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Research Paper

Electrocardiography for diagnosis of left ventricular hypertrophy in hypertensive patients with atrial fibrillation

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ABSTRACT

Left ventricular (LV) hypertrophy at electrocardiography (ECG) predicts incident atrial fibrillation (AF). However, the diagnostic performance of ECG for diagnosis of LV hypertrophy in patients with AF is still not well characterized.

We analyzed 563 hypertensive patients enrolled in the Umbria-Atrial Fibrillation (Umbria-FA) registry, an ongoing prospective observational registry in patients with AF. All patients underwent ECG and standard echocardiography at their entry in the Register. Mean age was 74 years and 43% of patients were women. Prevalence of ECG-LV hypertrophy, defined by Perugia criterion corrected for body mass index, was 23%. Echocardiographic LV mass was the reference standard. Sensitivity, specificity and diagnostic accuracy of ECG-LV hypertrophy were 37.4% (95% confidence interval [CI]: 31.6–43.4), 90.0% (95% CI: 86.0–93.2) and 64.5% (95% CI: 60.4–68.3), respectively. Performance was comparable in patients with AF or sinus rhythm at ECG recording. The area under the receiver-operating characteristic (ROC) curve was 0.622 (95% CI: 0.580–0.664) in the group with AF and 0.662 (95% CI: 0.605–0.720) in that with sinus rhythm ($p = 0.266$ for comparison). These data suggest that standard ECG is reliable for diagnosis of LV hypertrophy in patients with a history of AF, regardless of the presence of AF or sinus rhythm at the time of ECG recording.

1. Introduction

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia [1], which is associated with a 2–3 fold increased risk of cardiovascular (CV) mortality and sudden cardiac death, a 5-fold increased risk of stroke, and a 3-fold increased risk of heart failure (HF) [2–5]. AF affects 5.2 million individuals in the United States, and approximately 1 in 4 individuals will acquire this condition in their lifetimes [1,6,7].

Hypertension is the most prevalent CV risk factor in patients with AF and, at the same time, it is recognized as a predictor of new onset AF [8]. In a landmark analysis of the Framingham Heart Study, which involved 2090 men and 2641 women between the ages of 55 and 94 years, and free of a history of AF, hypertension was significantly associated with the risk of subsequent AF in both sexes, even after multivariable adjustment for several potential confounders [8].

Among the predictors of AF, electrocardiographic (ECG) left ventricular (LV) hypertrophy has a relevant impact. Watanabe et al. reported a significant association between ECG LV hypertrophy and incident AF (hazard ratio [HR]: 1.39, 95% confidence interval [CI]: 1.11 to 1.75) in a large Japanese cohort of community-dwelling adults [9]. Similarly, in the Multi-Ethnic Study of Atherosclerosis (MESA), LV hypertrophy either assessed by Sokolow-Lyon voltage, Sokolow-Lyon voltage product, or Perugia criterion, was a significant predictor of incident AF even after adjustment for several confounders [10].

Furthermore, a recent post-hoc analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Study [11], demonstrated that ECG-LV hypertrophy (as diagnosed by the Perugia criterion [12]) significantly improves risk stratification in AF anticoagulated patients with a prognostic value additive to CHA_2DS_2-VASc score.

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[1] See Appendix.

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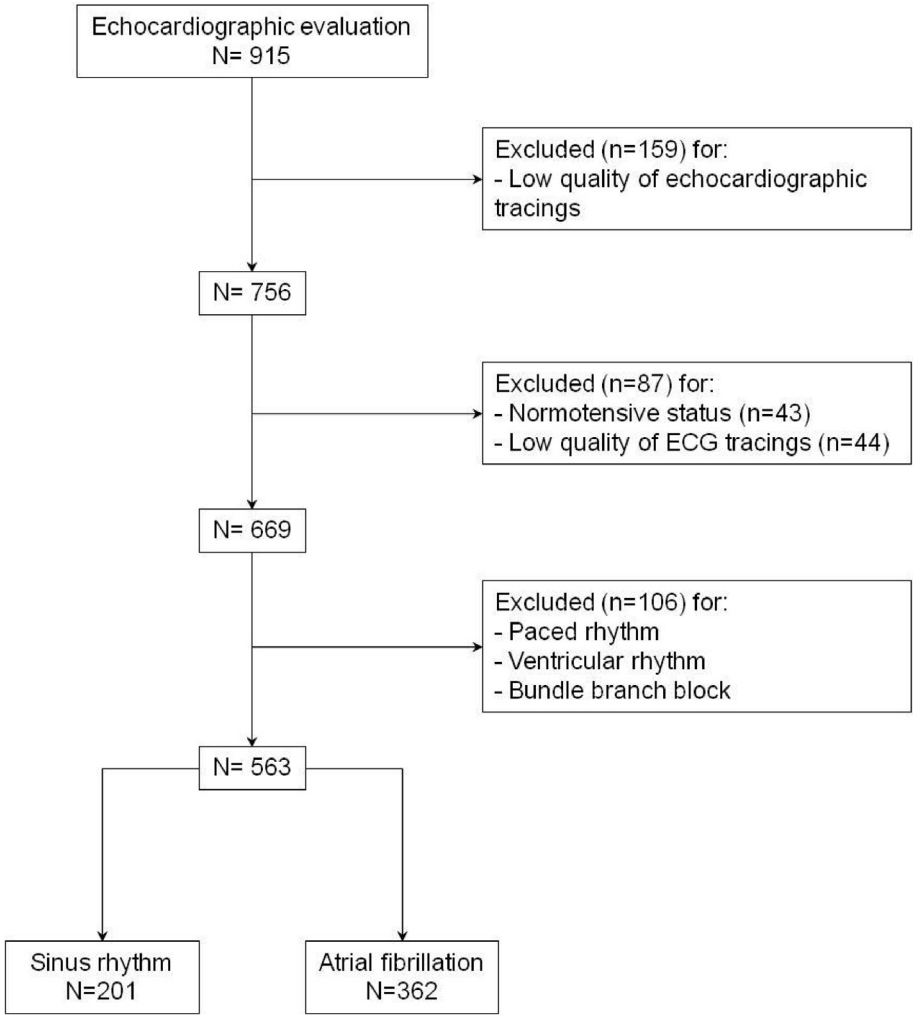

Fig. 1. Flow chart of subjects through the study. ECG: electrocardiography.

Nonetheless, the diagnostic accuracy of ECG in detecting LV hypertrophy in patients with AF in respect to patients with sinus rhythm has never been tested.

Consequently, the present cross-sectional study was designed to compare diagnostic accuracy of the ECG detection of LV hypertrophy between patients with AF and sinus rhythm in a modern population of hypertensive non-valvular AF patients.

2. Methods

2.1. Population

We performed a cross-sectional analysis of the *Umbria Atrial Fibrillation (Umbria-FA) Registry* (www.umbriafa.it), a multicenter, observational, prospective on-going registry of patients with non-valvular AF (see appendix). The objectives of this Registry on AF are to (i) describe key features of AF patients; (ii) analyze contemporary patterns in AF management; (iii) evaluate major gaps in the Guidelines [13] implementation in clinical practice; (iv) establish correlation between management of AF and clinical outcomes.

Patients are recruited, both as inpatients or outpatients, if they are aged ≥18 years and had non-valvular AF. We define non-valvular AF by the absence of mechanical heart valves or moderate or severe mitral stenosis. Enrollment is being performed in 22 Hospitals or out-patient facilities in the setting of the Italian Health System, beginning in January 2013. All patients sign a written informed consent and the study is conducted in accordance with the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

The initial evaluation includes a detailed clinical examination, 12-lead ECG, laboratory tests and, when feasible, an echocardiographic study. Periodical meeting are conducted among participating centers to standardize the technical procedures for echocardiographic study, as detailed below.

For enrollment, patients must be affected by AF at entry into the Registry or, in case of paroxysmal or persistent AF currently in sinus rhythm, by evidence of AF within one year before entry. Standard ECG, ECG-Holter monitoring, or pacemaker diagnostics are accepted for diagnosis of AF. Mechanical valve, severe mitral stenosis, and life-threatening conditions with life expectancy <1 year are exclusion criteria.

2.2. ECG

Standard 12-lead ECG is recorded during brief end-expiratory apnea. Subjects with conditions potentially precluding a correct ECG assessment of LV hypertrophy (i.e. complete right bundle branch block, left bundle branch block, and Wolf-Parkinson-White syndrome) have been excluded from the present analysis.

To detect LV hypertrophy at ECG we used the following criteria: Cornell voltage [14]; typical strain [15]; Perugia criterion [16] and the BMI-corrected Perugia criterion [17].

Briefly, the Cornell voltage was computed as the sum of the S wave in lead V_3 plus the R wave lead in aVL [14]; typical strain pattern [15]

was defined by a ≥0.5 mm depression of the J point, T-wave inversion with asymmetric branches and rapid return to baseline; the Perugia score [16] was defined by the presence of a typical strain pattern or a modified Cornell voltage (sum of the S wave in V_3 plus the R wave in aVL≥ 2.0 mV in women and ≥2.4 mV in men). For computation of the BMI-corrected Perugia score, the Cornell voltage [14] was amplified proportionally to BMI, thereby providing a simple correction for voltage attenuation at the skin surface. Thus, ECG LV hypertrophy was defined by a Cornell-BMI product ([R wave amplitude in lead aVL + S wave depth in lead V3] x BMI) > 604 mm kg/m^{2}or typical strain pattern [17].

2.3. Echocardiography

The M-mode echocardiographic study of the LV was performed under 2D guide. Only frames with optimal visualization of interfaces and showing simultaneous visualization of septum, LV internal diameter and posterior wall were used for reading. We calculated LV mass by using a necropsy validated formula [18]. We made an adjustment by height [19], and defined LV hypertrophy by a LV mass/height$^{2.7}$> 51.0 g/m$^{2.7}$. After correction for body surface area (BSA) [14], we used gender-specific definition of echocardiographic LV hypertrophy (LV mass index >95 g/m^2 for women and >115 g/m^2 for men) [20,21]. We also defined LV hypertrophy by an unadjusted LV mass >215 g [18,22].

2.4. Statistical analysis

We used STATA 14 (StataCorp, USA) and R software version 3 (R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org).

Data are presented as mean ± standard deviation (SD) for continuous variables and proportions for categorical variables. Differences in proportions between groups were analyzed using the χ^2 test. Mean values of variables were compared by independent sample t-test. The strength of the relations between variables was assessed by ordinary regression and partial correlation analysis [23].

To evaluate the performance of ECG for the diagnosis of LV hypertrophy (sensitivity, specificity, predictive value of a positive and negative test, and accuracy), echocardiographic LV hypertrophy was used as the reference standard. Definitions of test sensitivity, specificity, accuracy and predictive values conform to standard use [24]. Accuracy was estimated calculating the proportion of true positive and true negative in all evaluated cases.

To compare sensitivities and specificities of binary diagnostic tests we used the McNemar test [25]. Accuracy of ECG was also estimated by receiver-operating characteristics (ROC) curve analysis to identify differences in test performance. The ROC curves were compared statistically by means of a two-tailed univariate z test of the difference between the areas under two performance curves (AUCs) [26,27]. In 2-tailed tests, p values < 0.05 were considered statistically significant.

3. Results

Of the 2205 patients recruited on August 31, 2018 in the Umbria-AF Registry, 915 had an echocardiographic evaluation at baseline. Among these patients, 159 (17.4%) had sub-optimal or poor quality echocardiographic tracings, and 193 (21.1%) had ECG exclusion criteria (see methods) or normotensive status according to current Guidelines [28]. Thus, 563 hypertensive patients with complete clinical data, 12-lead ECGs and echocardiographic tracings of adequate technical quality in a non-paced rhythm (Fig. 1) were included in the final analysis.

The main characteristics of included patients are shown in Table 1. Overall, 362 patients (64.3%) had AF at entry-ECG with a mean heart rate equal to 86 ± 20 b.p.m. (median: 82 b.p.m.). The remaining 201 patients (35.7%) showed sinus rhythm at baseline with a mean heart rate of 65 ± 11 b.p.m. (p < 0.0001 vs patients with AF). The 362 patients with AF at entry-ECG were older (76 ± 10 vs 71 ± 10 years, p < 0.0001) and more likely to have increased BMI (27.1 ± 4.5 kg/m^2 vs 28.0 ± 5.0 kg/m^2, p = 0.019) than individuals forming the cohort with sinus rhythm. Gender distribution and BPs were similar (all p > 0.05, Table 1). Table 1 also summarizes echocardiographic characteristics of the 2 groups. Patients with AF had poorer ventricular function compared to those with sinus rhythm and 52% of patients with AF showed an abnormal LV mass.

The distribution of antiarrhythmic drugs in the two groups was not dissimilar (59.2% vs 59.1%, p = 0.984).

In the overall cohort, 432 patients (77%) were treated with BP lowering drugs; 333 (59%) and 144 (26%) patients achieved a BP < 140/90 mmHg and 130/80 mmHg, respectively.

Prevalence of LV hypertrophy at echocardiography (LV mass > 51.0 g/m$^{2.7}$) was 41.8% and 52.2% in patients with sinus rhythm and AF,

Table 1
Baseline characteristics of hypertensive patients included in the analysis (SR: sinus rhythm; AF: atrial fibrillation; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; EF: ejection fraction; CR: concentric remodeling; LVH: left ventricular hypertrophy).

Variable	Overall (n = 563)	SR at entry ECG (n = 201)	AF at entry ECG (n = 362)	p
Age (years)	74 (10)	71 (10)	76 (10)	<0.0001
Sex (% women)	43.0	44.3	42.3	0.644
Diabetes (%)	21.5	24.0	20.2	0.290
BMI (kg/m^2)	27.7 (4.8)	27.1 (4.5)	28.0 (5.0)	0.019
Office SBP (mmHg)	132 (17)	133 (18)	132 (17)	0.300
Office DBP (mmHg)	79 (10)	78 (10)	79 (10)	0.068
Haemoglobin (g/dl)	13.0 (2.0)	12.8 (1.9)	13.2 (2.0)	0.098
Creatinine (mg/dl)	1.07 (0.47)	1.11 (0.51)	1.04 (0.45)	0.162
Cholesterol (mg/dl)	170 (42)	167 (41)	171 (43)	0.354
Antiarrhythmics (%)	59.2	59.2	59.1	0.984
Electrocardiography				
Heart Rate (/min)	78 (20)	65 (11)	86 (20)	<0.0001
RaVL+SV_3 (mm)	15.3 (6.8)	15.2 (6.3)	15.4 (7.1)	0.759
Typical strain (%)	11.9	8.5	13.8	0.060
LVH (%)	23.3	20.4	24.9	0.230
Echocardiography				
LV mass (g/m$^{2.7}$)	52.2 (15.8)	49.9 (15.2)	53.5 (16.0)	0.009
LVH (%)	48.5	41.8	52.2	0.018
EF (%)	61 (13)	64 (12)	59 (13)	<0.0001
LV geometry				
Normal	32.1	38.3	28.7	0.085
CR	19.4	19.9	19.1	
Concentric LVH	27.7	23.9	29.8	
Eccentric LVH	20.8	17.9	22.4	

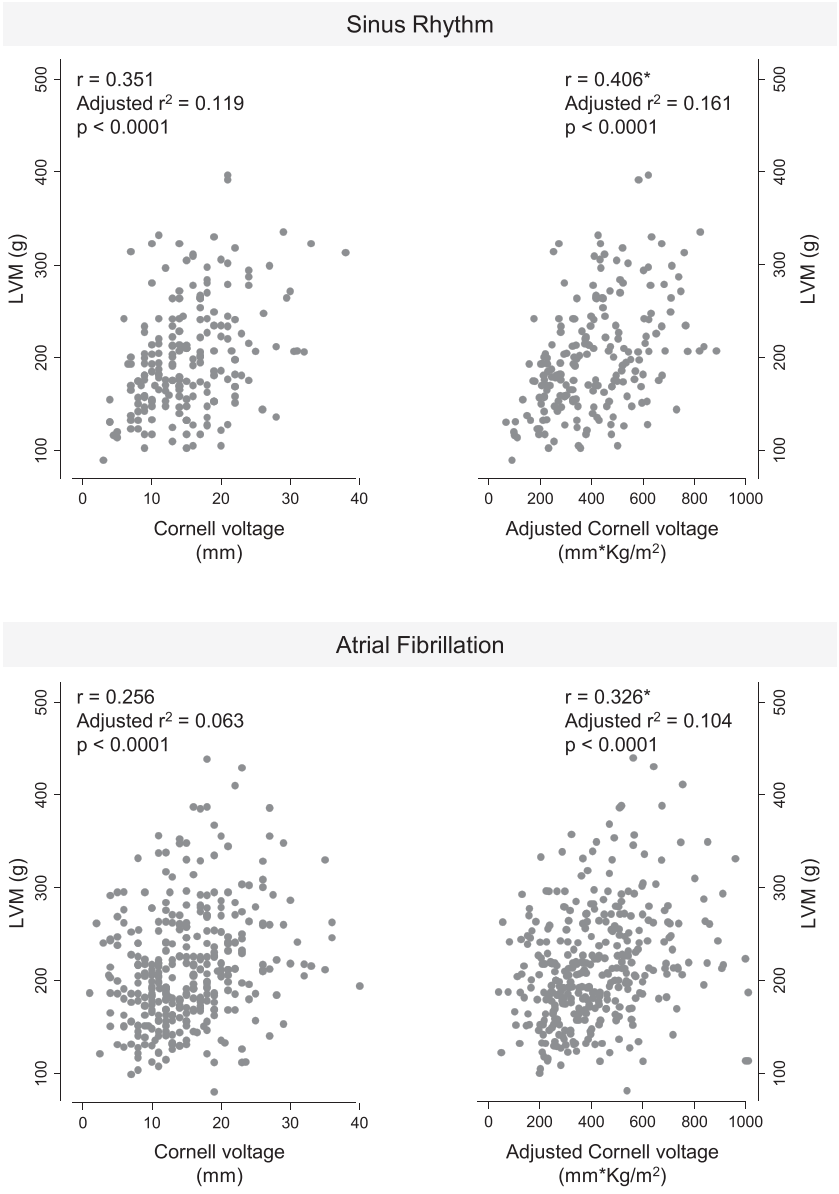

Fig. 2. Strength of the relations between left ventricular mass, Cornell voltage and BMI-adjusted Cornell voltage. Relations are depicted for hypertensive patients with sinus rhythm (SR) and atrial fibrillation (AF) at entry ECG. LVM = left ventricular mass; * = $p < 0.05$ vs Cornell voltage (see text for details).

respectively ($p = 0.018$). Prevalence of LV hypertrophy detected by BMI-corrected Perugia criterion was 24.9% and 20.4% in patients with AF and sinus rhythm, respectively. In the overall cohort, the Cornell voltage showed a direct association with LV mass ($r^2 = 0.0819$; $p < 0.0001$), but such association was significantly increased after accounting for the effect of BMI (BMI-adjusted Cornell voltage, $r^2 = 0.1241$; $p < 0.0001$; p for the comparison = 0.0001). Of note, a superimposable pattern of relationship between LV mass and BMI-adjusted Cornell voltage (Fig. 2) was observed in patients with AF with a stronger association when compared with the original Cornell voltage ($r^2 = 0.1062$ vs 0.0656, p for the comparison = 0.0004). Of note, the association between LVM and BMI-adjusted Cornell voltage was similar in subgroups defined by age (<78 and ≥ 78 years), sex (male vs female), heart rate (<75 and ≥ 75/min), and use of antiarrhythmic agents (all $p > 0.05$).

The operational characteristics and the diagnostic performance of ECG for the diagnosis of LV hypertrophy are reported in Table 2. As documented in our previous validation study, the BMI-corrected Perugia criterion was associated with significantly higher AUC values when compared with Perugia criterion and its components (typical strain and Cornell voltage) in the overall cohort. Notably, the diagnostic accuracy of BMI-corrected Perugia criterion was not significantly affected by the presence of AF when compared to sinus rhythm ($p = 0.266$). The comparisons of ROC curve areas for ECG LV hypertrophy between patients with AF and sinus rhythm are shown in Fig. 3.

Furthermore, similar results were obtained using definition of LV hypertrophy by an unadjusted LV mass >215 g [18,22] ($\chi^2 = 2.15$, $p = 0.1425$ for comparison between AUCs) or gender-specific [20] definition of echocardiographic LV hypertrophy ($\chi^2 = 1.25$, $p = 0.2638$ for comparison between AUCs).

Finally, among patients with AF, the diagnostic performance of the criterion was not statistically dissimilar in specific subgroups defined by patients characteristics (age, sex, heart rate and use of antiarrhythmic agents; Fig. 4).

4. Discussion

The present analysis of a cohort of patients included in the Umbria-AF Registry provides some novel findings on the diagnostic accuracy of ECG

Table 2
Operational characteristics and diagnostic performance of Perugia, BMI-corrected Perugia criteria and its components (typical strain and Cornell voltage) for LV hypertrophy. LV mass >51 g/h$^{2.7}$ was the reference value for echocardiographic LV hypertrophy.

Criterion	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy	AUC (95% CI)
Overall (n = 563)						
Typical strain	19.0 (14.6–24.2)	94.8 (91.6–97.1)	77.6 (65.8–86.9)	55.4 (50.9–59.9)	58.1 (54.0–62.1)	0.569 (0.543–0.596)*
Cornell voltage	23.1 (18.2–28.5)	92.8 (89.1–95.5)	75.0 (64.4–83.8)	56.2 (51.6–60.7)	59.0 (54.9–63.0)	0.579 (0.550–0.688)*
Perugia	33.2 (27.8–39.3)	89.3 (85.2–92.6)	74.6 (65.9–82.0)	58.7 (54.0–63.4)	62.2 (58.1–66.1)	0.613 (0.580–0.646)*
BMI-Perugia	37.4 (31.6–43.4)	90.0 (86.0–93.2)	77.9 (69.8–84.6)	60.4 (55.6–65.1)	64.5 (60.4–68.3)	0.637 (0.603–0.670)
Sinus Rhythm at entry ECG (n = 201)						
Typical strain	17.9 (10.4–27.7)	98.3 (94.0–99.8)	88.2 (63.6–98.5)	62.5 (55.1–69.5)	64.7 (57.9–71.0)	0.581 (0.538–0.624)*
Cornell voltage	25.0 (16.2–35.6)	95.7 (90.3–98.6)	80.8 (60.6–93.4)	64.0 (56.4–71.1)	66.2 (59.4–72.4)	0.604 (0.554–0.654)*
Perugia	34.5 (24.5–45.7)	94.9 (89.2–98.1)	82.9 (66.4–93.4)	66.9 (59.2–74.0)	69.7 (63.0–75.6)	0.647 (0.592–0.702)
BMI-Perugia	39.3 (28.8–50.5)	93.2 (87.0–97.0)	80.5 (65.1–91.2)	68.1 (60.3–75.3)	70.7 (64.0–76.5)	0.662 (0.605–0.720)
Atrial Fibrillation at entry ECG (n = 362)						
Typical strain	19.6 (14.2–26.0)	92.5 (87.5–95.9)	74.0 (59.7–85.4)	51.3 (45.6–57.0)	54.4 (49.3–59.5)	0.560 (0.526–0.595)*
Cornell voltage	22.2 (16.5–28.8)	90.8 (85.4–94.6)	72.4 (59.1–83.3)	51.6 (45.9–57.4)	55.0 (49.8–60.0)	0.565 (0.528–0.602)*
Perugia	32.8 (26.2–40.0)	85.5 (79.4–90.4)	71.3 (60.6–80.5)	53.8 (47.7–59.8)	58.0 (52.9–63.0)	0.592 (0.549–0.634)*
BMI-Perugia	36.5 (29.6–43.8)	87.9 (82.0–92.3)	76.7 (66.6–84.9)	55.9 (49.8–61.9)	61.1 (55.9–65.9)	0.622 (0.580–0.664)

Perugia criterion: (R wave amplitude in aVL + S wave amplitude in V3) ≥20 mm for women and ≥24 mm for men (Cornell voltage) or typical strain. BMI-Perugia (BMI-corrected Perugia criterion): ([R wave amplitude in lead aVL + S wave depth in lead V3] x BMI) > 604 mm kg/m^2 or typical strain pattern; *p < 0.05 vs BMI-corrected Perugia criterion.

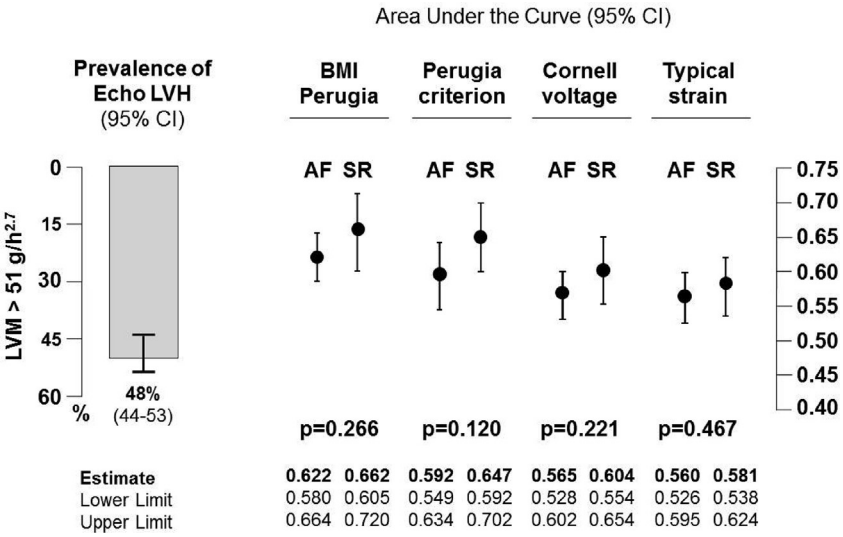

Fig. 3. Accuracy of Perugia and BMI-corrected Perugia criteria (including their components) as estimated by receiver-operating characteristics curve analyses. Performances are compared between hypertensive patients with sinus rhythm (SR) and atrial fibrillation (AF) at entry ECG. Perugia criterion: (R wave amplitude in aVL + S wave amplitude in V3) ≥20 mm for women and ≥24 mm for men (Cornell voltage) or typical strain. BMI-Perugia (BMI-corrected Perugia criterion): ([R wave amplitude in lead aVL + S wave depth in lead V3] x BMI) > 604 mm kg/m^2 or typical strain pattern. AF: atrial fibrillation; SR: sinus rhythm. LVM: left ventricular mass; CI: confidence interval; LVH: left ventricular hypertrophy; BMI: body mass index.

for diagnosis of LV hypertrophy in hypertensive patients with non-valvular AF. The main finding of this study is that the BMI-corrected Perugia criterion may be a reliable ECG tool for diagnosis of LV hypertrophy in AF patients with and without AF during the qualifying ECG. There were no significant differences in performance of ECG for identification of LV hypertrophy between patients with AF and those in sinus rhythm. These data seems to suggest that electric and conduction alternans (alternation of QRS complex and R-R interval, or combination of these), that may be present in the setting of AF [29] do not significantly affect the accuracy of BMI-corrected Perugia criterion. Furthermore, the BMI-corrected Perugia score showed a similar diagnostic performance in patients with sinus rhythm and AF, irrespective of the definition of LV hypertrophy at echocardiography.

Despite the high prevalence of AF and LV hypertrophy in the population, validation data for ECG diagnosis of LV hypertrophy in AF are scanty. A report by Casale and co-workers [30], explored criteria for LV hypertrophy using logistic regression models based on ECG and demographic variables with independent predictive value for LV hypertrophy, with separate equations for patients in sinus rhythm and those in AF. Given the impossibility to take into account morphology of P wave, the tested criterion included sex and other continuous ECG variables (i.e. duration of QRS and height of the T wave in V_1) multiplied by an empirically derived coefficient [30]. However, such computation is not simple for bedside use and requires computerized ECG reading. Conversely, the use of Perugia criterion with amplification of Cornell voltage by BMI allows an immediate diagnosis of LV hypertrophy through a simple rapid visual inspection of traditional ECG.

In our population, prevalence of LV hypertrophy was quite high both at ECG and echocardiography. In patients with AF it was 24.9% and 52.2%, respectively, whereas in those in sinus rhythm it was 20.4% and 41.8%. Although echocardiography is the procedure of choice for diagnosis of LV hypertrophy, it is more expensive than ECG and less broadly available [21]. In patients with AF, LV hypertrophy, either defined by ECG or echocardiography, refines CV risk stratification [7,13], although it cannot help in identifying AF patients requiring anticoagulation because of the lack of studies conducted in non-anticoagulated patients.

In a large group of patients with AF included in the RE-LY Study, LV hypertrophy at ECG was associated with a greater risk of stroke (HR: 1.51, p < 0.001), CV death (HR: 2.56, p < 0.0001), all-cause death (HR: 1.95, p < 0.0001), and myocardial infarction (HR: 2.07, p < 0.0001). In a multivariate analysis, the prognostic value of ECG-LV hypertrophy was additive to traditional CV risk factors and CHA_2DS_2-VASc score. However, because all patients received, by protocol, oral anticoagulants, these results could not clarify whether ECG-LV hypertrophy contributes to select patients for oral anticoagulation.

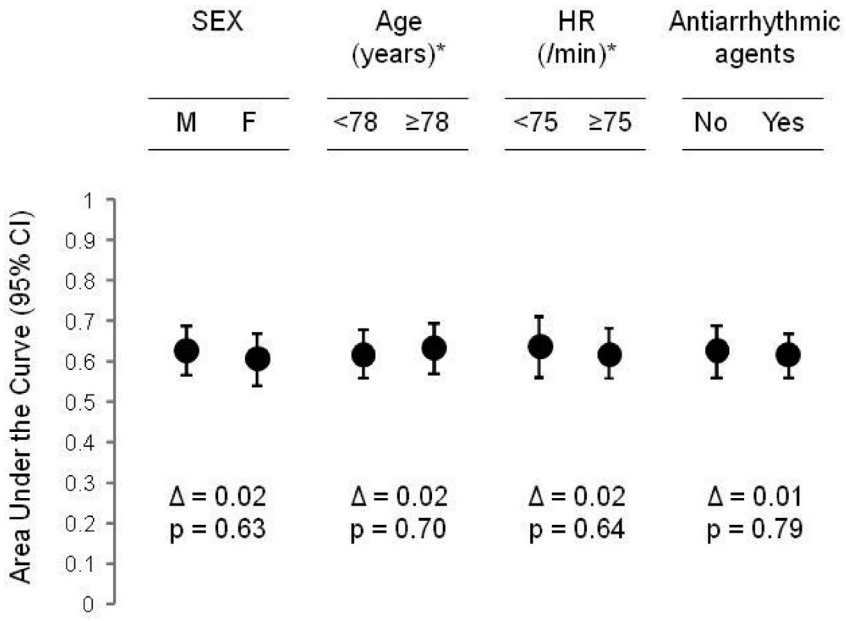

Fig. 4. Accuracy of BMI-corrected Perugia criterion as estimated by receiver-operating characteristics curve analyses in patients with atrial fibrillation at entry ECG. Performances are compared (as the difference between AUCs, Δ) in different subgroups of hypertensive patients. For age* and heart rate*, median values of their distribution are used to define subgroups. HR: heart rate; M: male; F: female.

4.1. Limitations

Our cross-sectional analysis has some limitations. Since white subjects were 99%, caution is needed in extrapolating results to different ethnic groups. Furthermore, we did not evaluate ECG scores that include measurements of total 12-lead QRS voltage [31] or criteria requiring digital acquisition of tracings (including the Cornell Voltage Duration product) [32]. Finally, analysis of ECG and echocardiographic tracings was not centralized, but conducted in the single Centers participating to the study. However, investigators of the Umbria-AF registry participated to periodical meetings with experienced cardiologists to improve standardization and reliability of ECG and echocardiographic procedures.

Although it is important to be aware of the predictive limitations of cross-sectional studies, these results indicate that standard ECG may be a reliable tool for diagnosis of LV hypertrophy even in patients with a history of AF, regardless of whether patients were in AF or sinus rhythm at the time of ECG recording.

Appendix A. Supplementary data

Supplementary data to this article, including the list of Investigators, can be found online at https://doi.org/10.1016/j.ijchy.2019.100004.

Conflicts of interest disclosure

P.V. participated in company-sponsored speaker's bureau from Boehringer-Ingelheim, Bayer, BMS-Pfizer and Servier. F.A. participated in company-sponsored speaker's bureau from Boehringer-Ingelheim, Bayer and BMS-Pfizer. C.C. participated in company-sponsored speaker's bureau from Astra-Zeneca and Sanofi-Aventis. None of the other authors of this study has financial or other reasons that could lead to a conflict of interest.

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