

ECG left ventricular hypertrophy as a risk predictor of sudden cardiac death

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ABSTRACT

Background: Electrocardiographic (ECG) left ventricular hypertrophy (LVH) is an established risk factor for cardiovascular events. However, limited data is available on the prognostic values of different ECG LVH criteria specifically to sudden cardiac death (SCD). Our goal was to assess relationships of different ECG LVH criteria to SCD.

Methods: Three traditional and clinically useful (Sokolow–Lyon, Cornell, R_{aVL}) and a recently proposed (Peguero–Lo Presti) ECG LVH voltage criteria were measured in 5730 subjects in the Health 2000 Survey, a national general population cohort study. Relationships between LVH criteria, as well as their selected composites, to SCD were analyzed with Cox regression models. In addition, population-attributable fractions for LVH criteria were calculated. **Results:** After a mean follow-up of 12.5 ± 2.2 years, 134 SCDs had occurred. When used as continuous variables, all LVH criteria except for R_{aVL} were associated with SCD in multivariable analyses. When single LVH criteria were used as dichotomous variables, only Cornell was significant after adjustments. The dichotomous composite of Sokolow–Lyon and Cornell was also significant after adjustments (hazard ratio for SCD 1.82, 95% confidence interval 1.20–2.70, $P = 0.006$) and was the only LVH measure that showed statistically significant population-attributable fraction (11.0%, 95% confidence interval 1.9–19.2%, $P = 0.019$).

Conclusions: Sokolow–Lyon, Cornell, and Peguero–Lo Presti ECG, but not R_{aVL} voltage, are associated with SCD risk as continuous ECG voltage LVH variables. When SCD risk assessment/adjustment is performed using a dichotomous ECG LVH measure, composite of Sokolow–Lyon and Cornell voltages is the preferred option.

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1. Introduction

Electrocardiographic (ECG) left ventricular hypertrophy (LVH) is an established risk factor for cardiovascular events [1–6]. ECG LVH is also associated specifically with increased risk for sudden cardiac death (SCD) [7,8], which is among the leading causes of death worldwide [9]. Association between ECG LVH and SCD remains significant also

after adjusting for anatomic measures of LVH (echocardiography [echo], magnetic resonance imaging) [8,10,11], indicating that adverse electrical remodelling per se conveys additional prognostic value.

ECG is widely used and a routine test, among others, in all individuals with hypertension. Because of its potential implications, searching for signs of LVH is one of the key steps in the ECG assessment. Several ECG LVH criteria have been developed, but their prognostic values have been compared in only a few studies [6,12–14] and there is even more limited data comparing the prognostic values of different LVH criteria specifically to SCD. The present study was performed to compare the relationships of three traditional and clinically useful (Sokolow–Lyon, Cornell, R_{aVL}) and one recently proposed (Peguero–Lo Presti) LVH voltage criteria, as well as their selected composites, to SCD in the general population.

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¹ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

2. Methods

2.1. Study population, electrocardiography

The Health 2000 Survey was a prospective, epidemiologic survey that was conducted in Finland between 2000 and 2001. The survey population ($n = 8028$) was a two-stage stratified cluster sample drawn from the population register and was representative of the entire Finnish adult (≥ 30 years) general population. Survey procedures consisted of a structured interview, a comprehensive health examination with questionnaires, measurements, and a physician's clinical examination. Survey was highly successful with almost 85% of the recruited subjects attending the health examination. Detailed Health 2000 Survey methodology report is available online [15]. Survey was conducted according to the recommendations of the Declaration of Helsinki, and was approved by the Institutional Ethics Committee and by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital District. Subjects gave written informed consent.

Digital 12-lead ECGs were recorded at the Health 2000 Survey baseline with Marquette MAC 5000 (GE Marquette Medical Systems, Milwaukee, WI). ECGs were available from 6305 subjects. Subject with low ECG quality, complete left/right bundle branch block, or incomplete covariate data were excluded. In addition, subjects aged >80 years at the survey baseline were excluded from adjudication of the cause of death because of the potential adjudication imprecision in this age group (due to high comorbidity rate and low autopsy rate). After exclusions, a total of 5730 Health 2000 Survey subjects were available for the present study. ECG measurements were performed on screen in a blinded fashion by a single observer with methods described previously [16].

ECG LVH voltage amplitude criteria known as Sokolow–Lyon, Cornell, R_{AVL} , and Peguero–Lo Presti were selected for the present study. Sokolow–Lyon amplitude was calculated as $S_{V1} + R_{V5}$ or $S_{V1} + R_{V6}$ (whichever was greater); dichotomous cutoff for LVH was ≥ 3.5 mV [17]. Cornell amplitude was calculated as $S_{V3} + R_{AVL}$; dichotomous cutoff for LVH was >2.0 mV in women and >2.8 mV in men [18]. R_{AVL} amplitude was measured as R_{AVL} ; dichotomous cutoff for LVH was >1.1 mV [19]. Peguero–Lo Presti amplitude was calculated as the deepest S among all 12 leads + S_{V4} ; dichotomous cutoff for LVH was ≥ 2.3 mV in women and ≥ 2.8 mV in men [20].

2.2. Follow-up and adjudication of the cause of death

Follow-up was from the Health 2000 Survey baseline until December 31, 2013. Adjudication of the cause of death was performed blinded to ECG data as described previously [21]. Briefly, adjudication was based on national registers of drug reimbursement, hospital admission and discharge diagnoses, and causes of deaths. Extensive national registers are maintained in Finland, and data on all deaths of Finnish citizens are collected systematically. Out-of-hospital deaths and deaths within 10 days of hospitalization were considered eligible for the SCD adjudication. Data from registers were analyzed independently by two physicians and classified deaths as probable, possible, unlikely SCD, and unknown cause of death. Deaths in which a cardiac cause was the immediate or underlying cause of death and the death was not known to be unrelated to arrhythmia were defined as probable SCDs. Deaths in which the immediate or underlying cause of death was noncardiac, but cardiac disease was present and could reasonably have contributed to arrhythmia based on mechanism (e.g., unexpected death due to aspiration in a patient with a prior myocardial infarction), or deaths that could have been arrhythmic based on circumstances (e.g., death of a driver in a motor vehicle crash, death while swimming) were defined as possible SCDs. Deaths in which there was an explained medical cause of death unrelated to cardiac disease (e.g., cancer, massive blood loss, sepsis, pulmonary embolism, stroke) or a cardiac cause of death known to be nonsudden or unrelated to lethal arrhythmia (e.g., myocardial rupture after myocardial infarction, endocarditis) were defined as unlikely SCDs. Deaths with insufficient data were defined as deaths with unknown cause. In case of disagreement on the cause of death, two additional independent physicians reviewed the case, and final decision was constituted by consensus. Autopsies were performed in 67.2% of SCDs. In the present study, probable and possible SCDs were pooled in the analyses and were classified as SCDs.

2.3. Statistical analysis

Analyses were performed with R Statistics (version 3.4.0, The R Foundation for Statistical Computing, Vienna, Austria; used for Cox regression analyses and spline figures), STATA 13.0 (StataCorp, College Station, TX; used to calculate population-attributable fractions), and SPSS (version 21, IBM, Armonk, NY; used for all other analyses). Values are given as mean \pm SD for continuous variables, and percentages and numbers for categorical variables. Bivariate correlations between continuous LVH variables were tested with Pearson's test. Firth's penalized maximum likelihood bias reduction method for Cox regression (R package: *coxphf*) was used to obtain the hazard ratios in the survival analyses [22,23]. Concordance probability estimate was used to compare the predictive accuracy of the continuous LVH variables for SCD (R package: *CPE*) [24]. The validity of proportional hazards assumption was verified graphically with partial residual plots (continuous variables) and survival probability plots (dichotomous variables). LVH variables were used both as continuous and dichotomous. Selected composite LVH criteria were also used. Gender, study baseline age, body mass index, heart rate, current smoking (yes/no), arterial hypertension (yes/no), previous myocardial infarction (yes/no), and diabetes mellitus (yes/no) were used as covariates in multivariable analyses. One LVH variable was used in the multivariable models at a time. Definitions for arterial hypertension, previous myocardial infarction, and diabetes mellitus have been published [16]. Interaction term (gender \times LVH criterion) was tested in the same model together with main effects

(i.e., LVH criterion, gender, all covariates). Cox models with penalized splines were used to assess and plot the relationship of continuous LVH variables to SCD risk. Population-attributable fractions were calculated for dichotomous ECG LVH criteria and selected composite criteria from models including all covariates with a previously described method [25] and implemented as the STATA module *punafcc*. Population-attributable fraction reflects the proportion of events that can be attributed to a given risk marker or the percentage of the cases that would be prevented if a specific exposure were to be eliminated from the population. Two-tailed $P < 0.05$ was considered significant for all analyses.

3. Results

After a mean follow-up of 12.5 ± 2.2 years, 134 SCDs had occurred. Baseline characteristics are shown in Table 1. Clinical variables showed that, compared with subjects without SCD, subjects with SCD were older, more often males, had higher body mass index and heart rate, were more often smokers, had more often hypertension, previous myocardial infarction, and diabetes. ECG variables showed that, compared with subjects without SCD, subjects with SCD had longer QRS and QTc durations, higher voltages, and had more often LVH. Depending on the criteria, LVH prevalence varied markedly. Peguero–Lo Presti showed the highest prevalence, and was fulfilled in $\approx 25\%$ of all study subjects.

Hazard ratios of SCD for continuous LVH criteria are shown in Table 2. In multivariable adjusted models, all criteria except for R_{AVL} remained significantly associated with SCD. As an example, one millimeter increase in Cornell was associated with a 1.04-fold (95% confidence interval [CI] 1.01–1.07, $P = 0.008$) risk of SCD. Concordance probability estimate was highest, 0.63 (95% CI 0.60–0.66), for Cornell, while it was 0.56 (95% CI 0.52–0.60) for Sokolow–Lyon, 0.60 (95% CI 0.57–0.63) for Peguero–Lo Presti, and 0.59 (95% CI 0.56–0.62) for R_{AVL} . When continuous ECG LVH variables were used to test gender–LVH interaction terms in multivariable Cox models, interactions were not found ($P > 0.114$ for all gender–LVH interaction terms). Adjusted, continuous associations between SCD risk and the three voltage criteria that were significantly associated with SCD in adjusted models are shown in Supplementary Fig. 1 (Panels A–C). Compared to Sokolow–Lyon and Peguero–Lo Presti, increase in Cornell was associated with a more pronounced SCD risk increase.

Hazard ratios of SCD for dichotomous LVH criteria are shown in Table 3. Of the single criteria, only Cornell remained significant after adjustments. Of the composite criteria, only composite of Sokolow–Lyon and Cornell remained significant after adjustments. Overlap of dichotomous Sokolow–Lyon, Cornell, and Peguero–Lo Presti criteria is shown in Fig. 1. Overlap between Sokolow–Lyon and Cornell was relatively small. By contrast, Cornell became mostly embedded by Peguero–Lo Presti. Bivariate correlation between continuous Cornell and Peguero–Lo Presti criteria was high ($r = 0.71$, $P < 0.001$), whereas other correlations were lower (Sokolow–Lyon vs. Cornell, $r = 0.20$, $P < 0.001$; Sokolow–Lyon vs. Peguero–Lo Presti, $r = 0.21$, $P < 0.001$). When population-attributable fractions were calculated for dichotomous ECG LVH criteria and selected composite criteria, population-attributable fraction was 4.8% (95% CI -1.9 –11.2%, $P = 0.158$) for Sokolow–Lyon, 6.1% (95% CI -0.2 –12.1%, $P = 0.059$) for Cornell, 9.5% (95% CI -2.3 –20.0%, $P = 0.111$) for Peguero–Lo Presti, 2.0% (95% CI -3.1 –6.8%, $P = 0.442$) for R_{AVL} , 11.0% (95% CI 1.9–19.2%, $P = 0.019$) for composite of Sokolow–Lyon and Cornell, 11.5% (95% CI -2.1 –23.3%, $P = 0.095$) for composite of Sokolow–Lyon and Peguero–Lo Presti, and 8.3% (95% CI -3.7 –18.9%, $P = 0.168$) for composite of Cornell and Peguero–Lo Presti. Thus, only composite of Sokolow–Lyon and Cornell was statistically significant.

4. Discussion

4.1. Main findings

Our study in white general population showed that Sokolow–Lyon, Cornell, and Peguero–Lo Presti ECG voltage LVH criteria provided prognostic information on SCD risk as continuous variables even after adjusting for

Table 1
Baseline characteristics of the study subjects.

	No SCD (n = 5596)	SCD (n = 134)	P value
Clinical variables			
Age, years	51 ± 13	62 ± 10	<0.001
Male gender, %(n)	46(2547)	78(104)	<0.001
Body mass index, kg/m ²	27 ± 5	28 ± 5	0.008
Heart rate, beats per minute	63 ± 11	68 ± 14	<0.001
Current smoking, %(n)	22(1248)	43(58)	<0.001
Arterial hypertension, %(n)	45(2503)	75(100)	<0.001
Previous myocardial infarction, %(n)	2(103)	19(25)	<0.001
Diabetes mellitus, %(n)	5(290)	15(20)	<0.001
ECG variables			
QRS duration, ms	93 ± 9	98 ± 14	<0.001
QTc duration, ms ^a	409 ± 25	423 ± 29	<0.001
Sokolow–Lyon voltage, mV ^b	2.5 ± 0.7	2.7 ± 0.9	0.022
Cornell voltage, mV ^c	1.5 ± 0.6	1.8 ± 0.7	<0.001
Peguero–Lo Presti voltage, mV ^d	2.1 ± 0.7	2.5 ± 1.0	<0.001
R _{aVL} voltage, mV ^e	0.4 ± 0.3	0.6 ± 0.3	<0.001
ECG LVH by voltage criteria			
Sokolow–Lyon, %(n) ^f	9(482)	14(19)	0.030
Cornell, %(n) ^g	7(386)	13(17)	0.016
Peguero–Lo Presti, %(n) ^h	25(1392)	34(45)	0.026
R _{aVL} , %(n) ⁱ	4(215)	8(11)	0.021

Values are given as mean ± SD for continuous variables, and percentages and numbers for categorical variables.

LVH indicates left ventricular hypertrophy; SCD, sudden cardiac death.

^a The maximum QT interval of all leads with Bazett's formula adjustment for heart rate.

^b S_{V1} + R_{V5} or S_{V1} + R_{V6} (whichever was greater).

^c S_{V3} + R_{aVL}.

^d S_{Deepest} + S_{V4}.

^e R_{aVL}.

^f S_{V1} + R_{V5} or S_{V1} + R_{V6} (whichever was greater) ≥ 3.5 mV.

^g S_{V3} + R_{aVL} > 2.0 mV (women), > 2.8 mV (men).

^h S_{Deepest} + S_{V4} ≥ 2.3 mV (women), ≥ 2.8 mV (men).

ⁱ R_{aVL} > 1.1 mV.

several risk factors, whereas R_{aVL} was not associated with SCD after adjustments. When single LVH criteria were used as dichotomous variables, only Cornell was significant after adjustments. The dichotomous composite of Sokolow–Lyon and Cornell was also significantly associated with SCD after adjustments and was the only LVH measure that showed statistically significant population-attributable fraction.

4.2. LVH as a modifier of SCD risk

Myocardial ischemia is central in SCD, and coronary disease has been estimated to account for ≈80% all SCDs [26]. The second most common etiology of SCD, with a proportion of 10–15%, is (hypertrophic and

dilated) cardiomyopathy [26]. Hypertrophied myocardium predisposes to malignant arrhythmias by various mechanisms. These include, among others, reduced coronary blood flow predisposing to ischemia; cardiomyocyte loss and increased fibrosis creating a substrate for electric reentry and increased dispersion of repolarization [27]; arrhythmogenic alterations in cardiomyocyte ion channel expression and function predisposing to afterdepolarizations [28]. In hypertrophic cardiomyopathy, SCD risk has been reported to increase with the maximum left ventricular (LV) wall thickness [29]. Importantly, even in the absence of coronary disease or cardiomyopathy, increase in echo LV mass already within normal to mildly elevated range is linearly associated with adverse changes in ECG repolarization measures [30]. Thus, in the presence of ischemia, SCD risk may be assumed to be modified, in addition to other factors (e.g., electrolyte disturbances, genetic factors), by the degree of pathological myocardial hypertrophy.

4.3. ECG LVH and anatomic LVH in relation to SCD risk

Increase in risk-factor adjusted hazard ratio for SCD has been reported in the general population both for ECG LVH [7,8,31] and echo LVH [32–35]. Of note, LVH diagnosed by ECG vs. echo or magnetic resonance imaging contains distinct prognostic value for SCD risk [8,10,11], showing that ECG LVH is a marker of adverse electric remodelling even in the absence of anatomic hypertrophy. Simulation studies indicate that electric properties of the heart, especially slowed electric conduction velocity (fibrosis), may also increase ECG QRS voltages and may thus explain why many subjects with ECG LVH do not present with anatomic LVH (and vice versa), and why both ECG LVH and anatomic LVH convey prognostic value independent of each other [36]. Highlighting the importance of LVH, echo LVH has been reported as at least equivalent to severely decreased LV ejection fraction as a predictor of mortality or SCD [37]. Recently, in an epidemiologic case-control study, the Oregon Sudden Unexpected Death Study (Oregon SUDS), an ECG risk score which included ECG LVH (composite of Sokolow–Lyon and Cornell voltages) as a score component resulted in significant additive improvement above LV ejection fraction in SCD risk estimation [38].

Despite the confirmed link between LVH and SCD, little has been known about the prognostic values of different ECG LVH criteria specifically to SCD. The prognostic values of different LVH criteria for incident cardiovascular events vary [14], suggesting that some criteria may outperform others in stratifying specifically SCD risk. Previous studies showing the relationship between ECG LVH and SCD have mainly reported one single LVH measure. In one of the earliest studies, Minnesota code 3–1 was used [31], whereas in another report from the 1970's the definition for ECG LVH was not specified [7]. In the Oregon SUDS, Sokolow–Lyon voltage was used as a dichotomous ECG LVH variable and was associated with sudden cardiac arrest also after adjusting for other risk factors, including echo LVH [8]. More recently in the Oregon SUDS, Romhilt–Estes score ≥ 5 (“definite LVH”) was associated with sudden cardiac arrest in the adjusted model [39].

Our present study may be the first comprehensive comparison on the performance of several LVH criteria as risk predictors of SCD. Three traditional and clinically useful and one recently proposed LVH criteria were analyzed both as continuous and dichotomous. Data were collected prospectively. First, as expected, significant associations between traditional risk factors and SCD was observed. Second, LVH prevalence varied markedly between criteria, which is not surprising as similar has been reported previously [6,14]. Prevalence of Peguero–Lo Presti showed a relatively high prevalence (≈25% of all subjects). Our study may be the first reporting the prevalence of this new criterion in the general population. In their work including mainly hypertensive hospital patients, Peguero et al. reported that, compared to Sokolow–Lyon, Cornell, and R_{aVL}, Peguero–Lo Presti criterion had markedly higher sensitivity and lower specificity for detecting echo LVH [20]. Thus, our results showing higher LVH prevalence rates for Peguero–Lo Presti compared to other criteria are in line with the previous report [20].

Table 2
Hazard ratios of SCD for continuous ECG LVH criteria from Cox models.

Model ^a	LVH voltage criteria	HR (95% CI) ^b	P value
Unadjusted	Sokolow–Lyon ^c	1.03 (1.01–1.06)	0.003
	Cornell ^d	1.09 (1.06–1.12)	<0.001
	Peguero–Lo Presti ^e	1.05 (1.03–1.07)	<0.001
	R _{aVL} ^f	1.12 (1.07–1.16)	<0.001
Multivariable adjusted	Sokolow–Lyon	1.02 (1.003–1.05)	0.030
	Cornell	1.04 (1.01–1.07)	0.008
	Peguero–Lo Presti	1.03 (1.01–1.05)	0.002
	R _{aVL}	1.03 (0.98–1.09)	0.262

CI indicates confidence interval; otherwise, abbreviations as in Table 1.

^a Covariates in the multivariate analyses: gender, age at the study baseline, body mass index, heart rate, current smoking (yes/no), arterial hypertension (yes/no), diabetes mellitus (yes/no), previous myocardial infarction (yes/no).

^b Hazard ratio per 100 μV (1 mm with the 10 mm/mV calibration) increase in the ECG LVH measure value.

^c S_{V1} + R_{V5} or S_{V1} + R_{V6} (whichever was greater).

^d S_{V3} + R_{aVL}.

^e S_{Deepest} + S_{V4}.

^f R_{aVL}.

Table 3
Hazard ratios of SCD for dichotomous ECG LVH criteria from Cox models.

Model ^a	LVH voltage criteria	HR (95% CI)	P Value
Single criteria Unadjusted	Sokolow–Lyon ^b	1.79 (1.07–2.81)	0.027
	Cornell ^c	2.06 (1.20–3.31)	0.010
	Peguero–Lo Presti ^d	1.53 (1.06–2.17)	0.023
	R _{aVL} ^e	2.40 (1.24–4.20)	0.012
Multivariable adjusted	Sokolow–Lyon	1.55 (0.92–2.48)	0.096
	Cornell	1.97 (1.12–3.29)	0.021
	Peguero–Lo Presti	1.40 (0.97–2.00)	0.072
	R _{aVL}	1.36 (0.69–2.43)	0.346
Composite criteria Unadjusted	Sokolow–Lyon and/or Cornell	1.98 (1.32–2.89)	0.001
	Sokolow–Lyon and/or Peguero–Lo Presti	1.56 (1.10–2.19)	0.013
	Cornell and/or Peguero–Lo Presti	1.44 (1.003–2.05)	0.048
Multivariable adjusted	Sokolow–Lyon and/or Cornell	1.82 (1.20–2.70)	0.006
	Sokolow–Lyon and/or Peguero–Lo Presti	1.40 (0.98–1.99)	0.061
	Cornell and/or Peguero–Lo Presti	1.33 (0.92–1.91)	0.124

Abbreviations as in Tables 1 and 2.

^a Covariates in the multivariate analyses as in Table 2.

^b $S_{V1} + R_{V5}$ or $S_{V1} + R_{V6}$ (whichever was greater) ≥ 3.5 mV.

^c $S_{V3} + R_{aVL} > 2.0$ mV (women), > 2.8 mV (men).

^d $S_{\text{Deepest}} + S_{V4} \geq 2.3$ mV (women), ≥ 2.8 mV (men).

^e $R_{aVL} > 1.1$ mV.

Assuming that echo LVH prevalence ranges from 36% to 41% [40] in hypertension and that echo is more sensitive than ECG in detecting anatomic LVH, it seems plausible that the cutoff value for Peguero–Lo Presti in the white adult general population should be higher than that proposed by Peguero et al. [20] We do admit that future studies are needed to answer this in more detail as data on echo LVH were not available in our study.

Third, when LVH criteria were analyzed as continuous variables in multivariable adjusted models, Sokolow–Lyon, Cornell, and Peguero–Lo Presti remained associated with SCD. By contrast, R_{aVL} lost its association with SCD. ECG Q, R, and S waves are believed to represent different parts of the depolarizing areas in the heart. Specifically, Q and R waves represent depolarization of the interventricular septum, conduction system, and LV endomyocardium, whereas S waves are believed to represent the depolarization of the ventricular free wall and myocardium [20]. It has been postulated that, compared to S waves, R waves are less sensitive in detecting mild to moderate anatomic LVH [20]. In contrast to this, R_{aVL} has also been reported to perform as good or

even better in echo LVH detection compared to Sokolow–Lyon and Cornell [5]. Risk-factor adjusted association between R_{aVL} and cardiovascular outcomes has been reported [5,14], but also conflicting results have been published [6]. We report here as a new finding that R_{aVL} as a sole criterion does not seem to capture the malignant arrhythmogenic risk of LVH in the general population.

Fourth, when LVH criteria were used in the present study as dichotomous variables, relationships of Sokolow–Lyon and Peguero–Lo Presti to SCD were nonsignificant in multivariable adjusted models although they were significant when used as continuous variables. One explanation for this may be diminished statistical power related to dichotomization. The composite of Sokolow–Lyon and Cornell was the only composite criterion that remained significantly associated with SCD after adjustments. In addition, composite of Sokolow–Lyon and Cornell was the only criterion that showed statistically significant population-attributable fraction. Use of composite LVH criteria is generally supported because of expected enhanced sensitivity in LVH detection. When criteria are selected, a logical step is to combine criteria that are both associated with outcome and also capture different patient categories, such as Sokolow–Lyon and Cornell. We have previously reported in the Health 2000 Survey that composite of Sokolow–Lyon and Cornell voltages performed the best in predicting incident cardiovascular events [14]. Results of the present study confirm that composite of Sokolow–Lyon and Cornell is also valid when SCD is the endpoint.

4.4. Limitations

Our study was performed in white general population. Future studies may evaluate whether our findings are reproducible also in multiracial populations as well as in populations with a more elevated SCD risk, such as in coronary heart disease and/or previous myocardial infarction.

4.5. Conclusions

Sokolow–Lyon, Cornell, and Peguero–Lo Presti ECG, but not R_{aVL} voltage, are associated with SCD risk as continuous ECG voltage LVH variables. When SCD risk assessment/adjustment is performed using a dichotomous ECG LVH measure, composite of Sokolow–Lyon and Cornell voltages is the preferred option.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2018.09.104>.

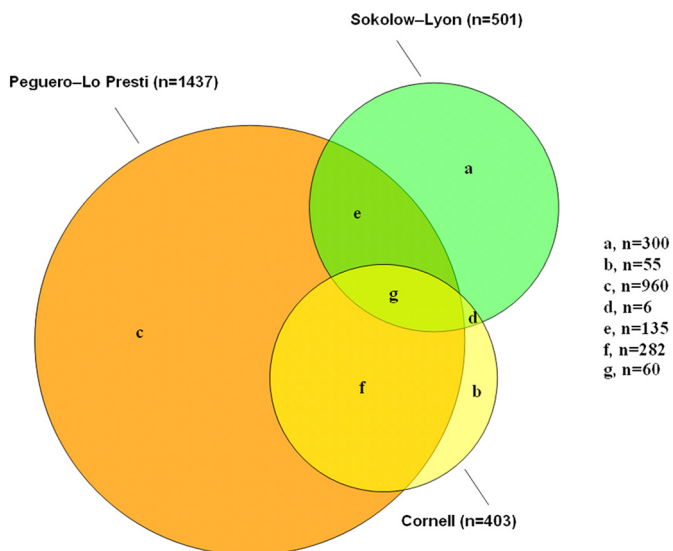


Fig. 1. Overlap of dichotomous ECG LVH voltage criteria. Sokolow–Lyon: $S_{V1} + R_{V5}$ or $S_{V1} + R_{V6}$ (whichever was greater) ≥ 3.5 mV; Cornell: $S_{V3} + R_{aVL} > 2.0$ mV (women), > 2.8 mV (men); Peguero–Lo Presti: $S_{\text{Deepest}} + S_{V4} \geq 2.3$ mV (women), ≥ 2.8 mV (men).

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Disclosures

Veikko Salomaa has participated in a conference trip sponsored by Novo Nordisk. Other authors have nothing to disclose.

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References

- [1] D. Levy, R.J. Garrison, D.D. Savage, W.B. Kannel, W.P. Castelli, Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study, *N. Engl. J. Med.* 322 (1990) 1561–1566.
- [2] D. Levy, M. Salomon, R.B. D'Agostino, A.J. Belanger, W.B. Kannel, Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy, *Circulation* 90 (1994) 1786–1793.
- [3] B.A. Vakili, P.M. Okin, R.B. Devereux, Prognostic implications of left ventricular hypertrophy, *Am. Heart J.* 141 (2001) 334–341.
- [4] M. Bombelli, R. Facchetti, S. Carugo, F. Madotto, F. Arenare, F. Quarti-Trevano, A. Capra, C. Giannattasio, R. Dell'Oro, G. Grassi, R. Sega, G. Mancia, Left ventricular hypertrophy increases cardiovascular risk independently of in-office and out-of-office blood pressure values, *J. Hypertens.* 27 (2009) 2458–2464.
- [5] P. Gosse, E. Jan, P. Coulon, A. Cremer, G. Papaioannou, S. Yeim, ECG detection of left ventricular hypertrophy: the simpler, the better? *J. Hypertens.* 30 (2012) 990–996.
- [6] C. Cuspidi, R. Facchetti, M. Bombelli, C. Sala, G. Grassi, G. Mancia, Accuracy and prognostic significance of electrocardiographic markers of left ventricular hypertrophy in a general population: findings from the Pressioni Arteriose Monitorate E Loro Associazioni population, *J. Hypertens.* 32 (2014) 921–928.
- [7] W.B. Kannel, J.T. Doyle, P.M. McNamara, P. Quickenton, T. Gordon, Precursors of sudden coronary death. Factors related to the incidence of sudden death, *Circulation* 51 (1975) 606–613.
- [8] K. Narayanan, K. Reinier, C. Teodorescu, A. Uy-Evanado, H. Chugh, K. Gunson, J. Jui, S.S. Chugh, Electrocardiographic versus echocardiographic left ventricular hypertrophy and sudden cardiac arrest in the community, *Heart Rhythm.* 11 (2014) 1040–1046.
- [9] Writing Group Members, D. Mozaffarian, E.J. Benjamin, A.S. Go, D.K. Arnett, M.J. Blaha, M. Cushman, S.R. Das, S. de Ferranti, J.P. Després, H.J. Fullerton, V.J. Howard, M.D. Huffman, C.R. Isasi, M.C. Jiménez, S.E. Judd, B.M. Kissela, J.H. Lichtman, L.D. Lisabeth, S. Liu, R.H. Mackey, D.J. Magid, McGuire DK, E.R. Mohler 3rd, C.S. Moy, P. Muntner, M.E. Mussolino, K. Nasir, R.W. Neumar, G. Nichol, L. Palaniappan, D.K. Pandey, M.J. Reeves, C.J. Rodriguez, W. Rosamond, P.D. Sorlie, J. Stein, A. Towfighi, T.N. Turan, S.S. Virani, D. Woo, R.W. Yeh, M.B. Turner, American Heart Association Statistics Committee, Stroke Statistics Subcommittee, Heart Disease and Stroke Statistics—2016 Update: a report from the American Heart Association, *Circulation* 133 (2016) e38–360.
- [10] J. Sundström, L. Lind, J. Arnlöv, B. Zethelius, B. Andrén, H.O. Lithell, Echocardiographic and electrocardiographic diagnoses of left ventricular hypertrophy predict mortality independently of each other in a population of elderly men, *Circulation* 103 (2001) 2346–2351.
- [11] L. Bacharova, H. Chen, E.H. Estes, A. Mateasik, D.A. Bluemke, J.A. Lima, G.L. Burke, E.Z. Soliman, Determinants of discrepancies in detection and comparison of the prognostic significance of left ventricular hypertrophy by electrocardiogram and cardiac magnetic resonance imaging, *Am. J. Cardiol.* 115 (2015) 515–522.
- [12] P. Verdecchia, G. Schillaci, C. Borgioni, A. Ciucci, R. Gattobigio, I. Zampi, C. Porcellati, Prognostic value of a new electrocardiographic method for diagnosis of left ventricular hypertrophy in essential hypertension, *J. Am. Coll. Cardiol.* 31 (1998) 383–390.
- [13] B.P. Hsieh, M.X. Pham, V.F. Froelicher, Prognostic value of electrocardiographic criteria for left ventricular hypertrophy, *Am. Heart J.* 150 (2005) 161–167.
- [14] K. Porthan, T.J. Niiranen, J. Varis, I. Kantola, H. Karanko, M. Kähönen, M.S. Nieminen, V. Salomaa, H.V. Huikuri, A.M. Jula, ECG left ventricular hypertrophy is a stronger risk factor for incident cardiovascular events in women than in men in the general population, *J. Hypertens.* 33 (2015) 1284–1290.
- [15] S. Heistaro, Methodology Report, Health 2000 Survey, Helsinki, National Public Health Institute, 2008<http://urn.fi/URN:NBN:fi-fe201204193320>, Accessed date: 14 June 2018.
- [16] K. Porthan, M. Viitasalo, A. Jula, A. Reunanen, J. Rapola, H. Väänänen, M.S. Nieminen, L. Toivonen, V. Salomaa, L. Oikarinen, Predictive value of electrocardiographic QT interval and T-wave morphology parameters for all-cause and cardiovascular mortality in a general population sample, *Heart Rhythm.* 6 (2009) 1202–1208.
- [17] M. Sokolow, T.P. Lyon, The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads, *Am. Heart J.* 37 (1949) 161–186.
- [18] P.N. Casale, R.B. Devereux, D.R. Alonso, E. Campo, P. Kligfield, Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings, *Circulation* 75 (1987) 565–572.
- [19] J.A. Schack, R.H. Rosenman, L.N. Katz, The aV limb leads in the diagnosis of ventricular strain, *Am. Heart J.* 40 (1950) 696–705.
- [20] J.G. Peguero, S. Lo Presti, J. Perez, O. Issa, J.C. Brenes, A. Tolentino, Electrocardiographic criteria for the diagnosis of left ventricular hypertrophy, *J. Am. Coll. Cardiol.* 69 (2017) 1694–1703.
- [21] P.A. Noseworthy, A.S. Havulinna, K. Porthan, A.M. Lahtinen, A. Jula, P.J. Karhunen, M. Perola, L. Oikarinen, K.K. Kontula, V. Salomaa, C. Newton-Cheh, Common genetic variants, QT interval, and sudden cardiac death in a Finnish population-based study, *Circ. Cardiovasc. Genet.* 4 (2011) 305–311.
- [22] D. Firth, Bias reduction of maximum likelihood estimates, *Biometrika* 80 (1993) 27–38.
- [23] G. Heinze, M. Schemper, A solution to the problem of monotone likelihood in Cox regression, *Biometrics* 57 (2001) 114–119.
- [24] M. Gonen, G. Heller, Concordance probability and discriminatory power in proportional hazards regression, *Biometrika* 92 (2005) 965–970.
- [25] D. Spiegelman, E. Hertzmark, H.C. Wand, Point and interval estimates of partial population attributable risks in cohort studies: examples and software, *Cancer Causes Control* 18 (2007) 571–579.
- [26] H.V. Huikuri, A. Castellanos, R.J. Myerburg, Sudden death due to cardiac arrhythmias, *N. Engl. J. Med.* 345 (2001) 1473–1482.
- [27] L. Choudhury, H. Mahrholdt, A. Wagner, K.M. Choi, M.D. Elliott, F.J. Klocke, R.O. Bonow, R.M. Judd, R.J. Kim, Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy, *J. Am. Coll. Cardiol.* 40 (2002) 2156–2164.
- [28] T. Furukawa, J. Kurokawa, Potassium channel remodeling in cardiac hypertrophy, *J. Mol. Cell. Cardiol.* 41 (2006) 753–761.
- [29] P. Spirito, P. Bellone, K.M. Harris, P. Bernabo, P. Bruzzi, B.J. Maron, Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy, *N. Engl. J. Med.* 342 (2000) 1778–1785.
- [30] K. Porthan, J. Virolainen, T.P. Hiltunen, M. Viitasalo, H. Väänänen, J. Dabek, T. Hannila-Handelberg, L. Toivonen, M.S. Nieminen, K. Kontula, L. Oikarinen, Relationship of electrocardiographic repolarization measures to echocardiographic left ventricular mass in men with hypertension, *J. Hypertens.* 25 (2007) 1951–1957.
- [31] B.N. Chiang, L.V. Perlman, M. Fulton, L.D. Ostrander Jr., F.H. Epstein, Predisposing factors in sudden cardiac death in Tecumseh, Michigan. A prospective study, *Circulation* 41 (1970) 31–37.
- [32] A.W. Haider, M.G. Larson, E.J. Benjamin, D. Levy, Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death, *J. Am. Coll. Cardiol.* 32 (1998) 1454–1459.
- [33] K. Reinier, C. Dervan, T. Singh, A. Uy-Evanado, S. Lai, K. Gunson, J. Jui, S.S. Chugh, Increased left ventricular mass and decreased left ventricular systolic function have independent pathways to ventricular arrhythmogenesis in coronary artery disease, *Heart Rhythm.* 8 (2011) 1177–1182.
- [34] J.A. Laukkanen, H. Khan, S. Kurl, P. Willeit, J. Karppi, K. Ronkainen, E. Di Angelantonio, Left ventricular mass and the risk of sudden cardiac death: a population-based study, *J. Am. Heart Assoc.* 3 (2014), e001285.
- [35] S.H. Konecny, R.J. Koene, F.L. Norby, T. Wilsdon, A. Alonso, D. Siscovick, N. Sotoodehnia, J. Gottdiener, E.R. Fox, L.Y. Chen, S. Adabag, A.R. Folsom, Echocardiographic predictors of sudden cardiac death: the atherosclerosis risk in communities study and cardiovascular health study, *Circ. Cardiovasc. Imaging* 9 (2016), e004431.
- [36] L. Bacharova, Left ventricular hypertrophy: disagreements between increased left ventricular mass and ECG-LVH criteria: the effect of impaired electrical properties of myocardium, *J. Electrocardiol.* 47 (2014) 625–629.
- [37] S.M. Stevens, K. Reinier, S.S. Chugh, Increased left ventricular mass as a predictor of sudden cardiac death: is it time to put it to the test? *Circ. Arrhythm. Electrophysiol.* 6 (2013) 212–217.
- [38] A.L. Aro, K. Reinier, C. Rusinaru, A. Uy-Evanado, N. Darouian, D. Phan, W.J. Mack, J. Jui, E.Z. Soliman, L.G. Tereshchenko, S.S. Chugh, Electrical risk score beyond the left ventricular ejection fraction: prediction of sudden cardiac death in the Oregon Sudden Unexpected Death Study and the Atherosclerosis Risk in Communities Study, *Eur. Heart J.* 38 (2017) 3017–3025.
- [39] N. Darouian, A.L. Aro, K. Narayanan, A. Uy-Evanado, C. Rusinaru, K. Reinier, K. Gunson, J. Jui, S.S. Chugh, The Romhilt-Estes electrocardiographic score predicts sudden cardiac arrest independent of left ventricular mass and ejection fraction, *Ann. Noninvasive Electrocardiol.* 22 (2017)<https://doi.org/10.1111/anec.12424>.
- [40] C. Cuspidi, C. Sala, F. Negri, G. Mancia, A. Morganti, Italian Society of Hypertension, Prevalence of left-ventricular hypertrophy in hypertension: an updated review of echocardiographic studies, *J. Hum. Hypertens.* 26 (2012) 343–349.