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ROLE OF PEGUERO LO-PRESTI CRITERIA IN THE DIFFERENTIAL DIAGNOSIS BETWEEN HYPERTROPHIC CARDIOMYOPATHY AND HYPERTENSIVE HEART DISEASE

FINAL DEGREE PROJECT

CARDIOLOGY DEPARTMENT

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“Wherever you go, go with all your heart”.

-Confucius

I am so grateful to the cardiology department of Josep Trueta Hospital for their hospitality and kindness. Thank you all for give me your time, specially to Dr. Ramón Brugada and Dra. Coloma Tirón. It has been a pleasure to work with you.

Special thanks to my family for always supporting me and let my dreams come true. Without you being a doctor would not be possible. Papá, Mamá y Leni quérovos moito.

Thanks Girona and all people I have meet here for make me feel like home.

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1. LIST OF ABREVIATIONS

BP: Blood Pressure

DBP: Diastolic Blood Pressure

ECG: Electrocardiogram

HHD: Hypertensive Heart Disease

HMC: Hypertrophic cardiomyopathy

LVH: Left Ventricle Hypertrophy

LVM: Left Ventricular Mass

LVMI: Left Ventricular Mass Index

SBP: Systolic Blood Pressure

SCD: Sudden Cardiac Death

2. ABSTRACT

BACKGROUND: Electrocardiogram is an easy tool to determinate left ventricular hypertrophy, but classical criteria have a low sensitivity. A new ECG criteria, Peguero-Lo Presti has demonstrated in patients with Hypertensive Heart Disease (HHD) that it is more sensible.

Hypertrophic Cardiomyopathy (HCM) is characterized by an heterogenous clinical and phenotypic expression that it is responsible of the mayor number of deaths in young people due to its arrhythmogenic capacity and sudden cardiac death. Moreover, more of patients are asymptomatic in early phases of the disease which makes very necessary to determinate a very sensible marker of this disease to make an early diagnosis and avoid these fatal consequences.

HYPOTHESES: Peguero-Lo Presti criteria is more sensible to detect HCM than Sokolow-Lyon voltage index. Moreover, due to the different hypertrophic pattern in HHD (concentric and symmetrical hypertrophy) and HCM (asymmetrical septal hypertrophy), Peguero-Lo Presti criteria could have a different expression reflected on the 12-lead ECG.

OBJECTIVES: The main of this study is to determinate the sensitivity of Peguero-Lo Presti criteria in patients with HCM and evaluate the role of this criteria in the differential diagnosis between HHD and HCM.

METHODS: A prospective analytic and observational case-control study will be designed. The case-group will be formed by 185 patients with HCM and the control-group will be formed by 185 patients with HHD. This study will be developed at Josep Trueta Hospital in Girona for the Cardiology Department for 2 years.

KEYWORDS: Hypertrophic Cardiomyopathy, Hypertensive Heart Disease, Peguero-Lo Presti Critera, Electrocardiogram, Sudden Cardiac Death

3. INTRODUCTION

Hypertrophic cardiomyopathy (HCM) and hypertensive heart disease (HHD) are two pathologies which both have in common the possibility to develop left ventricular hypertrophy (LVH) characterized by increased length and width of the myocyte.

Left Ventricular Hypertrophy (LVH) is one of the most frequent cardiac manifestations with an unfavourable prognosis due to its association with arrhythmic events and sudden cardiac death. (1) To determinate LVH, one of the most commonly used measurement is left ventricular wall thickness (LVWT) (2):

- Normal LVWT is < 11 mm.
- Mild LVWT 11–13 mm.
- Moderate LVMT 14–15 mm.
- Severe LVMT > 15 mm.

LVH could be physiological or be secondary to other diseases (Figure 1).

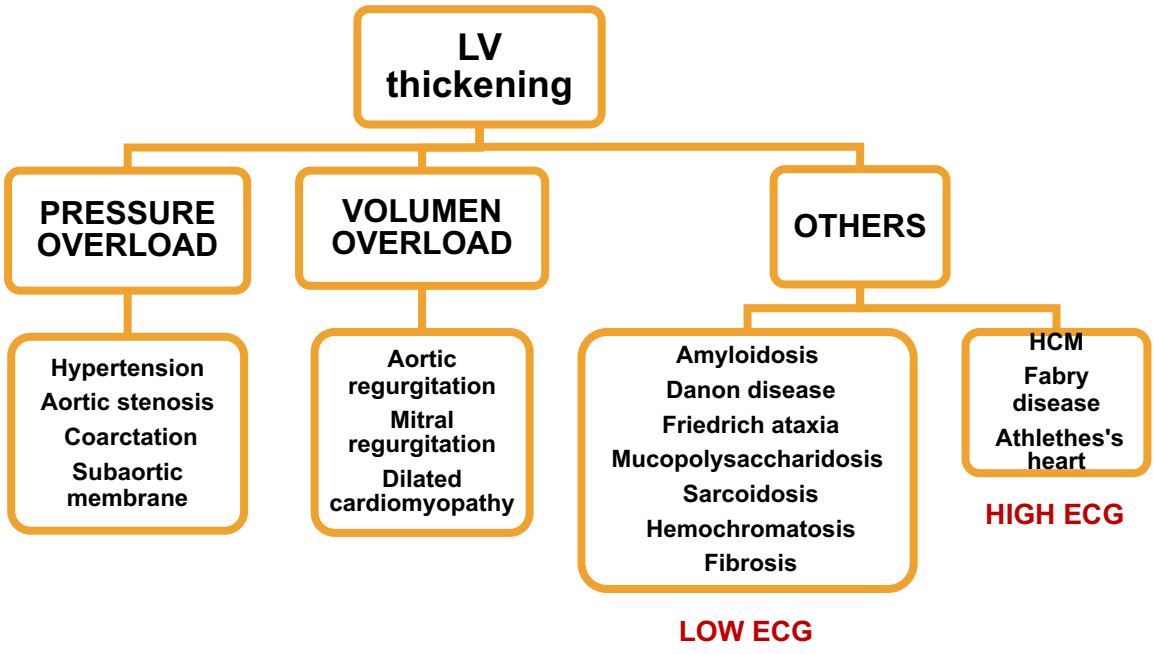

Figure 1. Different causes of left ventricular thickening (2)

Infiltrative diseases such as amyloidosis or Fabry Disease, cardiomyopathies (Hypertrophic Cardiomyopathy), valvopathies (aortic stenosis) and hypertension are pathological causes of LVH, being the latter one the most common issue. But athletes could have physiological hypertrophy as a heart adaptation due to intensive and prolonged aerobic exercise with an increased size of myocytes and absence of myocardial fibrosis. (3) Thus, it generates a high proportion of false-positive test results. (4)

Different hypertrophic patterns (concentric, eccentric, asymmetric) determined by imaging exist and there are associated with the physiopathological mechanisms that lead to LVH. (2)

Sudden Cardiac Death (SDC)

It is defined as natural death caused by heart pathology which is preceded by sudden loss of consciousness that takes less than one hour from the onset of acute symptoms, in an individual that could have a known pre-existent cardiopathy, but time and way of death are unexpected. (5)

The mechanism of SCD usually is primary ventricular tachycardia and ventricular fibrillation. It exists a direct association between sudden death risk and wall thickness. (6)

SCD is considered a devastating and unpredictable disease consequence so it is important to evaluate patient's risk to develop it and try to prevent it in high-risk patients. The risk factors are exposed in Table 1. The application of Implantable Cardioverter Defibrillator (ICD) made the opportunity to prevent these catastrophic events. Accordingly, the importance of risk stratification to select which patients would benefit most from this therapy.

Table 1 RISK FACTORS OF SUDDEN CARDIAC DEATH (7)

SECONDARY PREVENTION
• Cardiac arrest or sustained ventricular tachycardia
CONVENTIONAL PRIMARY PREVENTION RISK MARKERS
• Family history of SCD due to HCM
• Unexplained recent syncope
• Multiple repetitive non-sustained ventricular tachycardia (on ambulatory ECG)
• Hypotensive or attenuated blood pressure response to exercise
• Massive left-ventricular hypertrophy (thickness ≥30mm)
• Extensive and diffuse late gadolinium enhancement

Hypertrophic Cardiomyopathy (HCM)

It is the most frequent of the five types of cardiomyopathies classified by the European Society of Cardiology.(8) Its diagnosis is based on the presence of a non-dilated and hypertrophied left ventricle on 2-dimmensional echocardiography or cardiac magnetic resonance (CMR) showing a left ventricular maximal wall thickness at end-diastole ≥ 15mm in the absence of other cardiac or systemic diseases that could account for the hypertrophy. It can also be diagnostic lesser degrees of wall thickness (≥13-14 mm) when family members are affected. (9)(10)

It has an heterogenous clinical and phenotypic expression. Phenotype is present during birth and it develops during advanced phases of life, especially during puberty. Each phenotype is subclassified into familiar and no familiar forms. (5)

Patients could refer exercise intolerance, fatigue, palpitations, syncope, typic or atypical thoracic pain, dyspnoea, orthopnoea, light-headedness, systolic murmur that increases with Valsalva, ...

But patients are usually asymptomatic at the diagnosis moment. It is often done by a routine control or due to the apparition of arrhythmic events (Atrial fibrillation, ventricular tachycardias) or, worst, sudden cardiac death (SCD). Syncope is the only symptom that it has been probed it is associated with sudden death. (11) It is the leading cause of mortality in those patients.

Furthermore, HCM could course with ventricle infundibulum obstruction or not, being the ones with obstruction more often symptomatic.

50% of affected people present some degree of heart failure with diastolic dysfunction but preserve systolic function. The natural history of the disease provokes myocardial fibrosis linked with poor prognosis because its association with arrhythmias (9), microvascular ischemia, consecutive intracardiac pressure increase and contractile dysfunction. The end-stage HCM is defined as LV ejection fraction <50%. (5)

So, patients may be situated in or progress to develop adverse events that require specific treatment strategies: SCD, progressive heart failure with exertional dyspnoea and functional limitation and atrial fibrillation. (12)

Epidemiology and genetics

One of the most common and important genetic heart diseases that it is responsible of the 10% of sudden cardiac death specially in young people. (13) It affects 1:500 subjects (Global prevalence 0,2%) (14)(7) but there is an underestimate number of people affected because of many people are asymptomatic.

Its heterogenous clinical expression is attributed to more than 1400 mutations in over 11 sarcomere protein genes that could develop the disease. (13) In general, familiar and hereditary cardiomyopathies have an autosomal dominant inheritance pattern but penetrance depends also on ambient factors. (11)

60% of the patients have sarcomeres mutations in the genes which codify the proteins of the thin and thick microfilaments. 80% of these mutations are in MYH7 (β-myosin heavy chain) and MYBPC3 (Myosin-binding protein C), but there are other ones as TNNT2, MYL2 or MYL3. (5)(11)(15)

These sarcomeres mutations cause calcium increment which generates maximum strength and ATPase activity and consecutive relaxation disturbance. (5)

Also, it is important to emphasize that phenotype and mutations not have a correlation and the treatment will be based on the phenotype.

Treatment

The aim of the treatment in HCM is to avoid arrhythmic events and sudden death and improve the symptomatology and functional capacity of patients. It has to be individualized to each patient.

Asymptomatic patients should performance an aggressive modification of risk factors such as hypertension, diabetes, obesity and hyperlipidaemia as well as a low-intensity aerobic exercise program.

Beta-blocking drugs are good to treat dyspnoea or angina as a first line treatment, followed by verapamil therapy or oral diuretics.

High-risk patients of SCD are candidates to application of implantable cardioverter defibrillator to prevent malignant arrhythmias.

Atrial fibrillation is well controlled with beta-blocking drugs, calcium antagonists and digoxin besides anticoagulation treatment with vitamin K antagonists to prevent embolisms. In refractory cases, it is possible to do an ablation. Septal reduction therapy such as myomectomy and alcohol septal ablation are two possibilities in HCM with infundibulum obstruction.

In some cases, it is useful an implantation of a pacemaker. (16)

Hypertensive Heart Disease (HHD)

It is defined by LVH showed by echocardiography or cardio magnetic resonance in the absence of another evident cause in patients with a long-standing history of arterial hypertension and confirmed by clinical and ambulatory blood pressure monitoring with systolic blood pressure (SBP) >140 mm Hg and/or diastolic blood pressure (DBP) >90 mm Hg. (1)

Hypertension is considered as predisposing factor to develop heart failure (with reduced or preserved systolic function), coronary disease, nephropathies, peripheric arteriopathies and cerebrovascular accidents. The main cause of death in hypertensive patients are cardiopathies.

HHD is the result of structural and functionals adaptations to hypertension due to pressure overload and it ends in concentric LVH. Wall stress stimulates sarcomeres to proliferate in parallel by increasing protein synthesis, which increases myocyte width and fibrosis, resulting in an increase in the wall thickness/chamber dimension. Fibrosis and medial thickening of coronary arteries result on disturbances of myocardial blood flow, arrhythmogenic events and diastolic dysfunction. (17) However, when hypertrophy can no longer compensate for the increased afterload, patients start to have symptoms and then LV dilatation (eccentric hypertrophy) occurs and LV performance decreases. (18)

Clinically, patients with HHD have the same symptoms than patients with HCM.

<u>Epidemiology</u>

In Spain, the prevalence of hypertension is around 30-36% in population older than 45 years old. Previous studies have shown that 20% of hypertensive patients develop LVH and, as a consequence, heart failure. We can conclude that 9-13% of general population have HHD.(19)

This prevalence of LVH is higher in hypertensive patients that have more than one cardiovascular risk factors: Diabetes mellitus, smoking, BP no controlled, male gender, personal history of cardiovascular disease, nephropathies or aging. (20)

Treatment

LVH can be resolve with an intense control of hypertension and therefore, reduce cardiovascular risk. Treatment includes dietary modification, weight loss, regular aerobic exercise and pharmacotherapy. (21)(22)(23)

In the general population aged ≥ 60 years, pharmacologic treatment to lower BP is indicated at SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg and treat to a goal BP <140/90 mm. Population < 60 years initiate pharmacologic treatment at DBP ≥90 mm Hg and treat to a goal DBP < 90 mm Hg.

In diabetic, the goal BP is 130/80 mm Hg.

First line treatments are therapies with angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blocker (ARB) which have shown to reduce LV mass.

CLINICAL APPROACH HCM AND HHD

Symptoms classified patients according to New York Heart Association (NYHA) in four groups:

- **Class I.** Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or anginal pain.
- **Class II.** Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain.

- **Class III**. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnoea, or anginal pain.
- **Class IV.** Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

DIAGNOSTIC LVH IN HCM AND HHD

Several modalities of tests are available and utilized to study LVH: 12-lead ECG, transthoracic echocardiography and cardiac magnetic resonance (CMR) are the most common tools.

Twelve-lead electrocardiogram (ECG) provides an initial approach together with the physical examination, but they have a low sensitivity to detect LVH markers. It is necessary to obtain an image to discard other causes of LVH.

ECG ambulatory screening process has the advantages that it is a non-invasive and fast tool which can detect arrhythmias and abnormalities to identify LVH. Abnormal results on screening ECG can trigger an unsuspected diagnosis of LVH: high proportion of false positives test results. That it is why ECG there is not a reliable marker for HMC in mass participation screening of young healthy general athlete population. (4)

Several previous studies have investigated about the values of the different electrocardiographic criteria. The most frequent anomalies are alterations in repolarization and occurrence of Q waves. (11)

Different criteria to estimate LVH exist (Figure 2). The classic ones are Sokolow-Lyon voltage and Cornell voltage criteria versus the new one Peguero-Lo Presti. (24) All studies conclude in the poor sensitivity that those criteria have.

Montgomery J.V. et all. (6) studied the correlation between LV wall thickness in patients with HCM and the 12-lead ECG voltages, obtaining a weak correlation. Sokolow-Lyon index, Romhilt-Estes score and Cornell voltage were performance in each patient. Patients with massive degrees of LVH showed increased S and R waves voltages only in 50% what meant that ECG is not a strong predictor of the magnitude of LVH.

Konno T et all.(9) study showed also a weak correlation between Sokolow-Lyon Index with LV mass, and between Cornell Voltage Index and total QRS voltage with left ventricular mass wall thickness (LVMWT). These latter two criteria demonstrate in that sample the cut-off points for end-stage HCM where myocardial fibrosis has a key role.

As a conclusion, those previous studies agree in the weak correlation between LVH and classical criteria what makes the development of a new electrocardiographic criteria to detect LVH very necessary. So that was what Julio G. Peguero and Sabero Lo Presti did in a recent study in 2017. (24) They knew that classical criteria had low sensitivity and they designed a case-control study to detect LVH in patients with hypertensive emergency and urgency and patients who came to the cardiology department for other reasons. They studied in those patients the classical criteria as Sokolow-Lyon Voltage Index and Cornell Voltage Index with a new proposed criteria called Peguero-Lo Presti Criteria.

The results obtained in this study (Table 2) were in favour for the new criteria, which demonstrated a better sensitivity than the classic ones due to the better association between S waves in precordial and limb leads and an increased left ventricular mass.

Table 2: Results of Peguero J.G. and Lo-Presti S. study

	Sensitivity (IC 95%)	Specificity (IC 95%)
Sokolow-Lyon voltage	**23%**	**97%**
Cornell voltage	**40%**	**91%**
Peguero-Lo Presti	**70%**	**89%**

- Peguero-Lo Presti

It is obtained measuring the deepest S wave (S_D) in any lead plus S wave in V_4: S_D+ SV_4. If the S_D is found in lead V_4, the S amplitude will be doubled to obtain this value.

It is considered LVH values ≥2,3 mV in women and ≥2,8 mV in men (Figure 2, in red).

- Sokolow-Lyon Voltage

It is obtained by adding the amplitude of S wave in V_1 and the amplitude of R wave in V_5 or V_6.

LVH is considered ≥3.5 mV (Figure 2, in green).

- Cornell Voltage Criteria

It is obtained measuring the amplitude of R wave in aVL plus the amplitude of S or QS complex in V_3.

LVH is considered ≥ 2.0 mV in women and ≥ 2.8 mV in men (Figure 2, in blue).

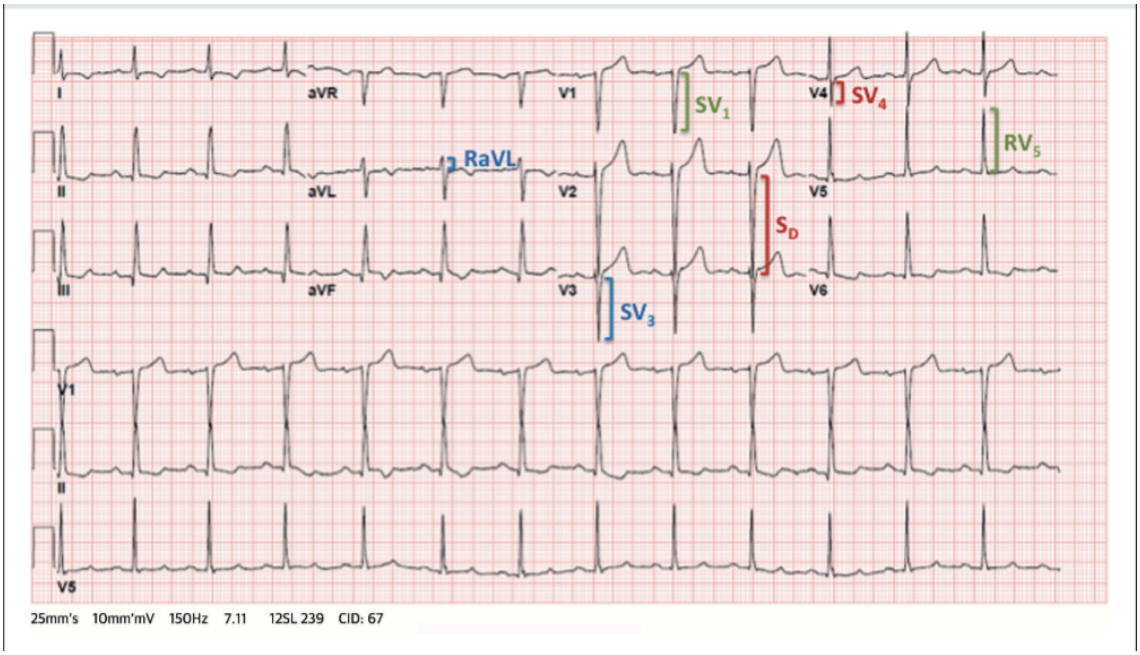

Figure 2. Electrocardiogram of a 71-year-old man. Criteria for LVH are shown. Peguero-Lo Presti criteria in red (deepest S wave in any lead and S wave in V_4), Cornell Voltage (R in aVL plus S wave in V_4) and Sokolow-Lyon voltage (S wave in V_3 plus R in V_5 or V_6).

Transthoracic echocardiography is used as a reference method to estimate left ventricular mass (LVM) that is calculated by the Devereux formula:

$$0.80 \times \{1.04 \times [(\text{septal thickness} + \text{internal diameter} + \text{posterior wall thickness})^3 - (\text{internal diameter})^3]\} + 0.6\ g = \text{LVM (g)}$$

The LVM is indexed with body surface area to obtain LVM index defined as >115 g/m^2 in men and >95 g/m^2 in women. (24)

The wall is measured at any site of LV wall regarded as the maximal thickness.

The frames of visualization to detect distribution and extension of LVH in echocardiography are: long and short parasternal axis, apical (four chambers) and short apical (two chambers). (6)(25)

It is common to find non-uniform ventricular increased thick being the most frequent at the interventricular septum (Figure 3) (septal asymmetric hypertrophy, 70%) followed by

concentric (15%) and apical (10%) in HCM (11) instead of a concentric pattern (Figure 4) in HHD (26) that it is usually symmetrical, ununiformly involving septum and left ventricular posterior wall. (27)

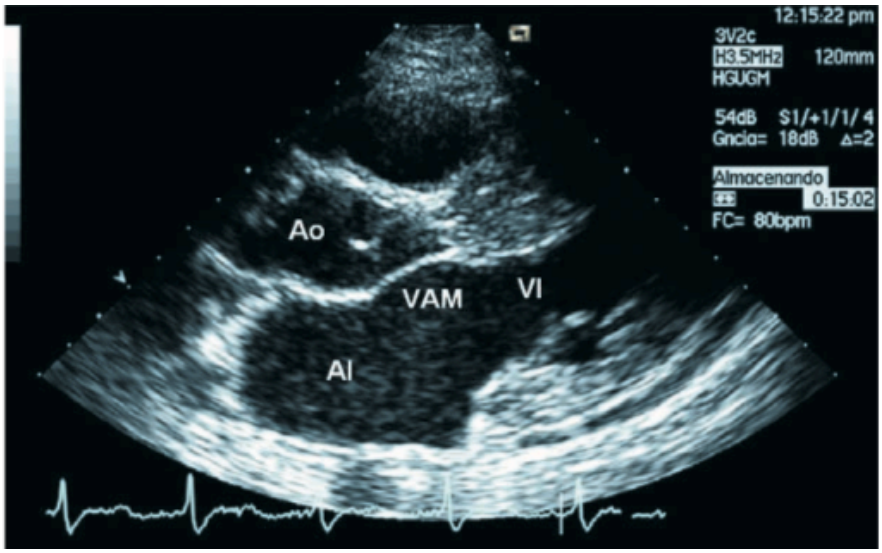

Figure 3: Long parasternal axis in a transthoracic echocardiography of HCM where Interventricular septum hypertrophy exist. (28)

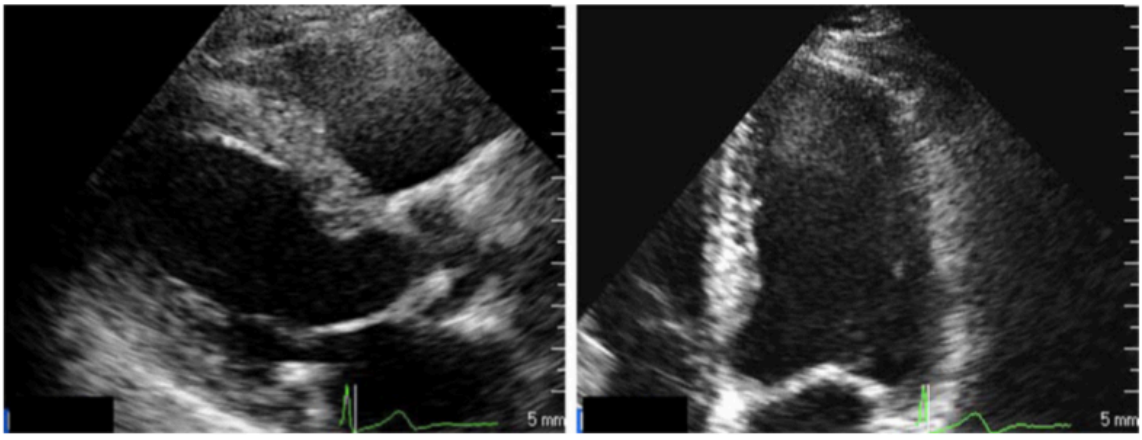

Figure 4: Long parasternal axis (left) and four chamber of concentric LVH. (29)

Also, echocardiogram is useful to measure LV outflow obstruction and provides the quantification of systolic and diastolic functions using real time imaging.

Cardiac magnetic resonance (CMR) has emerged as an indispensable non-invasive tool to provide high resolution images of myocardial wall with more accuracy that echocardiography. It is the gold-standard to evaluate myocardium. It enables to assess the degree of LV outflow obstruction and the presence of late gadolinium enhancement (LGE) that detects potential areas of myocardial fibrosis which are responsible to develop ventricular arrhythmias and adverse events in those patients, translating a poor prognosis. (9)(10)(13)

CMR enables to differentiate the specific LV geometric pattern which as therapeutic and prognostic implications. There are five different geometric patterns of LV thickening, namely concentric hypertrophy, asymmetric hypertrophy, eccentric hypertrophy, concentric remodelling and asymmetric remodelling. (2) (Figure 5).

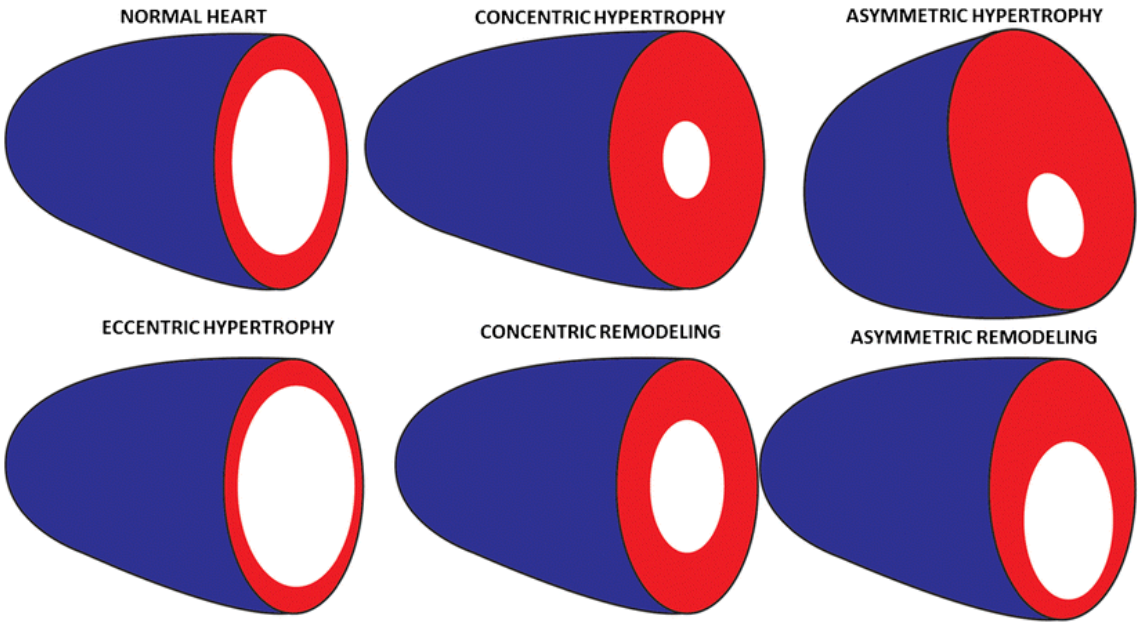

Figure 5: Different patterns of LVH. (2)

Moreover, it is possible to have findings in others supplementary tests such as cardiomegaly in a thorax radiography.

- **Justification**

ECG is an easy non-invasive and fast initial method to detect LVH, but it has a low sensitivity. In a previous study, a novel criteria Peguero-Lo Presti has been shown that it is more sensible than classical LVH criteria such as Sokolow-Lyon Voltage index or Cornell voltage criteria in patients with HHD.

There is no evidence about this ECG criterion in HCM, so it would be of special interest to investigate the sensitivity on this group of patients.

Both diseases involve LVH with a potential risk to develop heart failure, arrhythmias and even worst SCD, especially in those patients with HCM. Moreover, HCM affects young people who are often asymptomatic in early phases of the disease and it is important to make an early diagnosis and treatment to prevent arrhythmogenic events that could end with life or affect quality of life.

It would be also interesting to investigate about the value of Peguero Lo-Presti ECG Criteria to difference HHD and HCM because they have a distinct pattern of muscle affectation that could be reflected into the ECG: the LVH in patients with HHD is concentric, affecting symmetrically all the wall of the left ventricle, instead of the classical asymmetric hypertrophy of HCM, affecting the interventricular septum.

Those possible electrocardiogram findings could help in the future on the LVH screening in patients with those diseases, have a consistent suspect of the true cause of LVH previous to the realization of more complementary tests as echocardiography or cardiac magnetic resonance that provides the definitive diagnosis.

Furthermore, it will be an indispensable tool on the following on HHD after an adequate and intense treatment of hypertension which could regress the hypertrophy.

An early diagnosis could prevent these fatal consequences and propose the adequate treatment in accordance to the patient and the individual disease characteristics.

4. HYPOTHESIS

Hypothesis 1:

Peguero-Lo Presti criteria has more sensitivity in patients with HCM than Sokolow-Lyon Voltage Index.

Hypothesis 2:

Mayor number of patients with HCM has a septal asymmetric hypertrophy instead of concentric pattern that it is characteristic from HHD. Due to the different hypertrophic pattern, Peguero-Lo Presti criteria should reflect affecting different leads on the ECG.

5. OBJECTIVES

Objective 1: Determinate the value of Peguero-Lo Presti ECG criteria in the diagnosis of patients with HCM.

Objective 2: Evaluate the utility of ECG criteria Peguero-Lo Presti in the differential diagnosis between patients with hypertrophic myocardiopathy and hypertensive heart disease.

6. METHODS

STUDY DESIGN

This is an observational analytic and prospective case-control study, in which we will perform a 12-lead ECG in each participant. The case-group will be formed by patients with Hypertrophic Cardiomyopathy and the control-group patients with Hypertensive Heart Disease. The study will be carried out during 2 years at Josep Trueta Hospital in Girona.

STUDY POPULATION

Population with LVH caused by HHD and HCM who are attending to Cardiology Department at Josep Trueta Hospital in Girona.

INCLUSION AND EXCLUSION CRITERIA

CASES: HCM

- Inclusion criteria

  -Patients with hypertrophy myocardiopathy defined as a LV wall thickness >15mm by a transthoracic echocardiography.

  -Patients with family history of HMC and a LV wall thickness >13mm

- Exclusion criteria

  -Patients with a long-standing BP ≥140/90.

  -Complete left or right bundle branch block

  -Atrial Fibrillation

CONTROLS: HHD

- Inclusion criteria

  -Patients with a long-term history of hypertension defined as SBP>140 mmHg and/or DBP>90 mmHg and echocardiography suggestive of concentric LVH >11 mm.

- Exclusion criteria

  -Complete left or right bundle branch block.

  -Atrial fibrillation.

  -Personal history of coronary heart disease.

All ages and sex are included in both groups.

SAMPLE

The sample size of the study will be calculated by Granmo program.

Accepting alpha risk of 0.05 and beta risk less than 0.02 in a bilateral contrast, 185 cases and 185 controls are needed to detect a minima Odds Ratio of 2. We assume that the exposed rate in controls will be 0.6. We estimate than lost ratio in the tracing will be around 10%. The POISSON approximation has been used.

Sampling method

The recruitment of patients will be carried out randomly from the register of those diseases at Josep Trueta Hospital. Patients will be invited to participate by telephone and those who accept to be part of the study, they will get an appointment to attend to the hospital. They will be divided depending on their pathology into two groups formed by 185 patients each one. Both groups will be matched by age and sex.

Based on the number of patients we have under study conditions, two months will be enough to call and performance the ECG.

VARIABLES

Hypothesis 1

- Independent variables:

    a. Peguero-Lo Presti Criteria:

    Measured by adding the deepest S wave in any lead and S wave in V_4: S_D+ SV_4. If the S_D is found in lead V_4, the S amplitude will be doubled to obtain this value.

    It is a categorical dichotomic variable defined as

    -YES: ≥2.3 mV females, ≥2.8 mV males

    -NO: <2.3 mV females, <2.8 mV males

    b. Sokolow-Lyon Voltage Index

    It is obtained by adding the amplitude of S wave in V_1 and the amplitude of R wave in V_5 or V_6.

    It is a categorical dichotomic variable defined as:

    -YES: ≥3.5 mV

    -NO: <3.5 mV

- Dependent variable: Presence of Hypertrophy Cardiomyopathy.

Measured by transthoracic echocardiography or cardiac magnetic resonance and defined as the presence of a non-dilated and hypertrophied left ventricle showing a left

ventricular maximal wall thickness at end-diastole ≥ 15mm in the absence of other cardiac or systemic diseases that could account for the hypertrophy.

Hypothesis 2

- Independent variable: Peguero-Lo Presti ECG criteria

Measured by adding the deepest S wave in any lead and S wave in V_4: S_D+ SV_4. If the S_D is found in lead V_4, the S amplitude will be doubled to obtain this value.

It is a categorical dichotomic variable defined as

-YES: ≥2.3 mV females, ≥2.8 mV males

-NO: <2.3 mV females, <2.8 mV males

- Dependent variable: hypertrophy pattern

Measured by transthoracic echocardiography: wall thickness ≥11 mm.

It is a categorical dichotomic variable:

-Concentric hypertrophy (Symmetric)→ HHD

-Interventricular septum hypertrophy (Asymmetric)→ HCM

- Covariables

In general, these groups of patients are very different. Other variables that could affect the association between independent and dependent variables:

-Sex: Dichotomic variable defined as male/female.

-Age: This variable will be determined by years.

-Diabetes Mellitus: Determined by hyperglycaemia ≥200 mg/dl.

-Exercise: This variable will be defined as at least half an hour of exercise, three days per week.

-Smoking: Defined as number packages of cigarettes per year.

-Cardiologist experience: Cardiologist with 10 years of experience.

To avoid these confusing factors, both groups of patients will be match by age and sex.

STATICALLY ANALYSIS

Descriptive analysis

Continuous variables with a normal distribution will be reported as means ± SD and those with symmetric or asymmetric distribution as medians and interquartile range. Categorical variables will be reported as frequencies and percentages.

Bivariant analysis

The sensitivity of Peguero-Lo Presti criteria and Sokolow-Lyon Voltage Criteria in patients to HCM will be estimated with proportions and 95% of confidence interval. (Objective 1)

Sensitivity = True positive/ (True positive + False negatives)

	HCM
Peguero-Lo Presti +	A
Peguero-Lo Presti -	B

	HCM
Sokolow-Lyon +	a
Sokolow-Lyon -	b

Sensitivity of Peguero-Lo Presti in HCM will be measured by:

A / A + B

Sensitivity of Sokolow-Lyon Voltage Index in HCM will be measured by:

a / a + b

Objective 2: the Odds ratio will be estimated with proportions and 95% of confidence interval.

	CASES: HCM	CONTROLS: HHD
Peguero-Lo Presti +	A	C
Peguero-Lo Presti -	B	D

Odds Ratio: A x D/ B x C.

Multivariant analysis:

Although both groups will be matched, a multivariant analysis (logistic regression) will be performance to avoid confusion due to covariables.

MEASURAMENTS

12 lead-ECG will be performance following the classic recommendations with patients in a relaxed supine position in the stretcher with six precordial electrodes and four limb electrodes. A nurse will perform the task.

All 12-lead ECG interpretations will be independently reviewed by 2 cardiologists. S waves will be measured manually by two cardiologists in every lead of the ECG, selecting the deepest S wave in any lead and the S in V_4 to determinate Peguero-Lo Presti Criteria. Sokolow-Lyon Voltage Index will be also measured manually by the same two cardiologists by adding the amplitude of S wave in V_1 and the amplitude of R wave in V_5 or V_6.

Data will be introduced in a data base. Those specialists will not know which pathology is associated with each ECG to avoid information bias.

7. ETHICAL CONSIDERATIONS

This study will be performed following the basic principles established by the World Medical Association in the *Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects (1964).* Before the beginning of the study, this research protocol has to be presented, evaluated and approved by the Clinical Research Ethical Committee (CEIC) at the Hospital Josep Trueta in Girona. Again, at the end of the study, the final report should be presented to the CEIC.

According to "Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal" (Last review July 2018), personal and clinical information of participants will be confidential and only used for the purpose of the research. Moreover, all data will be analysed anonymously. Participants will have to sign voluntarily the informed consent (Annex 1) before being included in the study after receiving the appropriate information about procedures, according to "Ley 41/2002 Básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica" (Last review 2015). The participant, or the responsible of the participant, will always be allowed to modify or destroy their collected data or refuse to participate once the study has started.

8. STUDY STRENGTHS AND LIMITATIONS

Strengths:

- ECG is a non-invasive, safe and fast tool that is accessible in any hospital in develop countries.
- The cardiologist observers will not know the pathology associated to each ECG, so it will be avoided the information bias.
- Patients are recruited randomly by a probabilistic sampling method.

Limitations:

- ECG will be interpreted by two cardiologist who will measure manually S waves.
- Patients recruitment will be done by telephone. It will be difficult to contact with everyone due to wrong number, they will never pick up the telephone, ... but before starting the study we assume that we will lose 10% of patients to calculate the sample size.
- Single-center study.

9. WORK PLAN

This study will be carried out for the research team. The different tasks will be divided in seven stages. A chronogram is after the explanation to visualize in an easy way every task.

Stage 1: Initial meeting

The research team will meet to determinate and define the different roles in the study. A research coordination will be named to maintain the time, organize, solve problems and supervise the team work.

Stage 2: Bibliography research, study design and elaboration of the protocol

Bibliography research and revision will be performed by the whole team for three months. The objectives and hypothesis of the study will be the result of previous knowledge and clinical needs. The elaboration of the protocol will be carried out by the medical student.

Stage 3: CEIC approbation

Once it is written, it will be presented to the Clinical Research Ethical Committee (CEIC). The approbation could take 3 months.

Stage 4: Patients recruitment

Patients will be selected randomly for the register of those diseases of Josep Trueta Hospital. Each patient will have a number and we will select randomly some numbers, being those selected the ones who will participate in our study.

An administrative will call all patients by telephone to make the appointments to come to the hospital. Two months will be needed to call all patients.

Stage 5: Data collection

If the protocol is approved by the CEIC, data collection will be start. Each patient will have the informed consent signed before the ECG performance.

12-lead ECG will be performed by a nurse during two hours per day attending around ten patients daily. Each patient will take 10 minutes of time. All ECG will be done in two months.

Two cardiologists will receive all ECG, interpret and introduce the results in a data base for six months.

Stage 6: Statistical Analysis

Once data collection is ready, a statistician will be hired to analyse the results. It will take 3 months.

Stage 7: Publication and dissemination of results

Results have to be confirmed and processed and then, the research coordination will prepare a report with the results, discussions and conclusions that will be published and promulgated in written publications and international congresses. The ending part will take around 3 months.

10. CHRONOGRAM

	TASKS	November 2018	December 2018 - February 2019	March-May 2019	June-July 2019	August 2019-January 2020	February-April 2020	May-August 2020
STAGE 1	Initial meeting							
STAGE 2	Bibliography research, study design and protocol elaboration							
STAGE 3	CEIC approbation							
STAGE 4	Patient recruitment							
STAGE 5	Data collection							
STAGE 6	Statistical analysis							
STAGE 7	Publication and dissemination of the results							

11. BUGDET

To execute this study, we are expecting to need:

Personnel:

1. The research team formed by five cardiologists of Josep Trueta Hospital who will review bibliography and participate in the study. Two of them will read and interpret the electrocardiograms. The research team will be in charge for most of the task of the study.
2. An administrative who will call all patients by telephone and give them the appointments to come to the hospital. It will cost 1500 euros per month.
3. One nurse to performance ECG. It will cost 2000 euros per month.
4. A statistician will be hired to analyse data. We estimate that 30 hours will be needed. It will cost 25 euros per hour, so it will be 750 euros.

Diagnostic tests:

- 12-lead electrocardiogram: The ECG machines is already at the hospital, but paper and patches will cost for each patient 1 euro. We expect to have 370 patients, so we will performance 370 ECG that will cost 370 euros.

Writing and publication of final results in an article:

The research team will be responsible to write the final conclusions and results in the article but the peer reviewing and publication in a scientific journal will cost around 2000 euros.

EXPENSES	COSTS (Euros)
Administrative workers	1500 euros per month: 3000 euros in total
Nurse	2000 euros per month: 4000 euros in total
370 electrocardiograms	370 euros
Statistician	750 euros
Review and publication of final results in a scientific journal	2000 euros
TOTAL	**10120 euros**

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13. ANNEXES

- **ANNEX 1:** INFORMED CONSENT AND PATIENT INFORMATION (Spanish)

HOJA INFORMATIVA

Nos dirigimos a usted para proponerle su participación en un estudio sobre la miocardiopatía hipertrófica. Se trata de una enfermedad genética que afecta al miocardio del corazón que generalmente se desarrolla en etapas tempranas de la vida y no suele desarrollar síntomas inicialmente. Estos pacientes presentan riesgo de complicaciones fatales como arritmias y muerte súbita, pudiendo manifestarse por primera vez con estos síntomas.

Le agradeceríamos su participación con la finalidad de profundizar en el conocimiento de pruebas diagnósticas que puedan evitar tales consecuencias.

Para llevar a cabo este estudio, se realizará a cada paciente un ECG por lo que solo tendrá que venir una vez al hospital. La duración del estudio será de dos años.

Toda la información recogida será tratada de manera confidencial y analizada en conjunto para publicaciones científicas y difusión en congresos especializados. En ningún caso se publicarán resultados individuales ni ningún tipo de información que pudiera identificarles. Informaremos al paciente en todo momento y resolveremos las dudas que se le puedan plantear.

La participación es estrictamente voluntaria y puede retirarse en el momento que desee sin tener que dar explicaciones ni sufrir penalización por ello.

La participación en el estudio carece de ningún riesgo para la salud de los participantes.

CONSENTIMIENTO INFORMADO

D./Dña. _____, mayor de edad, de _____ años de edad, manifiesto que he sido informado/a sobre el estudio "Papel del criterio electrocardiográfico Peguero-Lo Presti en el diagnóstico diferencial entre Miocardiopatía Hipertrófica y Cardiopatía Hipertensiva" dirigido por el Dr. Brugada del Departamento de Cardiología del Hospital Josep Trueta de Girona.

- He recibido información suficiente sobre el estudio.
- He podido hacer y resolver todas las dudas que me han surgido.
- Comprendo que mi participación es voluntaria.
- Comprendo que puedo retirarme del estudio.
- He sido informado/a de que mis datos personales serán protegidos y sometidos a las leyes dispuestas en la Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal y que mis datos nunca serán cedidos a terceras personas o instituciones.

Tomando todo ello en consideración, OTORGO mi CONSENTIMIENTO a participar en este estudio para cubrir los objetivos especificados.

Firma del participante: Firma del investigador:

Nombre y fecha: Nombre y fecha:

Tutor/a legal del menor_____, de _____ años de edad, de D./Dña. _____, de _____ años de edad, manifiesto que he sido informado/a sobre el estudio “Papel del criterio electrocardiográfico Peguero-Lo Presti en el diagnóstico diferencial entre Miocardiopatía Hipertrófica y Cardiopatía Hipertensiva” dirigido por el Dr. Brugada del Departamento de Cardiología del Hospital Josep Trueta de Girona.

- He recibido información suficiente sobre el estudio.
- He podido hacer y resolver todas las dudas que me han surgido.
- Comprendo que mi participación es voluntaria.
- Comprendo que puedo retirarme del estudio.
- He sido informado/a de que mis datos personales serán protegidos y sometidos a las leyes dispuestas en la Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal y que mis datos nunca serán cedidos a terceras personas o instituciones.

Tomando todo ello en consideración, OTORGO mi CONSENTIMIENTO a participar en este estudio para cubrir los objetivos especificados.

Firma del tutor/a: Firma del investigador:

Nombre y fecha: Nombre y fecha: