Distinct role of electrocardiographic criteria in echocardiographic diagnosis of left ventricular hypertrophy according to age, in the general population: the Ikaria Study

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Objective **The age-dependent performance of electrocardiographic (ECG) criteria was examined for left ventricular hypertrophy (LVH) prediction.**

Methods **During 2009, 570 middle-aged (54 ± 7 years, 45% men) and 507 elderly (75 ± 6 years, 45% men) inhabitants of the Ikaria Island were studied. Seven ECG criteria were calculated (Sokolow–Lyon voltage and product, sex-specific Cornell voltage and product, Gubner–Ungerleider voltage, Lewis voltage and Framingham), whereas LVH was defined as left ventricular mass indexed for body surface area (BSA) at least 125 g/m^2 in men and at least 110 g/m^2 in women or left ventricular mass indexed for height$^{2.7}$ 49 g/m$^{2.7}$ or more in men and 45 g/m$^{2.7}$ or more in women.**

Results **The Framingham criteria had in hierarchical order the highest, although insignificant, sensitivity among the elderly individuals, either when LVH was indexed for BSA or for height$^{2.7}$ (18.4 and 16.7%, respectively). Cornell voltage and product criteria had hierarchically the highest sensitivity among middle-aged participants, either when LVH was indexed for BSA (19.0 and 23.8%, respectively) or for height$^{2.7}$ (17.2 and 20.3%, respectively). In the multiadjusted analysis applied in elderly participants, Cornell voltage, its product and Framingham criteria were associated with echocardiographic detection of LVH (indexed for BSA); however, when LVH was indexed for height$^{2.7}$, the Sokolow–Lyon and Framingham criteria were associated with LVH detection. In contrast, among middle-aged individuals, the Cornell product was the only ECG criterion that was associated with LVH detection (irrespective of indexation).**

Conclusion **Age should be taken into consideration in selection of appropriate ECG criteria for LVH detection. Indexation of left ventricular mass differentiates the diagnostic ability of ECG criteria, especially in older patients.**
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Keywords: age, echocardiography, electrocardiogram, left ventricular hypertrophy

Abbreviations: BSA, body surface area; ECG, electrocardiographic; LVH, left ventricular hypertrophy

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Introduction

Echocardiography is now considered as the gold standard for left ventricular hypertrophy (LVH) detection. However, the greater convenience and lower cost of the electrocardiogram (ECG) continue to support its widespread use for the diagnosis of left ventricular hypertrophy (LVH) in clinical practice, as well as in epidemiological studies and clinical trials [1]. LVH detected with standard electrocardiography is a strong and independent predictor of future cardiovascular complications, including myocardial infarction, stroke and sudden cardiac death [2–4]. The appropriate diagnostic workup of suspected LVH in the general population is unclear. More than 30 different indexes based on the standard 12-lead ECG have been described [5]. These criteria have demonstrated varying performance characteristics for the identification of LVH, particularly in relation to obesity and race [6–8]. In addition, a major limitation of commonly used criteria for electrocardiographic detection of LVH is their reliance on the same voltage thresholds for different age groups [9]. Therefore, it is suggested that each criterion identifies different patient subsets with different baseline risks for adverse cardiovascular outcomes.

In the present work, the performance of seven classic ECG criteria was examined for LVH prediction with the use of echocardiography as the gold standard in two distinct samples: one consisting of middle-aged men and women and the other of elderly people. All participants were inhabitants of the Ikaria Island, a place that has been recently recognized, worldwide, as having high longevity and low mortality rates from cardiovascular disease [10].

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Methods

Study's sample

The Ikaria epidemiological study has been carried out on the island of Ikaria. From June to October 2009, 1420 middle-aged and elderly inhabitants were voluntarily enrolled into the study [11]. All participants underwent a standard 12-lead ECG recording and a complete echocardiographic assessment and were interviewed by trained personnel (i.e. cardiologists, general practitioners, dietitians and nurses), who used a standard questionnaire. Inhabitants with complete bundle branch block ($n = 53$), previous myocardial infarction ($n = 51$), Wolff–Parkinson–White syndrome ($n = 2$) and digitalis treatment ($n = 42$) were excluded from the present study. Moreover, 195 individuals were subsequently excluded from the analysis due to poor-quality ECG tracings ($n = 88$) or poor left ventricular M-mode echocardiographic tracings ($n = 107$). Thus, the present work was based on a sample of 1077 individuals; of them, 570 were middle-aged (54 ± 7 years, 45% men) and 507 were elderly (75 ± 6 years, 45% men).

All individuals were informed about the aims of the study and gave written informed consent. The study was approved by the Ethics Committee of our institution and was carried out in accordance with the Declaration of Helsinki (1989).

Clinical and anthropometric measurements

Weight and height were measured following standard procedures and BMI was calculated in kg/m^2. Obesity was defined as a BMI higher than 29.9 kg/m^2. Waist circumference was measured at the midpoint between the bottom of the rib cage and the top of iliac crest from patients at minimal respiration. Body surface area (BSA), in m^2, was calculated according to Mosteller's equation ($0.20247 \times \text{weight}^{0.425} \times \text{height}^{0.725}$) [12].

Resting arterial blood pressure was measured three times in the right arm, at the end of the physical examination with the individual in sitting position. Patients whose average blood pressure levels were greater or equal to 140/90 mmHg or were under antihypertensive medication were classified as hypertensive patients. Hypercholesterolemia was defined as total serum cholesterol levels higher than 200 mg/dl or the use of lipid-lowering agents. Current smokers were defined as those who smoked at least one cigarette per day; former smokers were defined as those who had stopped smoking for at least 1 year and the rest were defined as noncurrent smokers. Diabetes mellitus type 2 was determined by fasting plasma glucose tests and was analyzed in accordance with the American Diabetes Association diagnostic criteria (fasting blood glucose levels >125 mg/dl or use of special medication, indicated the presence of diabetes) [13].

Electrocardiogram measurements designation

A resting 12-lead ECG was recorded during quiet respiration for each participant (duration 10 s) by the use of SE-1010 PC ECG (EDAN instruments Inc., Nanshan Shenzhen, China). Smart ECG Measurement and Interpretation Programs (SEMIP version 1.5), which is part of EDAN SE series electrocardiograph and PC ECG, was used for the automated measurement and interpretation of amplitudes and duration of ECG waves in each of the 12 leads. Adjustment of automatically designated amplitudes and duration of ECG waves were performed by two physicians blinded to the study (D.T., E.O.). From these measurements, we calculated seven ECG criteria considering their general acceptance and recognized performance, five 'pure-voltage' criteria based on wave amplitude measurements and two 'time-voltage' criteria:

(1) Sokolow–Lyon voltage (sum of the amplitudes of S wave on V_1 and R wave on V_5 or V_6 $\geq$3.5 mV) [14].
(2) Sex-specific Cornell voltage (sum of the amplitudes of S wave on V_3 and R wave on aVL >2.0 mV in women and >2.8 mV in men) [15].
(3) Gubner–Ungerleider voltage (sum of the amplitudes of R wave on lead I and S wave on lead III $\geq$2.5 mV) [16].
(4) Lewis voltage (sum of the amplitudes of R wave on lead I and S wave on lead III, minus the amplitudes of S wave on lead I and R wave on lead III, $\geq$1.7 mV) [17].
(5) Framingham criterion (coexistence of a definite strain pattern and at least one of the following voltage criteria: sum of the amplitudes of the R wave on lead I and the S wave on lead III $\geq$2.5 mV, sum of the amplitudes of the S wave on lead V_1 or V_2 and the R wave on lead V_5 or V_6 $\geq$3.5 mV, the S wave on the right precordial lead $\geq$2.5 mV and the R wave on the left precordial lead $\geq$2.5 mV) [9].
(6) Sokolow–Lyon product ($SV_1 + RV_5$ or $V_6 \times$ QRS duration $\geq$3000 mm ms for women and $\geq$ 4000 mm ms for men) [18].
(7) Cornell product [(RaVL + SV_3) + 8 mm for women] $\times$ QRS duration $\geq$ 2440 mm ms] [18,19].

Cardiac ultrasonography

Standard transthoracic echocardiographic examination was carried out by the same expert in a dimly light room using a Vivid e cardiovascular ultrasound system (General Electric, Milwaukee, Wisconsin, USA) equipped with a 2.0–3.6 MHz (harmonics) phased-array transducer. The two-dimensional guided M-mode echocardiographic study of the left ventricle was performed at the parasternal long-axis view, and left ventricular end-systolic and end-diastolic dimensions, as well as posterior wall and septal thicknesses, were measured as the mean from five consecutive cardiac cycles, according to current guidelines [20]. Reliability of the echocardiographic measurement of left ventricular mass has been demonstrated in previous studies [21].

Left ventricular mass was calculated with the method of Devereux *et al.* [22]

$$\text{left ventricular mass} = 0.8 \times (1.04 \times [(\text{LVID} + \text{VST} + \text{PWT})^3 - \text{LVID}^3]) + 0.6$$

where LVID is left ventricular internal diameter, VST the ventricular septal thickness and PWT posterior wall thickness. Left ventricular mass was indexed both for BSA and height$^{2.7}$. LVH was defined as left ventricular mass indexed for BSA 125 g/m^2 or more in men and 110 g/m^2 or more in women [23] or left ventricular mass indexed for height$^{2.7}$ 49 g/m$^{2.7}$ or more in men and 45 g/m$^{2.7}$ or more in women [20,24].

Statistical analysis

Continuous variables that followed a normal distribution are presented as mean ± SD. Categorical variables are presented as percentages. The *t*-test was used for comparisons between means of normally distributed continuous variables. Differences between categorical variables were tested by forming contingency tables and performing χ^2-tests. Sensitivity of ECG criteria, at specific specificity to that of Framingham, was calculated as the ratio of true positive individuals, using echocardiographic LVH (based on indexation either for BSA or height$^{2.7}$) as the gold standard. Comparison of sensitivities of the same test between young and older aged groups were evaluated using the Pearson's χ^2-test, whereas the sensitivities of different tests of the same individuals were compared using paired χ^2-test (McNemar). Logistic regression analyses were performed in order to examine the association between each ECG criterion and left ventricular hypertrophy (on the basis of indexation either for BSA or height$^{2.7}$) after adjustment for age, sex, BMI and hypertension. Because ECG variables (except from the Framingham criterion) lie on a continuous scale, an assessment of the value of the tests was also made through the analysis of receiver-operating characteristic (ROC) curves, which are independent of the choice of a particular partition value. The areas under the ROC curves of the various ECG criteria were compared using the *Z*-test. All reported *P* values were based on two-sided hypotheses. All statistical calculations were performed using SPSS software (version 18.0; SPSS Inc., Chicago, Illinois, USA).

Results

Elderly participants had lower BMI (by 0.9 kg/m^2), diastolic blood pressure (by 1.9 mmHg) and increased waist circumference (by 2.8 cm), systolic blood pressure (by 10.1 mmHg) and pulse pressure (by 11 mmHg), as compared with middle-aged participants (Table 1). In addition, elderly individuals were less frequently smokers (by 23.9%, $P < 0.001$) and exhibited higher prevalence of hypertension (by 35.6%), diabetes (by 9%) and LVH defined either according to indexation for BSA (22.2 vs. 7.5%, $P < 0.001$) or based on indexation for height$^{2.7}$ (30.8 vs. 11.5%, $P < 0.001$) (Table 1). As regards LVH detected by ECG, the prevalence was higher in elderly participants than in middle-aged participants using Sokolow–Lyon voltage and product, Cornell voltage and product as well as Framingham criteria, whereas no difference was observed using Gubner and Lewis criteria (Table 1). When ECG criteria as continuous parameters were compared between age groups, Cornell voltage and product, as well as Lewis voltage were higher in elderly individuals than in middle-aged ones, after

Table 1 Clinical, electrocardiographic and echocardiographic characteristics of the study's samples

Parameter	Age <65 years ($n = 570$)	Age ≥65 years ($n = 507$)	*P*
Age (years)	53.7 ± 7.3	75.1 ± 6.3	<0.001
Sex (male) (%)	43.9	45.7	0.55
BMI (kg/m^2)	29.0 ± 5.1	28.1 ± 4.6	0.005
Waist (cm)	100.2 ± 14.7	103 ± 12.4	0.001
Hypertension (%)	27.3	62.9	<0.001
Diabetes (%)	12.3	21.3	<0.001
Current smokers (%)	41.8	17.9	<0.001
Dyslipidemia (%)	39.2	39.5	0.93
Office SBP (mmHg)	134.9 ± 19.2	144.0 ± 20	<0.001
Office DBP (mmHg)	81.9 ± 10.4	80.0 ± 11.4	0.009
Office pulse pressure (mmHg)	53 ± 15.6	64 ± 17.3	<0.001
Office heart rate (beats/min)	67.8 ± 12.3	66.8 ± 14.3	0.29
LVMI^{BSA} (g/m^2)	86.8 ± 21.1	100.1 ± 25.6	<0.001
LVMI$^{height2.7}$ (g/m$^{2.7}$)	36.3 ± 8.9	42.4 ± 10.9	<0.001
LVH^{BSA} (%)	7.5	22.2	<0.001
LVH $^{height2.7}$ (%)	11.5	30.8	<0.001
QRS duration (ms)	90.7 ± 11.1	95.6 ± 19.1	<0.001
ECG-LVH (SL voltage) (%)	2.3	4.7	0.027
ECG-LVH (SL product) (%)	1.6	4.5	0.004
ECG-LVH (Cornell voltage) (%)	1.6	4.6	0.004
ECG-LVH (Cornell product) (%)	4.8	10.7	<0.001
ECG-LVH (Gubner) (%)	2.1	1.6	0.51
ECG-LVH (Lewis) (%)	10.4	11.4	0.61
ECG-LVH (Framingham) (%)	6.8	10.3	0.043

BP, blood pressure; BSA, body surface area; ECG, electrocardiographic; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; SL, Sokolow–Lyon.

Table 2 Comparison of electrocardiographic criteria of the study population according to age after adjustment for sex, BMI and left ventricular mass index indexed either for body surface area or for height$^{2.7}$

Parameter	Age <65 years ($n=570$)	Age ≥65 years ($n=507$)	P	P^a	P^b
SL voltage	19.8 (16.1–24)	19.4 (15.5–24.6)	0.658	0.70	0.68
SL product	1780 (1417.8–2210.8)	1849.5 (1441.2–2261.6)	0.223	0.98	0.99
Cornell voltage	11.65 ± 4.8	13.0 ± 6.1	<0.001	0.01	0.04
Cornell product	1469.1 ± 572	1658.6 ± 759	<0.001	0.01	0.002
Gubner	10.6 ± 5.6	11.4 ± 5.4	0.02	0.26	0.34
Lewis voltage	6.84 (2.03–12.47)	8.93 (4.49–13.47)	<0.001	0.005	0.009

LVMI, left ventricular mass index; BSA, body surface area; SL, Sokolow–Lyon. [a] After adjustment for sex, BMI and LVMI^{BSA}. [b] After adjustment for sex, BMI and LVMI$^{height2.7}$.

adjustment for sex, BMI and left ventricular mass indexed either for BSA or for height$^{2.7}$ (Table 2).

Sensitivities of the studied ECG at fixed specificities to that of the Framingham criteria, for the detection of LVH (using both indexation for BSA and height$^{2.7}$) according to age, are presented in Table 3. The Framingham criteria had in hierarchical order the highest sensitivity among the elderly individuals when LVH was indexed either for BSA or height$^{2.7}$ (18.4 and 16.7%, respectively). Moreover, Sokolow–Lyon product and Framingham criteria had significantly greater sensitivities compared only with Lewis voltage and Gubner criteria when LVH was indexed for BSA in elderly participants. When LVH was indexed for height$^{2.7}$, the sensitivity of Framingham criteria was significantly higher compared with other examined ECG criteria in elderly individuals. In middle-aged participants, Cornell voltage and product criteria provided the highest sensitivities, both hierarchically and by using paired χ^2-test (McNemar), when LVH was indexed for BSA (19.0 and 23.8%, respectively) or height$^{2.7}$ (17.2 and 20.3%, respectively). When LVH was indexed for BSA, Sokolow–Lyon product, Lewis voltage and Gubner and Framingham criteria had higher sensitivities in elderly individuals compared with middle-aged individuals, whereas Cornell product criterion had higher sensitivity in middle-aged participants compared with the elderly ones. When LVH was indexed for height$^{2.7}$, Sokolow–Lyon voltage, its product and Framingham criteria had higher sensitivities in elderly individuals compared with middle-aged ones, whereas Cornell voltage and product criteria provided the greater sensitivities in middle-aged participants.

The performance of ECG LVH criteria was also compared between middle-aged and elderly individuals according to BMI status (i.e. normal weight, overweight and obese) (Table 4). When LVH was indexed for BSA, Sokolow–Lyon voltage, Cornell voltage and product, Lewis voltage and Gubner criteria provided significantly higher sensitivities in normal-weight middle-aged individuals compared with elderly ones, whereas Lewis voltage, Gubner and Framingham criteria had higher sensitivities in obese elderly participants compared with their middle-aged counterparts. When LVH was indexed for height$^{2.7}$, Cornell voltage and product had significantly higher sensitivities in obese middle-aged indivuals compared with elderly ones, whereas Framingham criteria provided higher sensitivity in obese elderly compared with middle-aged participants. Notably, performance could not be tested in normal-weight young individuals, as none of them fulfilled Framingham criteria.

Table 3 Sensitivities at matched specificity to that of Framingham criteria of the electrocardiographic criteria studied for the detection of left ventricular hypertrophy (indexed either for body surface area or height$^{2.7}$) according to age

	Age <65 years ($n=570$)		Age ≥65 years ($n=507$)		
LVM indexed for BSA	Sensitivity at specificity 93.4% (%)	Cutoff value	Sensitivity at specificity 91.9% (%)	Cutoff value	P
SL voltage	12.2	30.2	15.5	30.2	0.13
SL product	9.8	2810	18.4	2875	0.0001
Cornell voltage	19.0	18.68	17.6	19.84	0.60
Cornell product	23.8	2260	17.6	2450	0.01
Gubner	4.8	20.66	13.6	18.75	<0.0001
Lewis voltage	7.1	18.6	12.6	17.05	0.003
Framingham	7.1	NA	18.4	NA	<0.0001
LVM indexed for height$^{2.7}$	Sensitivity at specificity 93.1% (%)	Cutoff value	Sensitivity at specificity 92.4% (%)	Cutoff value	P
SL voltage	4.8	30.4	11.2	30.6	0.0001
SL product	6.3	2810	11.2	2990	0.005
Cornell voltage	17.2	18.6	8.4	20.48	<0.0001
Cornell product	20.3	2244	12.6	2500	0.0009
Gubner	7.8	20.23	10.4	19.06	0.16
Lewis voltage	7.8	18.45	9.7	17.68	0.31
Framingham	4.7	NA	16.7	NA	<0.0001

BSA, body surface area; LVM, left ventricular mass; SL, Sokolow–Lyon.

Table 4 Sensitivities at matched specificity to that of Framingham criteria of the electrocardiographic criteria studied for the detection of left ventricular hypertrophy (indexed either for body surface area or height$^{2.7}$) according to age and BMI status

	BMI <25 kg/m^2			BMI 25–30 kg/m^2			BMI >30 kg/m^2		
LVM indexed for BSA	<65 years ($n=117$) Sensitivity at specificity 92.7% (%)	>65 years ($n=121$) Sensitivity at specificity 87% (%)	*P*	<65 years ($n=249$) Sensitivity at specificity 93.2% (%)	>65 years ($n=235$) Sensitivity at specificity 92.3% (%)	*P*	<65 years ($n=211$) Sensitivity at specificity 94% (%)	>65 years ($n=151$) Sensitivity at specificity 95.4% (%)	*P*
SL voltage	25	14.3	0.05	26.7	29.4	0.57	18.2	3.2	<0.001
SL product	25	19	0.33	20	21.6	0.74	9.1	9.7	0.99
Cornell voltage	75	23.8	<0.001	20	13	0.05	13	10	0.47
Cornell product	75	28.6	<0.001	13.3	15.7	0.53	13	10	0.47
Gubner	25	9.5	0.002	13.3	5.9	0.009	0	16.1	<0.001
Lewis voltage	25	9.5	0.002	13.3	11.8	0.71	0	16.1	<0.001
Framingham	25	23.8	0.94	13.3	19.6	0.08	0	12.9	<0.001
LVM indexed for height$^{2.7}$	NA <65 years ($n=117$)	>65 years ($n=121$) Sensitivity at specificity 87.1% (%)	*P*	<65 years ($n=249$) Sensitivity at specificity 93.2% (%)	>65 years ($n=235$) Sensitivity at specificity 93% (%)	*P*	<65 years ($n=211$) Sensitivity at specificity 93.6% (%)	>65 years ($n=151$) Sensitivity at specificity 97.4% (%)	*P*
SL voltage	NA	15–20	NA	21.4	23	0.75	8.2	4.8	0.29
SL product	NA	15	NA	28.6	14.8	<0.001	4.1	8.1	0.16
Cornell voltage	NA	15	NA	28.6	6.5	<0.001	10	1.6	0.002
Cornell product	NA	25	NA	21,4	12.9	0.018	12	3.3	0.005
Gubner	NA	5	NA	7.1	4.8	0.38	4	6.5	0.40
Lewis voltage	NA	5	NA	7.1	4.8	0.38	4	8.1	0.15
Framingham	NA	25	NA	14.3	19.4	0.16	2	11.3	<0.001

BSA, body surface area; LVM, left ventricular mass; SL, Sokolow–Lyon.

Furthermore, in elderly participants, Sokolow–Lyon product, Cornell voltage and product and Framingham criteria were associated with echocardiographic detection of LVH (defined on the basis of indexation for BSA). However, when the above ECG criteria were adjusted for age, sex, BMI and hypertension, Sokolow–Lyon product lost its significance. When similar models were performed for each ECG criterion using the threshold values that match the specificity of Framingham criteria, Sokolow–Lyon voltage and product were additionally associated with echocardiographic detection of LVH, after making various adjustments. As regards middle-aged individuals, Cornell product was the only ECG criterion that was associated with echocardiographic detection of LVH, even after various adjustments. After applying similar models for each ECG criterion using the threshold values that match the specificity of Framingham criteria, Cornell voltage and product were associated with echocardiographic LVH detection (Table 5). As regards the other variables, age and the presence of hypertension were associated with echocardiographic LVH detection (defined on the basis of indexation for BSA) in elderly individuals, whereas age, apart from ECG criteria, was the only independent predictor of LVH indexed for BSA (data not shown in text or tables).

As regards the associations of ECG criteria with echocardiographic detection of LVH (defined on the basis of indexation for height$^{2.7}$), only Sokolow–Lyon and Framingham criteria were related to LVH in elderly participants. After applying similar models using the threshold values that match the specificity of Framingham criteria, none of the rest criteria were associated with echocardiographic LVH detection. In contrast, Cornell product was the only ECG criterion that was associated with echocardiographic detection of LVH in middle-aged individuals even when the threshold values that match the specificity of Framingham criteria were used (Table 6). As regards the other variables, age and BMI were associated with echocardiographic detection of LVH (indexed for height$^{2.7}$) in middle-aged individuals, whereas age, female sex, BMI and the presence of hypertension were independent predictors in elderly individuals (data not shown in text or tables).

In sensitivity analysis, all examined ECG criteria showed good discriminating ability as regards echocardiographic detection of LVH (defined on the basis of indexation for BSA) in elderly participants, whereas only Sokolow–Lyon product, Cornell voltage and product and Gubner voltage predicted echo-detected LVH in middle-aged individuals. Moreover, the overall performance of the Cornell voltage and its product was significantly better in middle-aged individuals (Table 7). In addition, when AUC curves of ECG criteria were compared within the same age group, the overall performance of Cornell voltage was better than that of other ECG criteria, except Cornell product, in middle-aged participants, whereas no significant difference was observed between ECG criteria in elderly individuals. In contrast, when LVH

Table 5 Results from logistic regression models examining the association between electrocardiographic criterion and echocardiographic detection of left ventricular hypertrophy (indexed for body surface area) before and after adjustment for age, sex, BMI and presence of hypertension in elderly and young individuals (matched or not to the Framingham criterion)

	<65 years				>65 years			
	Univariate OR (95% CI)	*P*	Multiadjusted OR (95% CI)	*P*	Univariate OR (95% CI)	*P*	Multiadjusted OR (95% CI)	*P*
SL voltage	1.247 (0.156–9.993)	0.83			2.261 (0.910–5.613)	0.07	2.010 (0.790–5.113)	0.14
SL Voltage (Framingham)	1.940 (0.715–5.264)	0.19			2.112 (1.098–4.063)	0.02	2.118 (1.069–4.194)	0.03
SL product	1.793 (0.215–14.935)	0.58			2.456 (0.976–6.181)	0.05	2.150 (0.834–5.545)	0.11
SL product (Framingham)	1.559 (0.524–4.639)	0.42			2.503 (1.343–4.665)	0.004	2.579 (1.338–4.971)	0.005
Cornell voltage	1.753 (0.211–14.592)	0.60			2.871 (1.174–7.018)	0.02	2.496 (1.007–6.238)	0.04
Cornell voltage (Framingham)	3.401 (1.458–7.934)	0.005	2.802 (1.169–6.719)	0.021	2.329 (1.243–4.365)	0.008	2.128 (1.120–4.043)	0.02
Cornell product	4.083 (1.543–10.805)	0.005	3.453 (1.286–9.269)	0.014	2.407 (1.280–4.526)	0.006	2.241 (1.163–4.316)	0.01
Cornell product (Framingham)	4.375 (1.984–9.647)	<0.001	3.979 (1.697–9.328)	0.001	2.407 (1.280–4.526)	0.006	2.241 (1.163–4.316)	0.01
Gubner	0.001	0.99			3.687 (0.906–15.005)	0.06	3.404 (0.811–14.297)	0.09
Gubner (Framingham)	0.723 (0.167–3.122)	0.66			1.778 (0.904–3.495)	0.09	1.581 (0.789–3.167)	0.19
Lewis voltage	1.792 (0.748–4.293)	0.19			1.404 (0.708–2.787)	0.33		
Lewis voltage (Framingham)	1.112 (0.748–4.293)	0.86			1.632 (0.818–3.258)	0.16		
Framingham	1.084 (0.318–3.618)	0.89			2.556 (1.372–4.762)	0.003	2.287 (1.197–4.371)	0.01

CI, confidence interval; OR, odds ratio; SL, Sokolow–Lyon.

was defined on the basis of indexation for height$^{2.7}$, only Cornell product and Gubner voltage predicted LVH detection in elderly participants at ROC curve analysis. In middle-aged individuals, Cornell voltage and product, as well as Gubner voltage predicted echo-detected LVH. When AUC curves of ECG criteria were compared on the basis of different age groups, the overall performance of the Cornell voltage and its product was again better in middle-aged individuals (Table 7). Furthermore, in middle-aged individuals, the performance of Cornell product was significantly better compared with other ECG criteria, except Cornell voltage, whereas in elderly ones, the performance of Cornell product was better only than that of Sokolow–Lyon voltage.

Discussion

In the present work, the different diagnostic performance of seven classic ECG criteria was exhibited for echocardiographic detection of LVH in middle-aged and elderly individuals. It was revealed that ageing process differentiates the value of established ECG criteria even after adjustment for sex, BMI and hypertension status. Thus, age should be taken into consideration for the selection of appropriate ECG criteria for LVH detection in the general population.

ECG, although it was introduced in clinical practice a century ago, still represents one of the most extensively used diagnostic tools in cardiovascular medicine and is a

Table 6 Results from logistic regression models examining the association between each electrocardiographic criterion and echocardiographic detection of left ventricular hypertrophy (indexed for height$^{2.7}$) before and after adjustment for age, sex, BMI and presence of hypertension in elderly and young individuals (matched or not to the Framingham criterion)

	<65 years				>65 years			
	Univariate OR (95% CI)	*P*	Multiadjusted OR (95% CI)	*P*	Univariate OR (95% CI)	*P*	Multiadjusted OR (95% CI)	*P*
SL voltage	0.769 (0.097–6.113)	0.80			2.600 (1.078–6.270)	0.03	3.248 (1.228–8.588)	0.01
SL voltage (Framingham)	1.501 (0.447–5.038)	0.51			1.434 (0.744–1.765)	0.28		
SL product	2.628 (0.519–13.313)	0.24			1.899 (0.769–4.689)	0.16	1.966 (0.733–5.274)	0.10
SL product (Framingham)	1.072 (0.367–3.134)	0.89			1.564 (0.804–3.044)	0.18		
Cornell voltage	2.591 (0.512–13.121)	0.25			1.431 (0.580–3.533)	0.43		
Cornell voltage (Framingham)	2.771 (1.326–5.791)	0.007	1.939 (0.825–4.556)	0.12	1.105 (0.540–2.269)	0.78		
Cornell product	4.534 (1.928–10.659)	0.001	2.554 (1.009–6.595)	0.04	1.569 (0.848–2.903)	0.15	1.093 (0.559–2.136)	0.79
Cornell product (Framingham)	3.404 (1.687–6.865)	0.001	2.333 (1.040–5.843)	0.04	1.734 (0.914–3.291)	0.09	1.146 (0.568–2.313)	0.70
Gubner	1.542 (0.330–7.200)	0.58			3.897 (0.919–16.531)	0.06	3.076 (0.678–13.964)	0.14
Gubner (Framingham)	1.168 (0.439–3.110)	0.75			1.351 (0.692–2.634)	0.37		
Lewis voltage	1.449 (0.668–3.143)	0.34			1.081 (0.562–2.076)	0.81		
Lewis voltage (Framingham)	1.132 (0.426–3.007)	0.80			1.305 (0.657–2.591)	0.44		
Framingham	0.601 (0.197–2.217)	0.50			2.424 (1.332–4.411)	0.004	2.742 (1.416–5.310)	0.003

OR, odds ratio; SL, Sokolow–Lyon.

Table 7 Areas under the curves as regards echocardiographic detection of left ventricular hypertrophy (based on indexation for body surface area) according to age

	<65 years			>65 years			
	AUC	SE	*P**	AUC	SE	*P**	*P***
LVM indexed for BSA							
Sokolow–Lyon	0.566	0.050	0.16	0.566	0.033	0.04	1.00
Sokolow–Lyon product	0.604	0.048	0.02	0.591	0.033	0.005	0.82
Cornell voltage	0.731	0.041	<0.001	0.572	0.033	0.02	0.002
Cornell product	0.710	0.040	<0.001	0.583	0.033	0.01	0.01
Gubner	0.597	0.044	0.03	0.586	0.033	0.007	0.84
Lewis voltage	0.578	0.044	0.09	0.564	0.031	0.04	0.79
LVM indexed for height$^{2.7}$							
Sokolow–Lyon	0.452	0.040	0.21	0.510	0.029	0.72	–
Sokolow–Lyon product	0.495	0.040	0.88	0.535	0.029	0.22	–
Cornell voltage	0.670	0.036	<0.001	0.541	0.029	0.16	0.005
Cornell product	0.710	0.032	<0.001	0.600	0.028	0.001	0.009
Gubner	0.576	0.037	0.04	0.574	0.027	0.01	0.96
Lewis voltage	0.567	0.036	0.08	0.547	0.028	0.10	0.66

AUC, area under the curve; BSA, body surface area; LVM, left ventricular mass; SE, standard deviation. * *P* values for testing the null hypothesis AUC = 0.500. ** *P* values for between-group comparisons.

powerful index for the risk assessment in the general population. Several studies have demonstrated the prognostic significance of LVH, detected by ECG, even irrespective of the presence of arterial hypertension [2–4,25]. In addition, strong evidence exists that favorable changes over time of ECG indexes of LVH are associated with a better prognosis in different populations [26,27]. Similarly, LVH regression is accompanied by improved prognosis in elderly population [28].

An inherent limitation of the ECG in detecting LVH is its dependence on fixed-voltage criteria, which can be substantially altered by extracardiac factors such as sex, age, weight and chest wall configuration [9]. With respect to sex, although sex differences have been taken into account in partition value selection, ECG criteria for LVH still have lower accuracy in women suggesting that factors other than left ventricular dimensions and body size may play a role in the observed differences in QRS voltages and durations between men and women [29]. Furthermore, obesity is associated with the presence of LVH and, conversely, with decreased sensitivity of the ECG for LVH due to attenuating effects on QRS amplitudes [30]. In order to correct for the effects of sex and obesity, it has been shown that use of simple voltage–QRS duration products or even better calculation of the time–voltage area of the QRS minimizes the above effects on the accuracy of the ECG for LVH [19,31].

In the present study, a distinction in the diagnostic ability of examined ECG criteria was exhibited according to age. In particular, not only the prevalence of LVH based on different ECG criteria (i.e. Sokolow–Lyon voltage and product, Cornell voltage and product and Framingham criteria) was higher in elderly than in middle-aged individuals, but also Cornell voltage, its product and Lewis voltage (examined as continuous parameters) were significantly higher in the former group even after adjustment for sex, BMI and left ventricular mass indexed either for BSA or for height$^{2.7}$. In addition, the performance of examined ECG criteria for echo-LVH detection was different between young and old cohorts and was related to the selected indexation of left ventricular mass. In general, Sokolow–Lyon product and Framingham criteria provided significantly higher sensitivities in elderly individuals than in middle-aged ones, whereas Cornell product had larger sensitivity in the latter group irrespective of left ventricular mass indexation. Notably, these differences in the performance of the various ECG criteria between young and old cohorts exist also in separate BMI categories with higher sensitivities in normal-weight middle-aged individuals compared with elderly ones and the opposite in obese elderly participants compared with their middle-aged counterparts.

Similar results were derived from logistic analyses, wherein Cornell product has proven to be the only ECG criterion that can predict the presence of LVH (based on indexation either for height$^{2.7}$ or for BSA) in middle-aged individuals (aged <65 years), whereas predictive value of ECG criteria was related to the selected indexation of left ventricular mass in elderly individuals. In particular, when left ventricular mass was indexed for BSA, use of Cornell voltage, its product and Framingham criteria were associated with echo-LVH detection. Framingham criteria, along with Sokolow–Lyon voltage, were independently associated with LVH detection when left ventricular mass was indexed for height$^{2.7}$. When similar logistic models were performed for each ECG criterion using the threshold values that match the specificity of Framingham criteria, the discrimination in the diagnostic ability of ECG criteria for diagnosing echo-LVH between young and old cohorts is being reinforced.

Correcting left ventricular mass by BSA is an approach that allows more obese individuals to attain higher levels of left ventricular mass before achieving threshold levels for LVH, resulting in an attenuation of the relation of

obesity to anatomic hypertrophy [9]. The discrepancy of the ability of ECG criteria to detect LVH in elderly individuals according to the method of indexing left ventricular mass is in lines with previous reports concerning the association of increased BMI with Cornell voltage and product as well as of Sokolow–Lyon voltage with leaner body builds [7,8]. In general, the observed higher sensitivities of all examined criteria (with the exception of Cornell voltage and its product) in elderly individuals are in concordance with current knowledge, whereas the sensitivities of the same criteria in younger participants appear to be quite low [9]. Beyond the distinct diagnostic performance of ECG criteria based on age status, our results also exhibit the superiority of Cornell voltage and its product over the other examined ECG criteria among middle-aged individuals, whereas in elderly ones, the performance of Cornell product (when left ventricular mass was indexed for height$^{2.7}$) was better only than that of Sokolow–Lyon voltage. Notably, in a small sample size study that used cardiovascular magnetic resonance as a tool for defining left ventricular hypertrophy in young fit men, Sokolow–Lyon voltage demonstrated a better correlation than Cornell voltage and product with left ventricular mass [32]. However, in this study, LVH was defined as left ventricular mass indexed for BSA more than 93 g/m^2, whereas we should not overlook that ECG criteria were developed using echocardiography as the gold standard.

According to our findings, age dependence of ECG LVH criteria is not a function of age-related differences in left ventricular mass and therefore use of common criteria for ECG detection of LVH in young and old individuals constitutes a major limitation. The development of age-specific ECG criteria would seem indicated both on the basis of these results and knowledge of the substantial differences in normal R and S wave voltage, according to age [9]. Despite the previously described attenuation of QRS voltage with advancing age [33], there was a trend toward increasing sensitivity of the ECG for LVH in elderly individuals. This paradox might be attributed to the increasing prevalence of echocardiographic LVH with advancing age as well as to the presence of more severe forms of LVH in the elderly [9].

The present study might underestimate the sensitivity of the ECG because it is based on a primarily healthy population from which potential cases of LVH were excluded (e.g. bundle branch block, myocardial infarction and technically suboptimal echocardiograms). Moreover, our findings were obtained in a 100% white cohort and cannot be extended to other racial groups.

Clinical application

Electrocardiography is currently recommended as the first-line method for detection of LVH in the general population [1,23]. Development of new specific criteria according to age or selection of the ECG criteria with the better diagnostic performance in different age groups (as these are employed in the present study), such as Framingham criteria in elderly individuals and Cornell product in younger ones, may be suggested. It should also be taken into consideration that indexation of left ventricular mass differentiates the diagnostic ability of ECG criteria especially in older individuals. Increasing the use of more sophisticated computer-assisted techniques for ECG analysis and the availability of echocardiographically estimated left ventricular mass to serve as a standard will help in the creation of improved methods for ECG detection of LVH.

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