

Given the aforementioned limitations of ECG, there are also significant differences in our cohort compared the original test study conducted by Peguera et al. First, the original study was retrospective in design which comprised of 94 test and 130 validation patients whereas our prospective cohort was much larger. Second, the original study was based on highly selected hypertensive patients who were admitted to the hospital. Our cohort included patients who were referred to echocardiography lab due to different etiologies. Therefore our cohort comprised of unselected general outpatients. The number of patients enrolled, their baseline clinical and echocardiographic differences might have played a role in the accuracy of the newly developed criterion.

One other important factor that attenuates the predictive capability of ECG to detect hypertrophy is the geometry of LV. There is data showing that concentric LVH is more accurately detected by ECG compared to eccentric LVH which might have contributed to our study results in which 39% of the LVH were eccentric [14].

Since the publication of Peguero-Lo Presti criterion, a number of big-scale validation studies were conducted with different outcomes. Sun GZ et al assessed Peguero-Lo Presti criterion in approximately 10.000 Asian patients and concluded that the novel Peguero-Lo Presti voltage may not be better for screening LVH in Asians. (AUC: 0.66 for males, AUC: 0.68 for females) [15]. LD Ha et al. compared the major electrocardiogram indices for LVH including novel Peguero-Lo Presti criterion to predict cardiovascular mortality as a surrogate for pathological hypertrophy and found Peguero-Lo Presti criterion to be inferior for predicting cardiovascular mortality to the original Cornell index [16]. Recently, Clark E assessed Peguero-Lo Presti criterion in some 1500 apparently healthy individuals and found the specificity of the new Peguero-Lo Presti criterion to be quite poor in younger people <30 years), being only 50% males and 76% in females, and therefore offered this novel criterion to be age and sex adjusted [17]. In fact, the authors of the of Peguero-Lo Presti criterion have already declared that they were currently in the process of assessing further the accuracy of this novel criterion after adjustment for the aforementioned variables [18].

Limitations

Magnetic resonance imaging which is the gold standard for LV mass calculation was not performed in our study [7]. However, we believe that our results are still valid since echocardiogram is used to guide the treatment in the great majority of patients and also it would be impractical to use magnetic resonance imaging in a big prospective validation study. Finally, this was a single-center study so the results may not be applicable across a broader population and ethnicity.

Conclusion

Although the novel Peguero-Lo Presti criterion had the highest sensitivity compared to standard indices, it did not outperform the established Cornell or other limb criteria even when evaluated only in hypertensive patients. Age and body mass index-adjusted formulas may yield better results. However, the historical Sokolow-Lyon criterion has not shown to be predictive of LVH in our cohort probably related to baseline clinical characteristics.

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