

# A Phi-based electrocardiographic index predicting small left ventricular mass alterations. Influence of hypertension, overweight, and sex

Un índice electrocardiográfico basado en Phi previendo pequeñas alteraciones de la masa ventricular izquierda. Influencia de la hipertensión, sobrepeso, y el sexo

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## SUMMARY

**Background:** The current cutoff value for left ventricular hypertrophy (LVH) does not accurately discriminate against minor changes in ventricular mass.

**Objective:** To verify whether an electrocardiographic index can detect a 15 % increase in left ventricular mass (LVM) based on ideal chest diameter (ICD) using a Phi-based formula approach. **Methodology:** We assessed the records of 471 patients undergoing routine cardiac check-ups in a cross-sectional study, grouped by hypertension, overweight, and sex. The

index was the sum of the leads (DI, DII, DIII), with a threshold of less than 23 mm. The ideal cardiothoracic diameter (ICD) was defined as  $\text{height}(H)/8.1$  for men and  $H/7.8$  for women. The LVM was calculated as  $16 * ((ICD/10)^3)$ . The groups were compared using the Chi-Square test, T-test, and logistic multinomial regression, as appropriate. **Results:** Mean age was  $47 \pm 13$  years, 239 men and 232 women, 36.9 % were hypertensive. The index was present in 61.1 % ( $n = 288$ ) and lacked the ability to discriminate LVH by consensus. However, it was associated with small LVM increases in the general population (OR: 1.6 CI95 %: 1.088 – 2.352,  $p = 0.016$ ) and in men with or without hypertension (OR: 3.925, CI95 %: 1.377 – 11.186,  $p = 0.009$  and OR: 1.981, CI95 %: 1.126 – 3.487,  $p = 0.017$ , respectively). Normal BMI showed an inverse odds ratio (OR) of 0.034, CI95 % - 1.112-13.804,  $p = 0.034$ . **Conclusion:** The index can predict small Phi-based LVM values in men, especially

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in hypertensive men, and is influenced by body mass index (BMI); however, the link between this index and women remains unclear.

**Keywords:** *Electrocardiographic index, golden number, Phi, hypertensive hypertrophy, diagnosis.*

## RESUMEN

**Antecedentes:** El valor de corte actual para la hipertrofia ventricular izquierda (HVI) no discrimina con precisión los pequeños cambios en la masa ventricular. **Objetivo:** Verificar si un índice electrocardiográfico puede detectar un aumento del 15 % en la masa ventricular izquierda (MVI) basado en el diámetro torácico ideal (DTI), utilizando un enfoque con una fórmula basada en Phi. **Metodología:** Evaluamos 471 registros de pacientes debido a chequeo cardíaco rutinario en un estudio transversal, en grupos según hipertensión, sobrepeso y sexo. El índice fue la suma de derivaciones (DI, DII, DIII), con un umbral de <23 mm.  $DTI = \text{Altura (A)}/8,1$  en hombres y  $A/7,8$  en mujeres,  $MVI = 16 * ((ICD/10)^3)$ , para obtener una diferencia >15 %. Se compararon los grupos mediante las pruebas  $\chi^2$ , prueba T y regresión logística multinomial, según procediera. **Resultados:** La edad media fue de  $47 \pm 13$  años, 239 hombres y 232 mujeres, 36,9 % eran hipertensos. El índice estuvo presente en el 61,1 % ( $n=288$ ) y no discriminó la HVI por consenso. Sin embargo, se asoció a aumentos menores de la MVI en la población general, (OR: 1,6 IC95 %: 1,088 - 2,352,  $p = 0,016$ ), y en hombres con o sin hipertensión (OR: 3,925, IC95 %: 1,377 - 11,186,  $p = 0,009$  y OR: 1,98, IC95 %: 1,126 - 3,487,  $p = 0,017$ , respectivamente). En análisis multivariante, el IMC normal mostró un riesgo inverso, OR: 0,034 IC95 %: 1,112 - 13,804,  $p = 0,034$ . **Conclusión:** El índice puede predecir pequeños valores de MVI basados en Phi en hombres, especialmente hipertensos, es influido por el IMC, permaneciendo esquivo este vínculo en mujeres.

**Palabras clave:** *Índice electrocardiográfico, número áureo, Phi, hipertrofia hipertensiva, diagnóstico.*

## INTRODUCTION

Echocardiography has proven to be a valuable tool for evaluating left ventricular hypertrophy (LVH). LVM is an independent factor for long-term cardiovascular events (1). Some echocardiographic guidelines suggest that it is feasible to use index values when integrating

reference intervals for measuring left ventricular mass (LVM) (2).

In another scenario, it is commonly known that body mass index (BMI), age, hypertension, and sex impact electrocardiogram (EKG) readings. For instance, the anteroposterior diameter or thoracic thickness can be a valuable variable to help interrelate electrocardiographic measures assessing left ventricular mass (LVM). However, its use has been less commonly employed. However, it is a historical factor that affects EKG signals. Nonetheless, recent authors reported scores using this measure, showing that they outperform conventional ECG criteria for LVH (3).

Electrocardiography has primarily explored a combination of limb and precordial leads in search of LVH. Although the EKG Romhilt–Estes score is an independent predictor of cardiovascular disease, it exhibits an adverse prognostic ability, which is associated with false-negative results (4). Furthermore, it is well-established knowledge that EKG precordial voltage is influenced by the thoracic chamber, with some authors addressing this variable in scoring criteria by radiography in patients with prevalent cardiovascular disease (5). Macruz described an ideal anthropometric measure that yields fixed values for left ventricular mass (6). We can assume that using the original Einthoven leads can discriminate a ventricular mass 15 % above the value estimated by Macruz's formula.

## MATERIALS AND METHODS

From a database of patients' records, we consulted routine cardiac check-ups aiming for a green appraisal for non-competitive exercise practice. We initially screened 631 cases using a convenience sample strategy. Due to the use of anonymized medical records, obtaining patient consent was not necessary. Individuals above 70 years of age were excluded, primarily because frequent EKG pathologic changes are observed beyond this threshold (7,8). Similarly, there was a restriction for individuals with a low body surface area (BSA) and obesity, as a previous report had shown that this latter condition significantly reduced EKG sensitivity (9,10).

Upon clinical history in accordance with pertinent standards, patients with the following conditions were excluded: a) chronic cor pulmonale; b) myocardial infarction; c) valvular heart disease; d) bundle branch blockages; e) pre-excitation syndrome; or f) atrial fibrillation or atrial flutter. Regarding BMI, patients with a BMI of less than 18 or greater than 30 were excluded.

Additionally, other exclusion causes were those that could modify electrocardiographic

criteria for LVH such as athletic hypertrophy due to its controversial results (11,12), aortic valve disease, hypertrophic cardiomyopathy, and congenital heart disease. We also removed 9 records that were influencing the model's fit as outliers. Finally, after applying the selection-exclusion criteria, we analyzed a resulting sample of 471 cases and compared the results of their electrocardiograms, paired with the respective time echocardiograms (Figure 1).

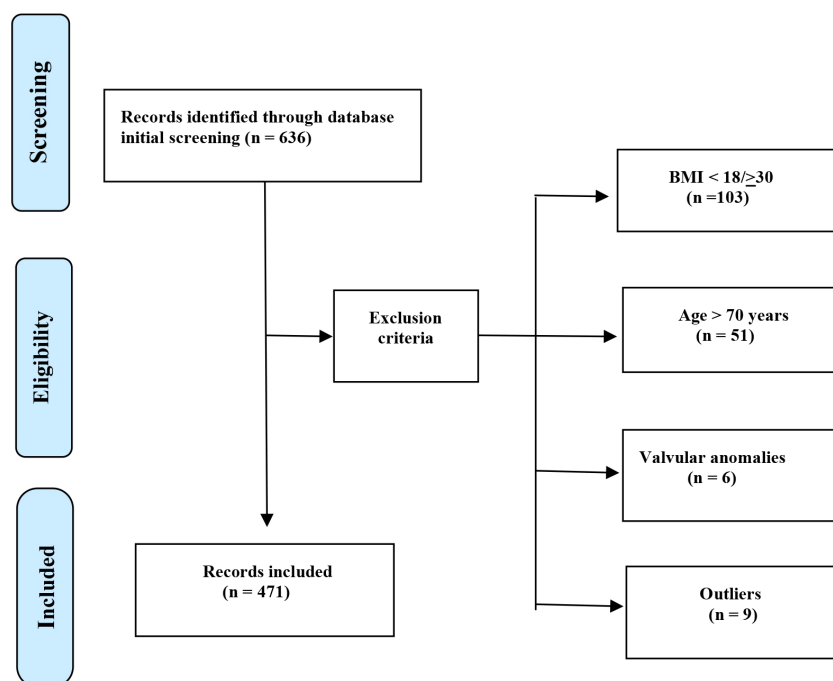


Figure 1. Flowchart of the population selection.

### Echocardiographic assessment

Two-dimensional echocardiography was performed using the Toshiba Nemio 30 Ultrasound System (Otawara-Shi, Tochigi, Japan), equipped with a multifrequency transducer operating at frequencies ranging from 2.5 to 5.0 MHz. The patients were positioned in a left lateral decubitus for image acquisition in the parasternal and apical views. Heart rhythm and frequency were monitored using an electrocardiographic lead during the test. The cardiac structures were assessed in accordance with the recommendations of the American Society of Echocardiography

(ASE) and the European Association of Cardiovascular Imaging (EACVI) (14). Left ventricular hypertrophy was defined by LVM/BSA. An observer performed the exams and immediately reviewed them by another, who was blind to the first assessment at the institution.

### Electrocardiogram assessment

A resting 12-lead standard EKG was acquired in a supine position during quiet respiration using a Hewlett-Packard Page writer 200i machine

(scale: 10 mm = 1 mV, 25 mm/s). All the tests were performed and analyzed at the Service of Electrocardiography in the same Institute. The vectorial sum of limb lead DI, DII, and DIII detailed the presence of the index when the value was less than 23 mm.

### Phi-based thoracic thickness measure

Based on our minor left ventricular mass alteration with the help of Macruz' formula describing ICD calculated based on height (H),  $TTi = H/8,1$  for males and  $H/7,8$  for females, when the patient had an ideal weight (height (cm) - 100), and  $LVM = 16 * ((ICD/10) ^3)$ , to obtain a >15 % difference between echocardiogram measures (6). ICD or anteroposterior chest diameter could also be integrated into a theoretical biometric equation  $(height - 1/5) * 0.618 \approx (\Phi)$  (15).

### Statistical analysis

The Kolmogorov-Smirnov test was used to determine the normality of the data, helping to identify and remove atypical records from the main variables. The initial dependent variable was LVM difference above 15 %. The continuous variables were expressed as mean and standard deviation and accounted for as percentages if they

were categorical variables. Categorical variables were analyzed by the Chi<sup>2</sup> method and Fisher's correction as appropriate. The Student T-test analyzed continuous variables. Multinomial regression analysis identified independent factors in the different setup groups. Data were evaluated using IBM Corp. (2015). IBM Statistics SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp program. All tests were two-tailed. A  $p < 0.05$  value was considered statistically significant.

## RESULTS

The selected population comprised 471 patients with a mean age of  $47 \pm 13$  years; 34.2 % (n = 161) had hypertension, and 65.8 % (n = 310) were normotensive. Regarding sex, hypertension tended to be more prevalent in women (37.9 %, n = 88) than men (30.5 %, n = 73), without significance ( $p = 0.091$ ). Sixty-five patients met the consensus criteria for LVH (13.8 %), and 189 (40.1 %) were classified as having an estimated ideal left ventricular mass greater than 15 %. No association was found between the EKG index and LVH or altered relative wall thickness by consensus (data not shown). Amidst the initial echocardiographic measures, only the septum showed differences between groups (Table 1).

Table 1. Echocardiographic parameters according to the index presence

	EGG index (DI-DII-DIII)		P
	Present n=344	Absent n=255	
Aorta (mm)	31.7 $\pm$ 4.0	30.5 $\pm$ 3.6	0.804
Left atrium (mm)	32.8 $\pm$ 4.1	33.3 $\pm$ 3.7	0.263
LV in diastole (mm)	48.0 $\pm$ 3.7	47.8 $\pm$ 4.1	0.565
LV in systole (mm)	29.8 $\pm$ 2.9	29.8 $\pm$ 3.5	0.205
Septum (mm)	8.2 $\pm$ 1.0	8.1 $\pm$ 1.0	0.006
Posterior wall (mm)	8.0 $\pm$ 1.0	7.9 $\pm$ 1.0	0.378
LV mass (g)	162.9 $\pm$ 38	161.4 $\pm$ 39	0.552
LV mass/BSA (g/m <sup>2</sup> )	89.2 $\pm$ 17.3	87.2 $\pm$ 16.9	0.222
Relative wall thickness	0.34 $\pm$ 0.04	0.33 $\pm$ 0.04	0.101

Legend: LV, left ventricle, BSA: body surface area

Nonetheless, in the general population, the EKG index showed a significant risk of having more than a 15 % difference in LVM based on the thoracic thickness formula (odds ratio: 1.600, CI95 %: 1.088 – 2.352,  $p = 0.016$ ). Although there was a lack of association regarding having or not having hypertension in the general population and the EKG index, there was an association after dividing the population by sex. In men, the index was associated with changes in left ventricular mass with a risk of 1.981, CI95 %: 1.126 – 3.487,  $p = 0.016$ , and if hypertension was present, the risk was greater (OR: 3.925, CI95 %: 1.377 – 11.186,  $p = 0.009$ ) (Figure 2). Also, we observed an association in the subgroup with overweight (odds ratio: 2.461 CI95 %: 1.266–4.784,  $p = 0.007$ ), with opposite behavior regarding sensitivity/specificity but balanced positive and negative predictive values. However, in men without hypertension, the odds were not significant due to crossing the basal mark of 1 (OR: 1.100, CI95 %: 0.366 – 3.303,  $p = 0.865$ ) (Tables 2 and 3).

Interestingly, if the sum of DIDIIDIII was more than 23 mm, it acted as a protective factor, resulting in a 15 % increase in left ventricular

mass (OR: 0.625, CI95 % 0.425–0.919,  $p = 0.016$ ) in the general group, before adjusting for the presence of HT, which lost significance (Tables 2 and 3). Similarly, in men, the odds ratio was 0.505, CI95 % 0.287–0.888, but not significant in women (data not shown). Furthermore, the EKG index did not show an association with HVE according to current consensus, using LVM/BMI in the general population, by sex, or by BSA (data not shown).

Although most of the mean odds ratios showed a positive association with a 15 % difference in LVM, they also crossed the basal value (1), indicating no significant difference between the arms, for example: men without hypertension (OR: 1.100, CI95 %: 0.366 – 3.303,  $p = 0.865$ ). Regarding women, the index presence showed a reverse association with a rise of LV mass. Surprisingly, only women with normal weight had a positive relationship (OR: 2.772, CI95 %: 1.004–7.658). On the other side, overweight and hypertensive women had a similar non-significant risk (OR: 0.840, CI95 %: 0.406 – 1.739,  $p = 0.639$  and OR: 0.818, CI95 %: 0.234 – 2.065,  $p = 0.671$ , respectively (Figure 2).

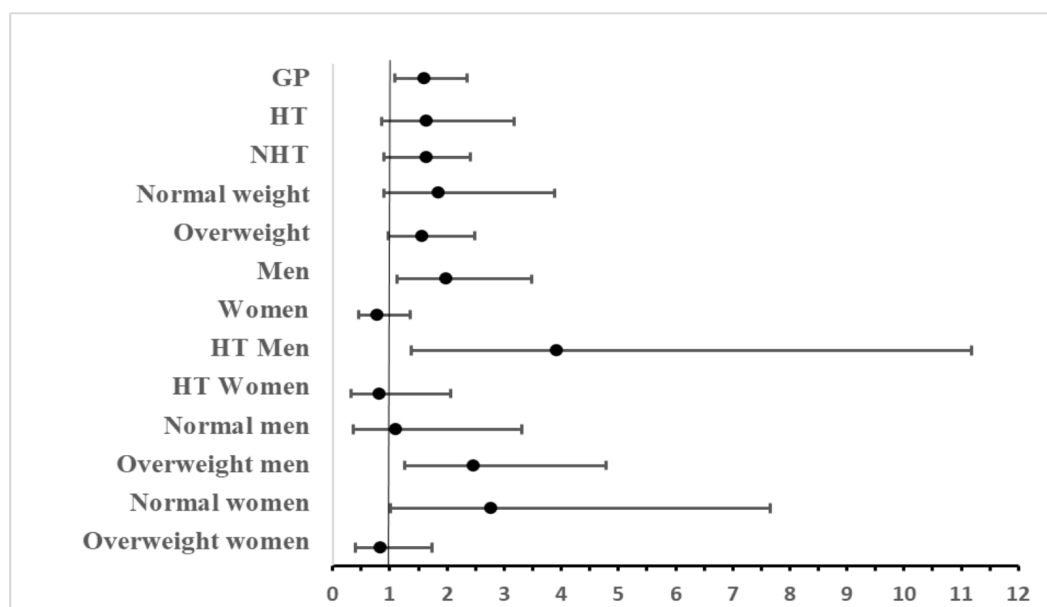


Figure 2. Odds ratios distribution for 15 % difference in LVM between groups. GP; General population, HT: hypertensive patients, NHT: non-hypertensive patients.

# A PHI-BASED ELECTROCARDIOGRAPHIC INDEX

Table 2. Electrocardiographic index, ventricular hypertrophy and 15 % difference in LVM depending on hypertension status

EKG index	15 % LVM Present	Absent	p	S	E	PPV	NPV
GP	128 (44.0 %)	160 (52 %)	0.016	67.62	43.26	67.72	66.67
HT	65 (61.3 %)	41 (38.7 %)	0.137	70.65	40.58	61.32	50.91
NHT	63 (34.6 %)	119 (65.4 %)	0.132	55.87	41.29	39.53	57.66
BMI							
Normal	33 (31.7 %)	71 (68.3 %)	0.096	71.74	42.28	31.73	80.00
Overweight	95 (51.6 %)	89 (48.4 %)	0.063	66.43	44.03	51.63	59.32
HT + Sex							
Men	29 (60.4 %)	19 (39.6 %)	0.009	48.65	80.56	60.42	72.00
Women	36 (62.1 %)	32 (37.9 %)	0.671	64.29	31.25	64.29	33.33
NHT + Sex							
Men	28 (30.1 %)	65 (69.9 %)	0.436	45.83	60.87	30.11	75.34
Women	35 (39.3 %)	54 (60.7 %)	0.212	41.94	68.63	39.33	70.91

Legend: GP: general population, HT: hypertensives, NHT: non hypertensives, BMI: Body mass index.

Table 3. EKG index and 15 % difference in LVM depending on hypertension and BMI for each sex

EKG index (n=128)		Present	Absent	P	S	E	PPV	NPV
HT	Men	29 (60.4 %)	19 (39.6 %)	0.009*	48.65	80.56	60.42	72.00
	Women	36 (62.1 %)	32 (37.9 %)	0.671	64.29	31.25	64.29	33.33
NHT	Men	28 (30.1 %)	65 (69.9 %)	0.436	45.83	60.87	30.11	75.34
	Women	35 (39.3 %)	54 (60.7 %)	0.212	41.94	68.63	39.33	70.91
BMI (men)	Normal	11 (26.8 %)	30 (73.2 %)	0.865	61.11	41.18	26.83	75.00
	OW	46 (46.0 %)	54 (54.0 %)	0.007	71.88	49.06	46.00	74.29
BMI (women)	Normal	22 (34.9 %)	41 (65.1 %)	0.044	78.57	43.06	34.92	83.78
	OW	49 (58.3 %)	35 (41.7 %)	0.639	62.03	33.96	58.33	37.50

Legend: HT: hypertensive patients, NHT: non-hypertensive patients, BMI: body mass index, OW: overweight, S: sensitivity, E: specificity, PPV: positive predictive value, NPV: negative predictive value, \*p < 0.05.

In multivariate analysis, the groups were divided by the presence of hypertension and by sex. Additionally, BSA and BMI were incorporated together. As a result, it was found that both variables were associated with the LVM difference in the absence of hypertension. In hypertensive patients, the association was maintained only for BMI, for both sexes. Regarding the EKG index, only men could discriminate between the small rise in left ventricular mass (Tables 4 and 5).

## DISCUSSION

Many, if not all, echocardiography parameters vary according to gender, body habitus, height, weight, or both, ethnicity, fitness level, and age. We did not include ethnicity or body habitus in the study, as these factors could modify the results. Nonetheless, apart from the groups of non-hypertensive and hypertensive patients, we had the opportunity to assess minor left ventricular mass changes in sex groups. A distinctly



Table 4. Non-hypertensive patients and independent factors for LVM changes by sex

Dif.15 %M Men	B	Wald	P	$\beta$	CI95 %	
					Lower limit	Upper limit
Age	-0.005	0.115	0.735	0.995	0.967	1.024
BSA	-4.879	11.801	0.001	0.008	0.000	0.123
EKG index	0.281	0.532	0.466	1.324	0.623	2.813
BMI (Normal)	-0.842	3.947	0.047	0.431	0.188	0.989

Dif.15 %M Women	B	Wald	P	$\beta$	CI95 %	
					Lower limit	Upper limit
Age	0.049	1.096	0.295	1.050	1.013	1.089
BSA	-3.208	3.924	0.048	0.040	0.002	0.967
EKG index	0.306	0.508	0.476	1.358	0.585	3.148
BMI (Normal)	-1.796	14.569	<0.001	0.166	0.066	0.417

Legend: Dif. 15 % M: 15 % difference in left ventricular mass, BMI: body mass index, BSA: body surface area.

Table 5. Hypertensive patients and independent factors for LVM changes by sex

Dif.15 %M Men	B	Wald	P	$\beta$	CI95 %	
					Lower limit	Upper limit
Age	-0.031	1.469	0.225	0.970	0.922	1.019
BSA	-5.646	5.719	0.017	0.004	3.453E-5	0.361
EKG index	1.366	4.516	0.034	3.918	1.112	13.804
BMI (Normal)	-1.829	4.170	0.041	0.161	0.028	0.929

Dif.15 %M Women	B	Wald	P	$\beta$	CI95 %	
					Lower limit	Upper limit
Age	0.030	1.744	0.187	0.187	0.985	1.079
BSA	-3.012	2.420	0.120	0.120	0.001	2.188
EKG index	-0.308	0.375	0.540	0.540	0.275	1.968
BMI (Normal)	-1.068	4.104	0.043	0.043	0.122	0.966

Dif.15 %M: 15 % difference in left ventricular mass, BMI: body mass index.

different approach to assessing and comparing electrocardiography and echocardiography has not been seen previously.

Furthermore, the cut-off values provided in the current literature are high, often missing a significant percentage of hypertrophy diagnoses when using Sokolow or Cornell criteria (16,17).

Considering a Phi-derived formula that accounts for a relatively small change based on anatomic proportion, we may encounter a valid relationship. Moreover, recent research has shown that the use of EKG voltage criteria in estimating LVH in a hypertensive population is low, with a positive predictive value of 3.9 % for Cornell and 1.9 % for the Sokolow-Lyon index (18).

Taking a simpler approach, just using the Einthoven triangle (standard limb leads), in contrast, our index predicted small changes with far higher accuracy (above 60 % for the general population and for men with or without hypertension). Other authors have already ascribed the importance of detecting such small changes. A study with 436 non-complicated hypertensive patients and more than five years of follow-up illustrated that a rise in the percentage predicted of theoretical LVM using a equation that include stroke work (predicted LVM (pLVM) =  $55.37 + 6.64 \text{ height (m}^{2.7}) + 0.64 * \text{stroke work} - 18.07\text{sex}$  (where sex was coded as male 1 and female 2) had an event rate (x 100 patient-years) of 3.18 in the group with inappropriate LVM persistent and of 0.81 amongst patients with persistent of appropriate LVM (log-rank test,  $p=0.0001$ ) (19). This result suggests the importance of small ventricular chamber variations as a risk in cohort studies, anticipating the known risk that brings actual LVH criteria.

### Weight influence

The overweight or obese patient experiences persistent myocardial stress as a result of increased cardiac output and minute volume, which is a consequence of an increase in cardiac output and minute volume proportional to excess body weight. This occurs due to increased blood flow from adipose tissue, with minimal compromise of resting heart rate but with an elevation of systolic volume. Ultimately, the patient exhibits a compensatory rise in LVM. It has been previously described in a larger population as the BMI-LVM association (20). In this study, we observed an initial tendency that was confirmed in men in the multivariate analysis.

### Sex influence

We believe that inconsistent associations in men and women imply different intrathoracic and corporal factors that affect impedance and conductance between the sexes. This relationship has been described in a large population of adults, demonstrating the link between fat percentage, age, and sex (21). In the EKG, sex differences have been more extensively explored, primarily

in the QRS voltage of precordial leads, which are part of the most commonly used index, as well as in QRS duration, the ST segment, and T amplitude, as compared in multiethnic databases (22). Moreover, we observed that the relationship between BMI, sex, and the EKG index was opposite. In this scenario, it can be hypothesized that the positive relation in women with normal BMI acts as the overweight in men, and a possible explanation lies in the bioimpedance similarities in both groups. Furthermore, age can also influence this, as described by some authors who found sex difference impedance to depend on BMI category and a decrease in fat-free mass with aging, which was attenuated in women (23).

### Limitations and advantages

Besides being a pilot study that introduces a new approach and yields valid findings by comparing the association between electrocardiography and echocardiography, it still involves a modest number of cases. Further research could help better define our findings in a prospective setting, including the alterations observed in individuals with optimal blood pressure control, and the type of exercise the patient used to do that might modify ventricular chambers. This pertinent first question may help explain the wider confidence interval observed in hypertensive men. On the other hand, characterizing women proved to be elusive. We suspect that two main factors could be involved, one of them is the proportional lean mass, and the second could be mammary tissue or sex reported differences in bioimpedance. Meanwhile, it is a significant advantage to predict proportional small changes in left ventricular mass using a straightforward tool, such as the index presented, instead of being based on a population cut-off. Setting a universal fixed value, rather than an epidemiological range of normality, could eventually prevent or guide treatments more effectively and individually. Finally, we must emphasize that none of the patients suffered from ischemia, inflammation, or interstitial fibrosis (conditions observed in some of the pathologies that comprised the exclusion criteria), all of which can accompany myocardial remodeling and could be studied further in future research.



## CONCLUSION

The index did not show utility for guidelines cut-off hypertrophy values. BMI influences the index prevalence. Moreover, in hypertensive men, the novel EKG index significantly predicted minor alterations in left ventricular mass based on Phi-based thoracic measures. However, it remained a challenge to foresee this association in women.

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