CAIO DE ASSIS MOURA TAVARES

Avaliação de critérios eletrocardiográficos para detecção da hipertrofia ventricular esquerda em pacientes acima dos 70 anos

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Programa de Cardiologia

Orientador: Prof. Dr. Carlos Alberto Pastore

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EPÍGRAFE

“Não chores, meu filho;

Não chores, que a vida

É luta renhida: Viver é lutar.

A vida é combate,

Que os fracos abate,

Que os fortes, os bravos,

Só pode exaltar.”

Trecho de “**Canção do Tamoio**” de **Gonçalves Dias**

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ABREVIATURAS E SIGLAS

AUC - Área sob a curva

BAVT - Bloqueio atrioventricular total

BB - Betabloqueadores

BCC - Bloqueadores de canal de cálcio

BRA - Bloqueadores dos receptores AT1 de angiotensina II

BRD - Bloqueio de ramo direito

BRE - Bloqueio de ramo esquerdo

CRM - Cirurgia de revascularização do miocárdica

DAOP - Doença arterial obstrutiva periférica

ECG - Eletrocardiograma

ERP - Espessura relativa da parede

FAp - Fibrilação atrial paroxística

FC - Frequência cardíaca

HAS - Hipertensão sistêmica

HVE - Hipertrofia ventricular esquerda

IC - Intervalo de confiança

IMVE - Índice de massa ventricular esquerda

IECA - Inibidores da enzima conversora de angiotensina

ICP - Intervenção coronária percutânea

LOA - Lesão de órgão-alvo

MSEG - Milissegundos

mV - milivolts

PPVED - parede posterior do ventrículo esquerdo

PA - Pressão arterial

RNM - Ressonância nuclear magnética

ROC - *Receiver Operating Characteristic*

RV- - Razão de verossimilhança negativa

RV+ - Razão de verossimilhança positiva

UTI - Unidade de terapia intensiva

VPN - Valor preditivo negativo

VPP - Valor preditivo positivo

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RESUMO

Tavares CAM. *Avaliação de critérios eletrocardiográficos para detecção da hipertrofia ventricular esquerda em pacientes acima dos 70 anos* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2022.

Introdução: Embora o eletrocardiograma (ECG) seja utilizado rotineiramente para detecção da hipertrofia ventricular esquerda (HVE), os critérios utilizados apresentam baixa sensibilidade. Poucos estudos que embasam a prática clínica incluíram pacientes idosos e a performance diagnóstica do ECG nesta população é incerta. Recentemente proposto, o critério de Peguero-Lo Presti (PLP) apresentou uma maior acurácia que critérios tradicionais do ECG, mas não incluiu uma amostra representativa de idosos. Ademais, poucos estudos avaliaram a performance diagnóstica do ECG em pacientes com bloqueio de ramo esquerdo (BRE). **Objetivo**: i) comparar a performance do critério de PLP com critérios tradicionais do ECG em pacientes idosos; ii) avaliar a capacidade do ECG para detectar HVE em pacientes com BRE; iii) analisar a utilidade clínica do ECG em ambos os cenários (com BRE e sem BRE). **Métodos:** Entre janeiro de 2017 e março de 2018, 4.621 pacientes foram avaliados, com inclusão de 660 pacientes (592 na análise sem BRE e 68 com BRE) com ECG e ecocardiograma realizado com intervalo menor que 180 dias. Duas análises totalmente separadas foram realizadas de acordo com a presença ou não de BRE (definido pelo critério de *Strauss*). Para pacientes sem BRE, a performance diagnóstica, através da avaliação de sensibilidade, especificidade, escore F1 e área sob a curva (AUC) do critério de PLP foi comparada a dos critérios de Cornell voltagem (CV), Sokolow-Lyon (SL) e Rohmilt-Estes (com cortes de 4 e 5 pontos, RE4 e RE5, respectivamente). Em pacientes com BRE, sensibilidade, especificidade, valores preditivos, razões de verossimilhança, AUC e escore Brier de dez critérios do ECG foram analisados para avaliar o desempenho no diagnóstico da HVE. Nos dois cenários (com e sem BRE), HVE foi definida pelo ecocardiograma transtorácico e uma análise de curva de decisão foi feita para avaliar a utilidade clínica do ECG. **Resultados:** Em pacientes sem BRE, o critério de PLP obteve a maior sensibilidade comparado ao SL, CV ($p<0,001$) e RE5 ($p=0,042$), nominalmente a maior AUC (0,70 [IC 95% 0,65-0,74) dos critérios analisados e a maior acurácia diagnóstica avaliada pelo escore F1 (58,3%). Os critérios de SL e CV apresentaram maior especificidade que PLP (0,93 [IC 95% 0,89-0,95] e 0,90 [IC 95% 0,86-0,93], versus 0,82 [IC 95% 0,78-0,86], respectivamente; $p<0,05$ para ambas as comparações). Em pacientes com BRE, nenhum dos dez critérios obteve desempenho diagnóstico satisfatório evidenciado pelo desequilíbrio entre sensibilidade e especificidade, e com baixo poder de discriminação (AUC entre 0,54 e 0,67). A análise da curva de decisão evidenciou que para os limiares de probabilidade testados, houve benefício líquido do ECG somente na população sem BRE, e o critério de PLP apresentou o maior benefício líquido. **Conclusão:** O critério de PLP obteve a maior acurácia diagnóstica e capacidade de informar a decisão de solicitar ou não exame complementar para avaliação de HVE, em pacientes idosos e sem BRE. Na subpopulação com BRE, nenhum dos critérios eletrocardiográficos tem

capacidade discriminatória suficiente para recomendar seu uso para diagnóstico da HVE nem utilidade clínica.

Descritores: Hipertrofia Ventricular Esquerda; Idoso; Eletrocardiografia; Hipertensão; Bloqueio de Ramo Esquerdo.

ABSTRACT

Tavares CAM. *Usefulness of ECG criteria do detect left ventricular hypertrophy in patients with advanced age* [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2022.

Background: Electrocardiography (ECG) criteria has low sensitivity for left ventricular hypertrophy (LVH) detection and data in patients with advanced age patients is limited. The recently published Peguero-Lo Presti (PLP) criteria had improved accuracy compared with other ECG criteria but with very few patients ≥ 70 years. Also, overall performance of ECG criteria in patients with left bundle branch block (LBBB) is also unknown. **Methods**: Retrospective single-center study including patients ≥ 70 years with ECG and echocardiogram less than 180 days apart from January 2017 to March 2018. From 4,621 screened patients, 660 were included, 592 without and 68 with LBBB, yielding two entirely separate analysis. LBBB was defined according to Strauss criteria. For patients without LBBB, the Peguero-Lo Presti (PLP) criteria was compared against Cornell voltage (CV), Sokolow-Lyon voltage (SL) and Romhilt-Estes criteria (cutoffs of 4 and 5 points, RE4 and RE5, respectively), with sensitivities and specificities compared by the Mc Nemar’s test, and diagnostic performance by the F1 score and diagnostic area under the receiver operating characteristic curve (AUC). For patients with LBBB – defined by the stricter criteria proposed by Strauss - sensitivity, specificity, predictive values, likelihood ratios, AUC, and the Brier score were used to evaluate diagnostic performance of the ECG. For both analyses, LVH defined by the echocardiogram was the gold standard and a decision curve analysis was performed to evaluate the clinical benefit of the ECG to inform decision-making. **Objective**: i) to compare the PLP diagnostic performance to more traditional ECG criteria in patients ≥70 years; ii) to analyse the overall performance of ECG criteria to diagnose LVH in patients with LBBB; and iii) to evaluate the clinical applicability of ECG criteria for LVH detection in patients with and without LBBB. **Results**: In patients without LBBB, the PLP had increased sensitivity compared with both the SL, CV ($p<0.001$ for both comparisons) and RE5 ($p=0.042$), also AUC of the PLP was higher than the CV, RE and SL (respectively, 0.70 [95%CI 0.65-0.74] vs 0.66 [95%CI 0.62-0.71] vs 0.64 [95%CI 0.60-0.69 vs 0.67 [95%CI: 0.62-0.71]). SL and CV had higher specificity compared to the PLP (respectively, 0.93 [95%CI 0.89-0.95] vs 0.90 [95%CI 0.86-0.93] vs 0.82 [95%CI 0.78-0.86], all $p<0.05$). Overall, the PLP criteria had the highest F1 accuracy score (58.3). In patients with LBBB, none of the tested ECG criteria provided an accurate discrimination of LVH (AUC range, 0.54 to 0.67) nor had a balanced tradeoff between sensitivity and specificity, indicating poor overall performance. In the decision curve analysis, for most probability threshold range, ECG criteria had net benefit only in patients without LBBB, with the PLP achieving the highest net benefit in this scenario. **Conclusions**: In older individuals without LBBB, the Peguero-Lo Presti criteria had the highest diagnostic accuracy, can potentially be used to inform the clinical decision to ordering for echocardiogram ordering, but cannot rule out LVH consistently due to low sensitivity. in patients with LBBB defined by stricter

criteria, ECG-based criteria for LVH diagnosis lack diagnostic accuracy or clinical utility.

Descriptors: Hypertrophy, left ventricular; Aged; Electrocardiography; Hypertension; Left bundle-branch Block.

1. INTRODUÇÃO

1. INTRODUÇÃO

A hipertrofia ventricular esquerda (HVE) é um preditor independente de mortalidade e morbidade cardiovascular em pacientes com hipertensão sistêmica (HAS)(1-5). Em pacientes com idade avançada, a HVE também é um fator de pior prognóstico, embora exista uma carência na literatura sobre o impacto da HVE nesta população(6). O eletrocardiograma (ECG) de 12 derivações é recomendado como parte do *screening* universal de lesão de órgão-alvo (LOA) em pacientes com hipertensão arterial de acordo com as diretrizes internacionais(7, 8) e nacionais(9). Dado as características do ECG como exame complementar – ampla disponibilidade, baixo custo – e já ter sido validado como uma ferramenta prognóstica em paciente com HAS(10), seu uso para indivíduos sob risco é extremamente interessante pois tem grande alcance populacional. Adiciona-se a isto o fato de que o uso de critérios eletrocardiográficos de HVE somados a calculadoras de risco cardiovasculares aumenta a acurácia preditiva deste escores(11, 12). A repetição sequencial do ECG traz ainda mais informações prognósticas: em pacientes sob tratamento farmacológico de HAS que tem regressão da HVE eletrocardiográfica apresentam risco reduzido do desfecho combinado de morte, acidente vascular encefálico, infarto agudo do miocárdio e insuficiência cardíaca. Caracteriza-se, portanto, a importância do ECG para screening em pacientes sob risco de HVE, em avaliações seriadas de HVE em função do tempo e como ferramenta auxiliar para decisões terapêuticas.

O ECG apresenta, no entanto, uma série de limitações para diagnóstico da HVE, como a ausência de consenso sobre quais critérios devem ser utilizados - são descritos na literatura mais de 30 critérios eletrocardiográficos disponíveis(13, 14) – e sobretudo sua baixa sensibilidade em estudos que utilizaram a HVE definida através do índice de massa ventricular esquerda (IMVE) avaliada anatomicamente por ecocardiograma transtorácico ou por estudo de ressonância nuclear magnética (RNM) cardíaca(14-17). Existem diversos fatores que justificam a baixa acurácia do ECG, relacionados ao fato de que vetores da despolarização ventricular esquerda podem ser afetados por diversos fatores extra cardíacos, como a anatomia do tórax, peso corporal, presença de derrame pericárdico, doenças pulmonares, além da possibilidade de posicionamento incorreto de eletrodos(18, 19).

Essa limitação do ECG é ainda maior em pacientes idosos, nos quais dados sobre a sensibilidade, especificidade e outras métricas para avaliação da acurácia diagnóstica do ECG para a detecção de HVE são extremamente limitados(20, 21). Trata-se, no entanto, da população que mais irá crescer em nosso país nos próximos anos: estimativas atuais são de que em 2030, mais de 20,4 milhões de brasileiros terão mais que 70 anos. Espera-se, também aumento concomitante de doenças relacionadas a idade(22), especialmente da HAS, a doença cardiovascular mais comum nesta faixa etária(23). A combinação de envelhecimento populacional, atrelada a carência de critérios eletrocardiográficos voltados para paciente idosos, caracteriza importante lacuna de conhecimento e uma área com necessidade urgente de desenvolvimento de pesquisas científicas. O objetivo é evitar que o cuidado destes idosos seja

baseado apenas na extrapolação de achados de indivíduos jovens. Deve-se, portanto, incentivar estudos científicos para esta população tanto para validar achados de outras populações como para gerar conhecimento específico para esta faixa etária.

O cenário fica ainda mais complexo ao considerarmos que ativação elétrica anormal do ventrículo esquerdo pela presença de bloqueio de ramo esquerdo (BRE) também limita a aplicabilidade de critérios eletrocardiográficos para reconhecimento da HVE, visto que os critérios eletrocardiográficos baseados na voltagem da despolarização ventricular (QRS) usualmente excluíram de suas análises pacientes com distúrbio de condução ou bloqueios de ramo e que a validação de critérios para estes pacientes também é muito infrequente(24). Alguns autores até consideram que o diagnóstico de HVE não deva ser tentado em pacientes com BRE(25) dada as suas limitações em identificar aumento da massa ventricular esquerda diante de alterações da ativação elétrica do ventrículo esquerdo. Elucidar esta questão tem também aspecto prático importante, dado que o envelhecimento também é associado ao BRE e o número de indivíduos hipertensos com BRE deve aumentar progressivamente nos próximos anos(26-28). Recentemente, *Strauss* e colaboradores, propuserem uma nova classificação do BRE(29) e até o presente momento nenhuma publicação científica havia analisado a performance diagnóstica de critérios eletrocardiográficos em pacientes em pacientes com BRE de acordo com os critérios de *Strauss* (**Tabela 1**).

Tabela 1. Critérios de *Strauss* para definição de BRE

Critério ECG	**Descrição**
1) Duração QRS	≥140 mseg homens ≥130 mseg mulheres
2) Critério morfológico para derivações direitas (V1, V2)	QS ou rS em V1 e V2
3) Onda R entalhada ou empastada na porção média do QRS*	≥2 derivações (V1, V2, V5, V6, I, ou aVL

Mseg: milissegundos. A positividade do critério de *Strauss* necessita do preenchimento de todos os critérios. * = A porção média do QRS é definida por entalhe ou empastamento que se inicia 40mseg após o início do QRS e antes de 50% da duração total do QRS.

Recentemente, um novo critério eletrocardiográfico, nomeado Peguero-Lo Presti, foi proposto(30): através da soma da onda S na derivação V4 com a maior S nas outras derivações (SD + SV4) com o corte de 2.3mV para mulheres e 2.8mV para homens para definição de HVE. Na publicação, o critério de PLP obteve melhor área sob a curva (AUC) que critérios tradicionais do ECG (Sokolow-Lyon, Cornell voltagem, onda R em AvL e onda R em DI) porém poucos pacientes com idade maior que 70 anos foram incluídos.

Neste contexto, uma avaliação da performance diagnóstica do critério de Peguero-Lo Presti, comparada a critérios tradicionais de ECG especificamente em pacientes idosos trará informações relevantes sobre a aplicabilidade deste critério nesta população. A avaliação deste e de outros critérios em pacientes com BRE, definido pelos critérios de *Strauss,* também se faz necessária para avaliar a utilidade do ECG na detecção de HVE diante de cenário comum em pacientes idosos: a presença concomitante de HAS e BRE. Outro aspecto interessante de ser estudado é a capacidade do ECG de excluir a presença de

HVE dado que os tempos de espera para realização de exame confirmatório desta patologia pode ser extremamente longo – chegando a 540 dias em nosso país para realização de ecocardiograma transtorácico(31). Se critérios de ECG pudessem auxiliar a decisão médica referente a quem deve realizar ecocardiograma transtorácico para confirmação da HVE, teoricamente haveria potencial para redução das filas de espera para este exame, assim como otimizar o número de exames que detectam a HVE para número fixo de exames.

2. OBJETIVOS

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Analisar a performance diagnóstica do critério de Peguero-Lo Presti em pacientes com idade avançada, comparativamente a critérios eletrocardiográficos tradicionais para a detecção de HVE.

Analisar a utilidade diagnóstica de critérios eletrocardiográficos para detecção de HVE em pacientes com critério de BRE proposto por *Strauss.*

Analisar a utilidade de critérios eletrocardiográficos em pacientes com e sem BRE para auxiliar a decisão clínica de pedir exame complementar confirmatório.

3. MÉTODOS

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3.1 População do estudo

Dados de pacientes com ≥ 70 anos atendidos no Instituto do Coração (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo entre 01/01/2017 e 31/03/2018. Paciente em que havia ao menos um ECG de repouso de 12 derivações e um ecocardiograma transtorácico na instituição foram coletados retrospectivamente, após aprovação do projeto no comitê de ética (CAAE 08797119.1.0000.0068, parecer 3.210.301).

3.2 Critério de inclusão

ECG e Ecocardiograma transtorácico realizados com intervalo de tempo menor ou igual a 6 meses.

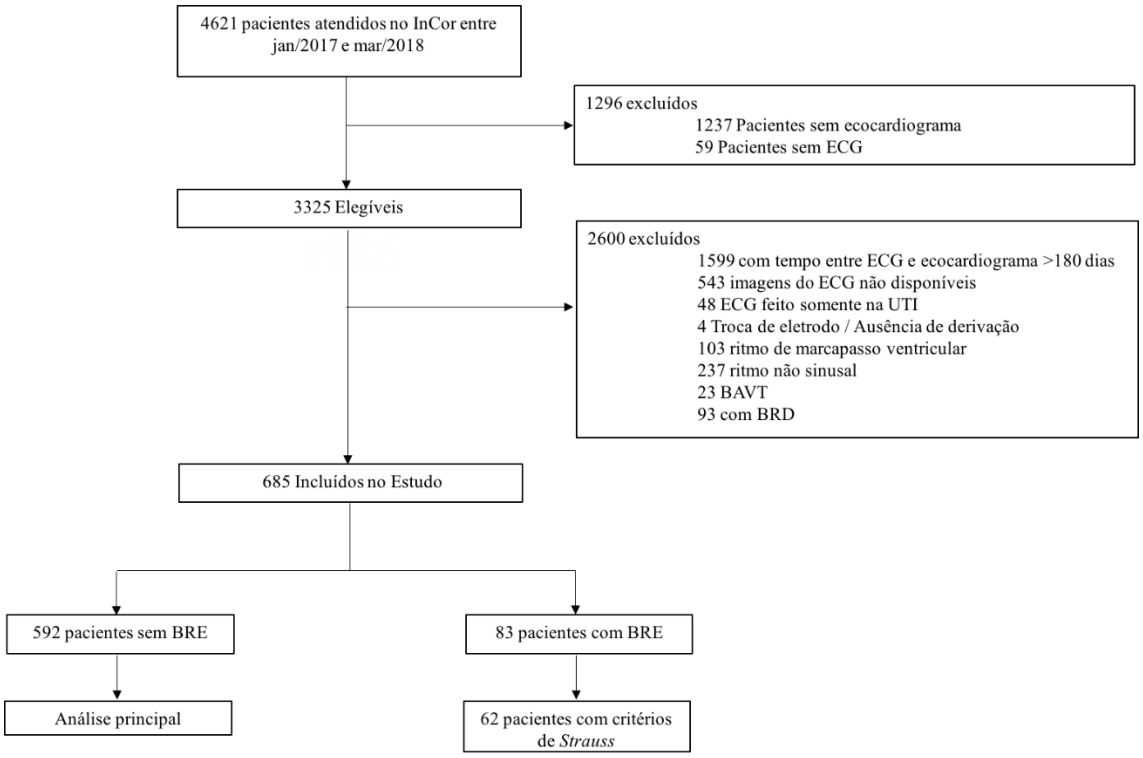
3.3 Critérios de exclusão

a. ECG ou Ecocardiograma transtorácico realizados apenas durante internação em unidade de terapia intensiva
b. ECG com ausência de traçado de qualquer uma das 12 derivações
c. ECG realizado com troca de eletrodos
d. ECG com Bloqueio de ramo direito (BRD)
e. ECG com Bloqueio atrioventricular total
f. ECG com ritmo não sinusal
g. ECG em ritmo de marcapasso ventricular
h. Ecocardiograma transtorácico com derrame pericárdico moderado ou importante

3.4 Delineamento da população para as diferentes análises

Para as análises dos critérios eletrocardiográficos com seus respectivos cortes, a população foi subdividida em pacientes sem BRE (análise principal) e pacientes com BRE, como descrito no fluxograma do estudo (**Figura 1**). Pacientes com BRE foram então avaliados de acordo com o critério de Strauss para inclusão na análise final (subanálise BRE).

Figura 1. Fluxograma para seleção e inclusão dos pacientes e subdivisão entre grupos (sem BRE (**análise principal**) e com BRE (**subanálise BRE**))



BAVT: bloqueio atrioventricular total, BRD: Bloqueio de ramo direito, BRE: Bloqueio de ramo esquerdo, UTI: unidade de terapia intensiva

3.5 Análise do ECG

ECG de 12 derivações com velocidade padrão de 25mm/segundo e calibração de 10 mm/mV (milivolt) foram realizados em todos os pacientes.

3.5.1 Análise principal

Para pacientes sem BRE, todos os traçados eletrocardiográficos foram avaliados por dois cardiologistas, cegos para comorbidades clínicas e avaliação ecocardiográfica, realizaram o cálculo de 4 critérios eletrocardiográficos: Peguero-Lo Presti, Cornell voltagem, Sokolow-Lyon e Romhilt-Estes. Em casos de discordância entre os examinadores o critério eletrocardiográfico era revisto por um terceiro examinador

a) Critério de Sokolow-Lyon

Utiliza-se da soma da amplitude da onda S na derivação V1 com a amplitude da onda R na derivação V5 ou V6 (qual for maior) sendo diagnóstico de HVE se ≥35mm(32).

b) Critério de Cornell voltagem

Soma-se a amplitude da onda R em avL com a amplitude da onda S (ou QS) em V3 (RavL + SV3) com o corte específico por sexo de >20mm para mulheres e >28mm para homens(33)

c) Critério de Peguero-Lo Presti

Soma-se a onda S com maior amplitude das doze derivações do ECG com a amplitude da onda S em V4, sendo diagnóstico de HVE se ≥23mm para mulheres e ≥28mm para homens. Em casos em que a onda S de maior amplitude for a

onda S de V4 a medida é calculada multiplicando-se o valor da amplitude da onda S em V4 por 2 (2 x SV4)(30)

d) Critério de Romhilt-Estes

Este critério analisa através de um sistema de pontos diversas alterações eletrocardiográficas de hipertrofia ventricular esquerda (**Tabela 2**), a HVE é provável quando soma total é de 4 pontos e definitiva quando somados 5 pontos. Individualmente cada um dos componentes do sistema de pontos é relacionado de maneira independente a desfechos cardiovasculares(34, 35)

3.5.2 Subanálise BRE

Dois examinadores revisaram os 83 traçados eletrocardiográficos com critérios de BRE de acordo com a diretriz brasileira de traçados eletrocardiográficos(36)

e avaliaram quais traçados tinham também definição de BRE de acordo com o critério de *Strauss.* 62 pacientes com critérios de BRE como proposto por *Strauss* foram analisados por outros 2 cardiologistas, cegos para comorbidades clínicas e ecocardiográficas. Os critérios de ECG avaliados para pacientes com BRE estão resumidos na **Tabela 2**. Em caso de discordância entre os examinadores para o algum dos critérios, o ECG foi revisto por um terceiro examinador.

Tabela 2. Critérios eletrocardiográficos utilizados para pacientes com BRE e seus respectivos valores de corte para definição de HVE.

Critério	Cálculo	Corte para HVE	Referência
Peguero-Lo Presti	SV4 + onda S mais profunda	≥28mm homens ≥23mm mulheres	(30)
Cornell voltagem	R_{avL} + S_{V3}	≥2.8mV homens ≥2.0mV mulheres	(37)
Cornell duração	Homens: (R_{aVL}+S_{V3}) * duração QRS Mulheres: (R_{aVL}+S_{V3}+0.6 mV) * duração QRS	>2440 mm * mseg	(38)
SV2 + SV3	S_{V2} + S_{V3}	>60mm	(39)
R aVL	R_{aVL}	≥11mm	(40)
R aVL duração	R_{aVL} * duração QRS	>1030 mm * mseg	(41)
Sokolow-Lyon voltagem	S_{V1} + Maior onda R (V5 or V6)	≥35mm	(40)
Sokolow-Lyon produto	S_{V1} + Maior onda R (V5 or V6) * duração QRS	>3674 mm* mseg homens >3224 mm *mseg mulheres	(38)
Gubner-Ungerleider	R_{I} + S_{III}	>25mm	(42)
Dalfó	R_{aVL} + S_{V3}	>16mm homens >14mm mulheres	(43)

mm: milímetros; mseg: milissegundos; mV: milivolts.

3.6 Avaliação ecocardiográfica

Todos os ecocardiogramas foram realizados em nossa instituição de acordo com diretrizes internacionais(44). A massa ventricular esquerda foi calculada com base na fórmula de Devereux: massa ventricular (em gramas) = 0,80 x 1,04 [(0,8 X {1,04 [(SIVD + DDVE + PPVED)^3 – (DDVE)^3]} + 0,6 g. Sendo a espessura do septo interventricular em diástole (SIVD) e da parede posterior do VE no final da diástole (PPVED) e o diâmetro diastólico final do VE (DDVE) as variáveis necessárias para cálculo da massa ventricular esquerda. O índice de massa ventricular esquerdo (IMVE) foi então obtido indexando a massa do ventrículo esquerdo pela superfície corpórea, calculada pela fórmula de Dubois. HVE foi definida como IMVE >95mg/m^2 para mulheres e >115g/m^2 para homens e o

ecocardiograma foi definido como o padrão-ouro para diagnóstico de HVE em todas as análises.

3.7 Variáveis Clínicas

Através da revisão do prontuário eletrônico, foram obtidas informações referentes a variáveis antropométricas (peso, altura e IMC), idade em anos (na data do ecocardiograma transtorácico), comorbidades e medicações descritas no último atendimento clínico (HAS, diabetes mellitus, Doença arterial coronária (DAC), cirurgia de revascularização do miocárdica (CRM) prévia, intervenção coronária percutânea (ICP) prévia, fibrilação atrial paroxística (FAp), doença arterial obstrutiva periférica (DAOP), uso de medicações (beta-bloqueadores (BB), bloqueadores de canal de cálcio (BCC), diuréticos, inibidores da enzima conversora de angiotensina (IECA), bloqueadores dos receptores AT1 de angiotensina II (BRA), hidralazina e nitratos). Sinais vitais também foram obtidos através do prontuário eletrônico (frequência cardíaca (FC) e pressão arterial (PA))

3.8 Análise estatística

As variáveis clínicas e ecocardiográficas quantitativas foram apresentadas como mediana e intervalo interquartil ou média e desvio padrão após análise de normalidade pelo teste de Kolmogorov-Smirnov. As variáveis categóricas foram apresentadas como percentuais e valores absolutos. As variáveis quantitativas foram comparadas pelo teste t ou pelo teste de Wilcoxon conforme apropriado. Variáveis categóricas foram comparadas pelo teste de qui-quadrado ou teste exato de Fisher. Para todas as análises, testes realizados foram com nível de significância de 5%. As análises foram realizadas com os softwares STATA

versão 14.2 (Stata Corp LLC)(45) e R versão 3.6.2 (R Project for Statistical Computing)(46).

3.8.1 Análise principal

Sensibilidade, especificidade, valor preditivo positivo e negativo para cada um dos critérios eletrocardiográficos foi calculado com base na definição de HVE do ecocardiograma. Para comparação entre os critérios eletrocardiográficos, testamos a ausência de concordância entre os critérios pelo teste de McNemar separadamente para pacientes com e sem HVE, com intuito de comparar sensibilidade e especificidade de cada critério de ECG (47). Utilizando os valores de cada um dos critérios eletrocardiográficos como variáveis contínuas, curvas ROC (*Receiver Operating Characteristic*) foram construídas através da representação gráfica dos pares sensibilidade (ordenadas) e 1- especificidade (abcissas) para cada critério e a área sob a curva (AUC)(48). Para comparação adicional, foi calculado o escore F1, definido como a média harmônica da precisão e do *recall*, calculado como $F1=2*(\text{sensibilidade}^{-1} + \text{valor preditivo positivo}^{-1})^{-1}$, sendo o valor preditivo positivo definido como o número de testes corretamente identificados como positivos dividido pelo número total de testes positivos e a sensibilidade o número de testes positivos divido pelo número total de pacientes com HVE. O escore F1 varia de 0 a 100%, com valores mais altos indicando uma melhor acurácia(49).

3.8.2 Subanálise BRE

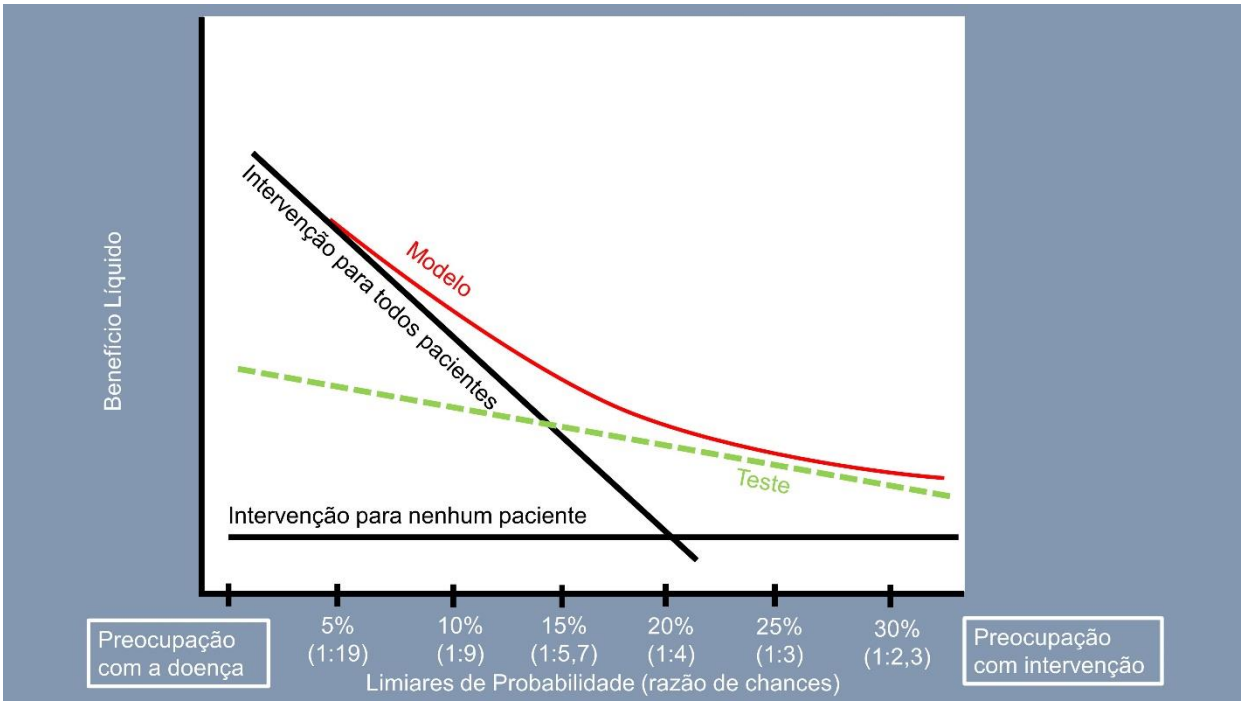
Sensibilidade, especificidade, valor preditivo positivo e negativo, razão de verossimilhança positiva e negativa foram calculados para cada um dos critérios com base na classificação do ecocardiograma de HVE. Coeficientes de correlação de Pearson entre os critérios de ECG e IMVE isoladamente para cada critério também foi calculado. Utilizando os valores de cada critério eletrocardiográfico como variáveis contínuas, curvas ROC (*Receiver Operating Characteristic*) foram construídas através da representação gráfica dos pares sensibilidade (ordenadas) e 1- especificidade (abcissas) para cada critério e a área sob a curva (AUC). O escore de Brier foi calculado através da diferença média entre o desfecho observado (HVE no ecocardiograma) pelo desfecho predito (HVE pelo ECG, individual para cada critério) elevada ao quadrado. O escore de Brier varia entre 0 e 1, com escores mais baixos indicando uma melhor performance do critério eletrocardiográfico.

3.8.3 Análise do impacto do ECG na prática clínica

Com o intuito de analisar como os critérios eletrocardiográficos poderiam impactar a prática clínica de pacientes sob risco de HVE, utilizamos um modelo de curva de decisão para avaliar individualmente o impacto que cada critério poderia ter na prática clínica. O benefício líquido de cada critério é calculado através da subtração da proporção de falsos positivos dos verdadeiros positivos, ponderado pelo dano relativo de um teste falso positivo ou falso negativo. Cada critério é então comparado individualmente a estratégias diametralmente

opostas (intervenção para todos os pacientes e intervenção para nenhum paciente), em uma faixa pré-determinada de limiares de probabilidade. Permite-se assim a comparação de um modelo ou um teste diagnóstico com estas duas estratégias (intervenção para todos ou intervenção para nenhum paciente). Os limiares de probabilidade testados indicam diferentes pesos para os quais o médico estaria disposto a aceitar tratar falsos positivos para evitar um falso negativo. O modelo teórico proposto por *Vickers* está resumido na **Figura 2**.

Figura 2. Modelo teórico da curva de decisão (adaptado de (50)).

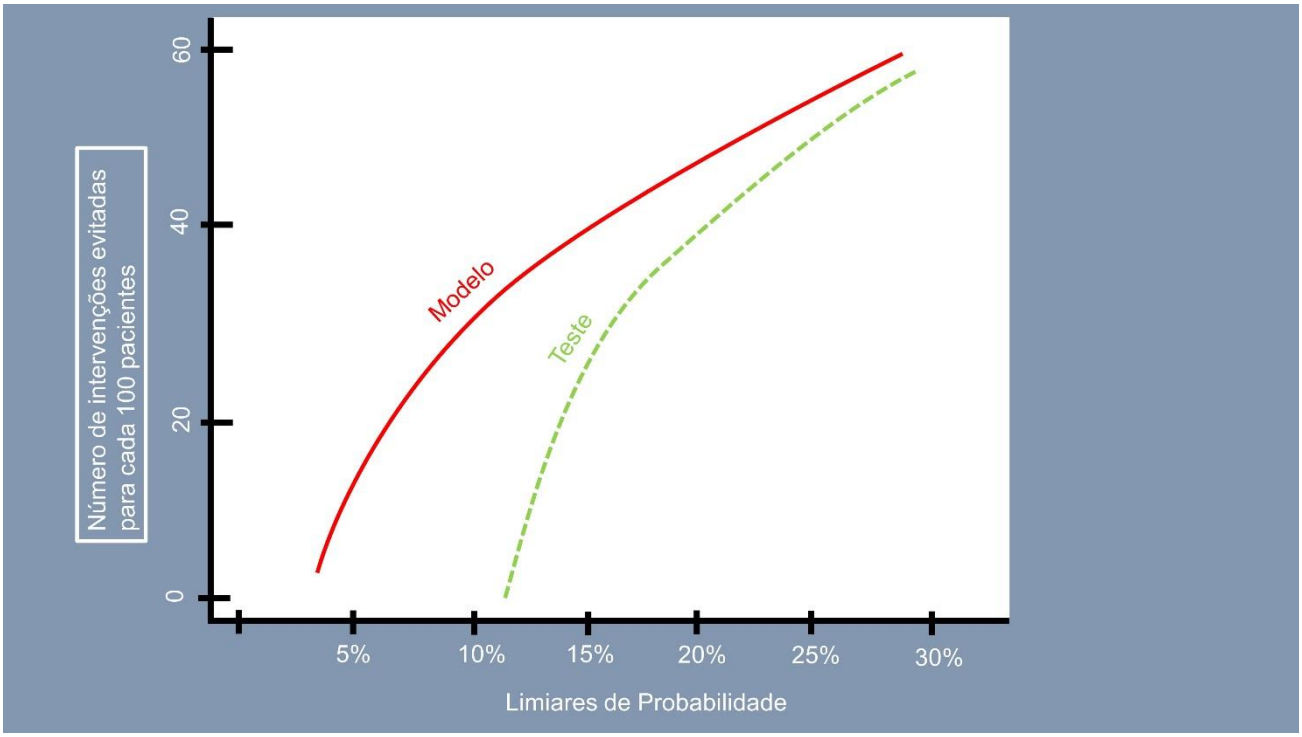


A adição de um teste diagnóstico inclui considerações sobre intervenções para todos" ou "intervenção para nenhum paciente" porque usualmente são estratégias que podem ser adotadas diante de uma situação clínica. O benefício de um teste diagnóstico/modelo, que tem o intuito de identificar se o paciente tem ou não uma dada doença, é estratificado de acordo com limiares de probabilidades (calculados a partir de razão de chances) e variam de acordo o

quanto o médico ou o paciente se preocupam com relação a doença em si ou a realização de intervenções desnecessárias. Com base na **Figura 2**, note que se o médico/paciente tem muita preocupação com a doença e não tem receio algum da intervenção, a estratégia “intervenção para todos” deverá ser a melhor; enquanto se a preocupação com a doença é menor e há intenção de se evitar intervenções possivelmente desnecessárias a utilização de testes ou modelos diagnósticos ganha utilidade, pois o seu benefício líquido é maior que a estratégia “intervenção para todos”. Os limiares de probabilidade podem ser interpretados como uma métrica denominada “número-necessário-para-testar”, utilizando ainda a **Figura 2** como exemplo, no limite de 10% são necessários de 10 testes para a detecção de 1 exame positivo e assim sucessivamente.

Organiza-se, portanto, ao longo dos limiares de probabilidades um raciocínio didático que permite a decisão de testar ou não testar, com base no julgamento do binômio médico-paciente. A métrica de benefício líquido pode ainda ser expressa como o número de verdadeiros negativos (ao invés do benefício líquido como na **Figura 2**) e avaliada em um cálculo por 100 pacientes, indicando o número de intervenções evitadas para cada 100 pacientes em que o teste é aplicado. A **Figura 3** resume a aplicação da curva de decisão construída com a métrica de número de intervenções evitadas para cada 100 pacientes.

Figura 3. Modelo teórico da curva de decisão expressa em número de intervenções evitadas (adaptado de (50)).



Neste estudo, a curva de decisão reflete quantos ecocardiogramas sem HVE o médico estaria disposto a aceitar para evitar não reconhecer um paciente com HVE, o que poderia auxiliar na sua decisão clínica de pedir ou não o exame, além de fornecer uma métrica de quantos exames poderiam ser evitados de acordo com cada critério eletrocardiográfico para cada 100 pacientes. Os limiares de probabilidade foram selecionados previamente com grande margem de limiares (0,1 a 0,6) com intuito de refletir locais com diferentes disponibilidades e acesso para agendamento de exames complementares(50). Limiares de probabilidade entre 0,1 e 0,3 teoricamente representando locais com ampla disponibilidade e acesso a exames complementares, e entre 0,3 e 0,6 locais com acesso limitado/restrito.

4. RESULTADOS

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4.1 Artigo 01: Clinical applicability and diagnostic performance of electrocardiographic criteria for left ventricular hypertrophy diagnosis in older adults. *Sci Rep*. 2021;11(1):11516. Published 2021 Jun 1. doi:10.1038/s41598-021-91083-9 **(Anexo 1)**.

Abstract: Recently, a new ECG criterion, the Peguero-Lo Presti (PLP), improved overall accuracy in the diagnosis of left ventricular hypertrophy (LVH)—compared to traditional ECG criteria, but with few patients with advanced age. We analyzed patients with older age and examined which ECG criteria would have better overall performance. A total of 592 patients were included (83.1% with hypertension, mean age of 77.5 years) and the PLP criterion was compared against Cornell voltage (CV), Sokolow-Lyon voltage (SL) and Romhilt-Estes criteria (cutoffs of 4 and 5 points, RE4 and RE5, respectively) using LVH defined by the echocardiogram as the gold standard. The PLP had higher AUC than the CV, RE and SL (respectively, 0.70 vs 0.66 vs 0.64 vs 0.67), increased sensitivity compared with the SL, CV and RE5 (respectively, 51.9% [95% CI 45.4–58.3%] vs 28.2% [95% CI 22.6–34.4%], $p < 0.0001$; vs 35.3% [95% CI 29.2–41.7%], $p < 0.0001$; vs 44.4% [95% CI 38.0–50.9%], $p = 0.042$), highest F1 score (58.3%) and net benefit for most of the 20–60% threshold range in the decision curve analysis. Overall, despite the best diagnostic performance in older patients, the PLP criterion cannot rule out LVH consistently but can potentially be used to guide clinical decision for echocardiogram ordering in low-resource settings.

4.2 Artigo 02: Usefulness of ECG criteria to rule out left ventricular hypertrophy in older individuals with true left bundle branch block: an observational study. *BMC Cardiovasc Disord*. 2021;21(1):547. Published 2021 Nov 17. doi:10.1186/s12872-021-02332-8 **(Anexo 2)**.

Abstract:

Background: Advanced age is associated with both left bundle branch block (LBBB) and hypertension and the usefulness of ECG criteria to detect left ventricular hypertrophy (LVH) in patients with LBBB is still unclear. The diagnostic performance and clinical applicability of ECG-based LVH criteria in patients with LBBB defined by stricter ECG criteria is unknown. The aim of this study was to compare diagnostic accuracy and clinical utility of ECG criteria in patients with advanced age and strict LBBB criteria.

Methods: Retrospective single-center study conducted from Jan/2017 to Mar/2018. Patients undergoing both ECG and echocardiogram examinations were included. Ten criteria for ECG-based LVH were compared using LVH defined by the echocardiogram as the gold standard. Sensitivity, specificity, predictive values, likelihood ratios, AUC, and the Brier score were used to compare diagnostic performance and a decision curve analysis was performed.

Results: From 4621 screened patients, 68 were included, median age was 78.4 years, (IQR 73.3-83.4), 73.5% with hypertension. All ECG criteria failed to provide accurate discrimination of LVH with AUC range between 0.54 and 0.67, and no ECG criteria had a balanced tradeoff between sensitivity and specificity. No ECG criteria consistently improved the net benefit compared to the strategy of performing routine echocardiogram in all patients in the decision curve analysis within the 10-60% probability threshold range.

Conclusion: ECG-based criteria for LVH in patients with advanced age and true LBBB lack diagnostic accuracy or clinical usefulness and should not be routinely assessed.

5. DISCUSSÃO

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Nosso estudo é o primeiro a analisar diversos aspectos relacionados ao papel da eletrocardiografia em pacientes idosos sob risco de hipertrofia ventricular esquerda. Iniciando pelos achados referentes a análise principal – que comparou a performance diagnóstica do critério de Peguero-Lo Presti a critérios tradicionais do ECG – o presente estudo identificou que a utilização deste critério eletrocardiográfico tem grande utilidade clínica tanto para o reconhecimento da HVE, com maior sensibilidade do que os critérios tradicionais de Sokolow-Lyon e Cornell voltagem (**Anexo 1**, ***Tabela 2***), e que potencialmente pode ser utilizado como uma ferramenta de decisão para guiar a solicitação de exames de imagem confirmatórios de hipertrofia ventricular esquerda (**Anexo 1**, ***Figura 3***), como o ecocardiograma transtorácico e a ressonância nuclear magnética cardíaca. Estes achados são extremamente relevantes, pois informam a prática médica, e tem potencial de indicar modificações das diretrizes nacionais de eletrocardiografia e hipertensão arterial sistêmica, as quais ainda não citam o critério de Peguero-Lo Presti como ferramenta para diagnóstico da hipertrofia ventricular(36, 51).

Os resultados da análise de pacientes sem BRE, ainda sugerem uma possível alternativa para suplementar a deficiência histórica do ECG para detecção da HVE, sua baixa sensibilidade(14). Através de algumas das combinações de critérios eletrocardiográficos (dois ou três critérios), foi possível aumentar a sensibilidade do ECG para detecção da HVE para acima de 60%, sem que a especificidade ficasse abaixo de 75%, inclusive com incremento do Escore F1 (**Anexo 1**, ***Material Suplementar***, ***Tabela 4***). Esta análise, no entanto, deve ser interpretada com cautela dada a sua natureza puramente exploratória.

Para confirma ou refutar esta hipótese, devemos aguardar estudos propriamente desenhados para esta finalidade, com plano de análise estatística e cálculo amostral propostos *a priori*.

Validamos também a utilidade clínica do critério de Peguero-Lo Presti em uma população brasileira - com características clínicas e epidemiológicas únicas e comparamos, pela primeira vez na literatura, a performance do critério de Peguero-Lo Presti com o critério de pontos Rohmilt-Estes.

O achado de que acurácia diagnóstica do critério de Peguero-Lo Presti é numericamente superior ao sistema de pontos de Rohmilt-Estes, com sensibilidade superior ao valor de corte de 5 pontos (51,9% versus 44,4%, Peguero-Lo Presti *versus* Romhilt-Estes com corte de 5 pontos, valor de P = 0,042) e sensibilidade comparável ao valor de corte de 4 pontos (51,9% versus 54,4%, Peguero-Lo Presti *versus* Romhilt-Estes com corte de 5 pontos, valor de P = 0,497) tem grande implicações práticas (**Anexo 1**, ***Tabela 2***).

Pela clara diferença esperada no tempo gasto para cálculo de cada critério (Peguero-Lo Presti (medida de voltagem isolada) e Romhilt-Estes (diversas análises morfológicas, medidas de voltagem e soma de pontos totais)), a utilização preferencial do critério de Peguero-Lo Presti poderia: i) auxiliar serviços de saúde com alta demanda, em que a otimização dos processos envolvidos no cuidado ao paciente é etapa fundamental para fornecer uma assistência à saúde de alta qualidade(52); e ii) impactar o que deve ser determinado como ensino obrigatório do ECG no currículo de estudantes de medicina, cenário no qual deve-se evitar a saturação dos estudantes por excesso de informação ou complexidade de conteúdo(53).

A subanálise de pacientes com bloqueio de ramo esquerdo também possibilitou conclusões relevantes. Nenhum dos critérios do ECG estudados apresentam performance diagnóstica suficiente para ser utilizados como ferramenta de triagem em pacientes com BRE pelo critério de *Strauss*, pois nenhum apresentou um balanço entre sensibilidade e especificidade (**Anexo 2**, ***Tabela 3***), refletido também pela péssima capacidade discriminativa dos critérios de ECG para a HVE neste contexto, com obtenção de valores baixos de área sob a curva para todos os critérios (intervalo de 0,53 a 0,67) (**Anexo 2**, ***Tabela 4***). Analisamos ainda, pela primeira vez, o desempenho do critério de Peguero-Lo Presti em pacientes com BRE, com resultados insatisfatórios para recomendar sua utilidade clínica, semelhante aos outros critérios estudados (**Anexo 2**, ***Tabelas 3 e 4***). Diante desta performance diagnóstica muito pior em pacientes com BRE do que naqueles sem BRE, nenhum dos critérios foi capaz de informar a prática clínica – exemplificado pelo modelo da curva de decisão em pacientes com BRE (**Anexo 2**, ***Figura 3***).

Neste modelo hipotético, nenhum critério de ECG foi superior a estratégia “intervenção para todos” em todas os limiares de probabilidade testados (**Anexo 2**, ***Figura 3***). A interpretação destes resultados reflete a incapacidade do ECG de descartar a presença da HVE em cenário de elevada prevalência de cardiopatia estrutural, como em pacientes com BRE (acima de 40%)(54). A principal hipótese para a baixa performance dos critérios do ECG possivelmente se deve a nossa metodologia: ao selecionarmos um subgrupo de indivíduos com evidência clara de doença do sistema de condução (BRE com critério de *Strauss*) é muito improvável que um exame que avalie isoladamente a ativação elétrica do coração seja capaz de discernir esse acometimento do sistema de condução

de manifestações relacionadas ao miocárdio, como a HVE. Trata-se, portanto, de uma limitação técnica do ECG - a detecção de HVE em pacientes com doença do sistema de condução - e não uma ineficiência dos critérios do ECG em si ou de seus respectivos pontos de corte. De fato, a baixa correlação entre o valor do índice de massa do ventricular pelo ecocardiograma transtorácico e o valor absoluto de cada um dos critérios de ECG, com coeficientes de correlação de Pearson variando entre 0,39 e 0,53 (todos com valor de $P < 0,001$) (**Anexo 2**, ***Figura 2***), suporta a hipótese da limitação do método para detecção de HVE. Novamente, estes achados informam a prática clínica: decisões clínicas, como a intensificação de tratamento anti-hipertensivo(55), não devem ser baseadas na detecção de HVE pelo ECG para pacientes com BRE.

Diversas limitações do estudo precisam ser reconhecidas: 1) Trata-se de análise retrospectiva de um único hospital cardiológico de alta complexidade, com uma população com elevada prevalência de doenças cardiovasculares e de hipertrofia ventricular esquerda – e os resultados aqui descritos de performance diagnóstica dos critérios do ECG podem ser diferentes se aplicados em outras populações(56) e, portanto, a extrapolação dos nossos achados para outros níveis de atenção precisa ser feita com cautela; 2) Os critérios eletrocardiográficos não foram ajustados por superfície corpórea, no qual teoricamente o ajuste pelo índice de massa corpórea poderia aumentar a performance diagnóstica do ECG em pacientes obesos(57); 3) Como o intuito do estudo era comparar a performance do ECG para detecção de HVE utilizando o ecocardiograma como referência, não testamos a hipótese de que o ECG é um marcador de risco cardiovascular independente da HVE confirmada por exames de imagem, como propõe os autores Aro e Chugh(58), com a subdivisão da HVE

em “elétrica” e “anatômica”, neste cenário, apesar da grande intersecção das duas entidades, a detecção da HVE “elétrica” seria a representação de alterações intersticiais, celulares e de propriedades eletrofisiológicas do miocárdio, que servem de substrato para arritmias ventriculares e morte cardiovascular, independente da HVE “anatômica”; 4) A subanálise BRE foi realizada com uma amostra relativamente pequena, apesar do rastreio de mais de 4.000 pacientes, refletindo a baixa prevalência do BRE na população em geral(59). Finalmente, devido a exclusão de pacientes cujo ECG não apresentava ritmo sinusal, assim como pacientes com marca-passo artificial e com bloqueio de ramo direito, a validade do critério de Peguero-Lo Presti e de outros de ECG para detecção da HVE nessa população ainda precisa ser investigada.

6. CONCLUSÃO

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Para pacientes sem BRE, o ECG apresentou utilidade clínica para detecção da HVE em pacientes idosos e pode auxiliar a tomada de decisão sobre a solicitação de exame confirmatório da HVE. Ainda neste cenário, o critério de Peguero-Lo Presti obteve acurácia e performance diagnóstica superiores a critérios eletrocardiográficos tradicionais.

Em pacientes com BRE, todos os critérios de ECG estudados apresentaram baixa capacidade discriminatória, sugerindo que o ECG não deve ser utilizado rotineiramente para detecção de HVE nem como ferramenta para auxiliar o processo de tomada de decisão.

7. REFERÊNCIAS

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ANEXO 1

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Clinical applicability and diagnostic performance of electrocardiographic criteria for left ventricular hypertrophy diagnosis in older adults

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Recently, a new ECG criterion, the Peguero-Lo Presti (PLP), improved overall accuracy in the diagnosis of left ventricular hypertrophy (LVH)—compared to traditional ECG criteria, but with few patients with advanced age. We analyzed patients with older age and examined which ECG criteria would have better overall performance. A total of 592 patients were included (83.1% with hypertension, mean age of 77.5 years) and the PLP criterion was compared against Cornell voltage (CV), Sokolow-Lyon voltage (SL) and Romhilt-Estes criteria (cutoffs of 4 and 5 points, RE4 and RE5, respectively) using LVH defined by the echocardiogram as the gold standard. The PLP had higher AUC than the CV, RE and SL (respectively, 0.70 vs 0.66 vs 0.64 vs 0.67), increased sensitivity compared with the SL, CV and RE5 (respectively, 51.9% [95% CI 45.4–58.3%] vs 28.2% [95% CI 22.6–34.4%], p < 0.0001; vs 35.3% [95% CI 29.2–41.7%], p < 0.0001; vs 44.4% [95% CI 38.0–50.9%], p = 0.042), highest F1 score (58.3%) and net benefit for most of the 20–60% threshold range in the decision curve analysis. Overall, despite the best diagnostic performance in older patients, the PLP criterion cannot rule out LVH consistently but can potentially be used to guide clinical decision for echocardiogram ordering in low-resource settings.

Abbreviations

AUC	Area under the curve
CI	Confidence interval
CV	Cornell voltage criterion
ECG	Electrocardiogram
LVH	Left ventricular hypertrophy
PLP	Peguero-Lo Presti criterion
RE	Romhilt-Estes criterion
SL	Sokolow-Lyon voltage criterion

Left ventricular hypertrophy (LVH) is an independent predictor of mortality, and cardiovascular morbidity in hypertensive individuals[1–5]. LVH is a marker of poor prognosis also in elderly patients, although few data are available in this population[6]. The 12-lead ECG is recommended as a universal screening of LVH for patients with hypertension according to international guidelines[7,8]. ECG is accessible worldwide, inexpensive and has established its prognostic capacity[9]. Also, the addition of the ECG-based LVH criteria to common cardiovascular risk scores can increase the prediction performance of such scores[10,11]. However, the diagnosis of LVH by the ECG has some limitations, namely the great number of available criteria[12,13] and poor sensitivity (4–48%) when

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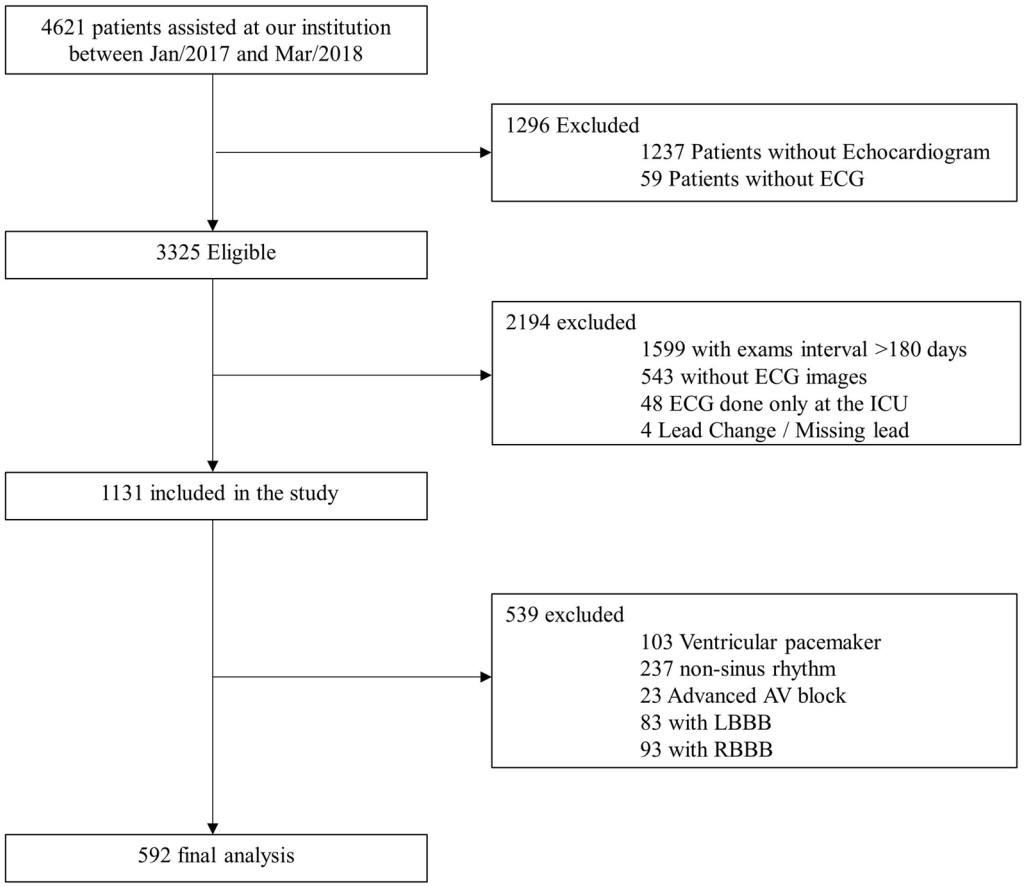

Figure 1. Study flowchart. *ECG* electrocardiography; *ICU* intensive care unit; *LBBB* left bundle branch block; *RBBB* right bundle branch block.

compared to echocardiogram and cardiac magnetic resonance imaging (MRI)[13–16]. Additionally, extra cardiac factors can mitigate the depolarization vector (such as body habitus, weight, pericardial fluid, lung disease, lead positioning)[17,18].

There are limited data regarding ECG sensitivity and specificity for detection of LVH in patients with advanced age[19,20]. This age group will grow in the next years—current estimates are that by 2030 there will be more than 73 million Americans over 65 years[21] and 20.4 million Brazilians over 70 years[22]—and so will the prevalence of age-related diseases. Recently, a new criterion for LVH detection was proposed[23]—the Peguero Lo-Presti criterion: the sum of the S wave in lead V4 with the deepest S wave in the 12-lead ECG (SD + SV4) with a cutoff of 2.3 mV for female subjects and 2.8 mV for male subjects being considered positive for LVH. The criterion had better AUC than other ECG criteria (Sokolow-Lyon, Cornell voltage, RAvL, RL1). We aim to evaluate the diagnostic performance and clinical applicability of the PLP criterion for LVH detection in older adults, compared to traditional ECG criteria.

Methods

Population. We retrospectively collected data from patients ≥ 70 years old (as of March/31/2018) assisted at our institution—a tertiary care teaching hospital in Sao Paulo, Brazil. From January/2017 to March/2018, all outpatients and inpatients in non-critical units who underwent at least one 12-lead ECG test were evaluated, as outlined in the study flowchart (Fig. 1). All patients with Left Bundle Branch Block (LBBB), Right Bundle Branch Block (RBBB), Atrial Fibrillation/Flutter, Atrial Tachycardia, Supraventricular Tachycardia, Advanced AV Block or Ventricular paced rhythm were excluded from the analysis (see Fig. 1).

ECG analysis. Standard 12-lead ECGs were acquired at 10 mm/mV calibration and speed of 25 mm/s and all tracings were independently reviewed by two experienced cardiologists from the ECG Unit (NS and MF), blinded to echocardiogram and clinical analysis. In case of discordance, the ECG tracing was reviewed by a third cardiologist (CAMT). Four LVH criteria were calculated from the ECG tracings: Peguero-Lo Presti, Cornel, Sokolow-Lyon, and Romhilt-Estes. The value for the Peguero-Lo Presti criterion was obtained with the sum of the deepest S wave in the tracing plus the S wave amplitude in V4 (SD + SV4), with a cutoff for LVH as described previously[23]: ≥ 2.3 mV for female and ≥ 2.8 for male. The Cornell voltage used a sex-specific voltage criterion as a sum of the R wave in avL plus the S or QS wave in V3 (RavL + SV3) with a cutoff of > 2.0 mV for female and > 2.8

for male[24]. The Sokolow-Lyon was calculated by adding the S wave amplitude in V1 plus the R wave amplitude in V5 or V6, with a cutoff of ≥ 3.5 mV considered positive for LVH[25]. The Romhilt and Estes scoring system was obtained through a sum of 6 characteristics obtained from the ECG: voltage criteria, ST-T abnormalities, left-atrial involvement, QRS axis and duration, intrinsicoid deflection; the point system is summarized in the Supplementary Table S1, available in the supplementary information—for patients with ≥ 4 points the LVH is termed probable and ≥ 5, definite[26].

Echocardiography analysis. All echocardiograms were performed at our institution, in accordance with national[27] and international guidelines[28]. Left Ventricular Mass was calculated using the Devereux formula: left ventricular mass (g) = 0,80 × 1,04 [(septal thickness + internal diameter + posterior wall thickness)^3 − (internal diameter)^3] + 0.6 g[29], and indexed by the Body Surface Area (BSA), calculated by the Dubois Formula (BSA = 0.007184 × height (m)$^{0.725}$ × weight (kg)$^{0.425}$, with LVH defined as > 95 g/m^2 in females and > 115 g/m^2 male subjects. Echocardiograms were used as the gold-standard method to diagnose LVH.

Clinical data. Epidemiological data from all patients were retrieved from the electronic medical record: anthropometric data (height, weight, body mass index), age in years (at the day of echocardiogram exam), comorbidities as diagnosed by the attending physician (hypertension, diabetes, coronary artery disease, prior myocardial infarction, coronary artery by-pass surgery, prior percutaneous coronary intervention, atrial fibrillation, peripheral artery disease, chronic obstructive pulmonary disease), medications prescribed (beta blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptors blockers (ARB), hydralazine/nitrate). Vital signs were obtained through chart review (blood pressure and heart rate).

Statistical analysis. Baseline clinical and echocardiographic variables were summarized as mean ± standard deviation for continuous variables and proportions for categorical variables, according to the diagnosis of LVH assessed by the echocardiogram. Continuous variables were compared between groups by means of Student's t-test or the Wilcoxon rank sum test and categorical variables were compared using the chi-square test.

Sensitivity, specificity and positive and negative predicted values for each ECG criteria were calculated, based on the detection of LVH on the echocardiogram. For comparison between the ECG criteria, we tested for lack of agreement between the tests using the McNemar's test separately for those with echocardiogram-detected LVH and those without[30]. Receiver operating characteristic (ROC) curves were created by plotting the sensitivity over 1-specificity of each test and the areas under the curves (AUC) were estimated and compared[31], using the voltage sums for the Peguero-Lo Presti, Sokolow-Lyon and Cornell voltage criteria and the sum of points for the Romhilt and Estes scoring system.

Further performance comparison was done with the F1 score, defined as the harmonic mean of precision (positive predictive value) and recall (sensitivity), ranging from 0 to 100%, with higher scores indicating better model. The F1 score was calculated as F1 = 2*(sensitivity^{-1} + positive predictive value^{-1})$^{-1}$, where positive predictive value is defined as the number of tests correctly identified as positive divided by the total of positives tests[32]. An additional exploratory analysis was carried out to evaluate the diagnostic performance of combined ECG criteria in a stepwise fashion (combining two, three or all ECG criteria).

We used the decision curve analysis framework to incorporate clinical decision making[33] in our analysis. Following this approach, the net-benefit (NB) for each ECG criteria was calculated by subtracting the proportion of false positives from the true positives, weighted by the relative harm of a false positive and false negative result. Scores were then compared against common strategies of treating all and none of the patients, by subtracting the estimated net-benefit of treating-all strategy from the respective criteria. The resulting net benefit was further used to calculate the number of avoidable interventions (for every 100 patients). Briefly, this method considers how much the physician is willing to treat false positives to avoid not treating a false negative patient. A detailed explanation can be found elsewhere[33]. In our study, the evaluated intervention is ordering an echocardiogram to screen or confirm the diagnosis of LVH. In high resource settings, where echocardiogram is widely available, physicians might tolerate more false positives to avoid missing a true positive (low threshold), whereas in under-resourced settings, the same strategy can lead to waste of scarce resources. Threshold probabilities were selected a priori and chosen to mimic both high (0.1–0.3) and under-resourced (0.3–0.6) theoretical clinical scenarios where elective echocardiogram availability and waiting times are supposed to vary.

We based our manuscript in the 2015 Standards for Reporting of Diagnostic Accuracy Studies (STARD)[34,35] (Supplementary Table S2, available in the Supplementary Information). A two-sided $p < 0.05$ was considered statistically significant in all analyses and no adjustment for multiple comparisons was performed. Statistical analyses were performed using STATA version 14.2, Stata Corp LLC[36] and R software, version 3.6.2.[37].

Ethics and consent. The study was approved by the Ethics Committee of the Hospital das Clínicas, Medicine School, University of São Paulo, Brazil (protocol number 3.210.301, project number 08797119.1.0000.0068 on 03/20/2019) and the need for individual signed informed consent was waived. We declare that all methods were performed in accordance with relevant guidelines and regulations.

Demographic data	Non-LVH patients (n = 351)	LVH patients (n = 241)	P value
Age (years)	77.2 ± 5.9	77.9 ± 5.8	0.075
Female	162(46.2%)	139(57.7%)	0.006
BMI (kg/m^2)	26.3 ± 4.32	26.3 ± 3.9	0.837
SBP (mmHg)	130.5 ± 20.4	135.8 ± 23.4	0.004
DBP (mmHg)	76.0 ± 10.6	75.9 ± 11.9	0.880
Heart rate (bpm)	68.0 ± 14.3	69.2 ± 19.1	0.361
Hypertension	288 (82.1%)	204 (84.7%)	0.408
Type 2 diabetes	118 (33.6%)	95 (39.4%)	0.149
Dyslipidemia	196 (55.8%)	122 (50.6%)	0.211
Paroxysmal atrial fibrillation	62 (17.7%)	35 (14.5%)	0.310
Coronary artery disease	184 (52.4%)	124 (51.5%)	0.817
Previous myocardial infarction	105 (29.9%)	76 (31.5%)	0.674
Previous CABG	58 (16.5%)	45 (18.7%)	0.498
Previous PCI	105 (29.9%)	57 (23.7%)	0.093
Peripheral artery disease	18 (5.1%)	28 (11.6%)	0.004
Chronic obstructive pulmonary disease	30 (8.6%)	32 (13.3%)	0.065
Medication use			
ACEi	85 (24.2%)	82 (34.0%)	0.009
ARBs	138 (39.3%)	87 (36.1%)	0.428
CCBs	86 (24.5%)	69 (28.6%)	0.262
Beta blocker	197 (56.1%)	151 (62.7%)	0.113
Hydralazine/nitrate	25 (7.1%)	36 (14.9%)	0.002
Diuretic	140 (39.9%)	143 (59.3%)	< 0.001
Days between echocardiogram and ECG*	7 (0–39)	14 (0–42)	0.269

Table 1. Demographic data. Demographic data of the cohort, according to the left ventricular hypertrophy status evaluated by echocardiography. Values are mean ± standard deviation or n (%). *ACEi* angiotensin-converting enzyme inhibitors; *ARBs* angiotensin receptor blockers; *BMI* body mass index; *CABG* coronary artery bypass graft; *CCBs* calcium channel blockers; *DBP* diastolic blood pressure; *PCI* percutaneous coronary intervention; *SBP* systolic blood pressure. *Median and interquartile rate.

Results

Characteristics of the study population. *Demographic data.* A total of 592 patients were included, 351 without LVH and 241 with LVH, as defined by the echocardiogram. Table 1 summarizes the demographic data of the study population.

Echocardiographic parameters. Patients with LVH had distinctive echocardiographic features: lower ejection fraction, higher mass index, increased diameters (left atrium, interventricular septum, posterior wall, left-ventricular end systolic and diastolic) and relative wall thickness (RWT) and higher prevalence of valvular heart disease (moderate or severe aortic stenosis, aortic regurgitation and mitral regurgitation, $p < 0.001$ for all comparisons) (available in the Supplementary information, Table S3).

Interobserver agreement. Voltage-based criteria had a near perfect agreement as assessed by Cohen's kappa statistic, with all criteria above 0.90 (Cornell Voltage 0.90, Sokolow-Lyon 0.93 and Peguero-Lo Presti 0.95, all p-values < 0.001). For the Romhilt-Estes scoring system, the agreement between the two observers was moderate (Cohen's kappa 0.48, $p < 0.001$).

Diagnostic performance of the ECG criteria. *Discriminative power assessed by the area under the curve (AUC).* The Peguero-Lo Presti criterion had a significantly higher AUC than the Cornell Voltage and Romhilt-Estes criteria (respectively, 0.70 (95% CI 0.65–0.74) vs 0.66 (95% CI 0.62–0.71) vs 0.64 (95% CI 0.60–0.69), respectively, $p < 0.05$) and a similar AUC compared to the Sokolow-Lyon criterion (AUC = 0.67 (95% CI 0.63–0.71), $p = 0.311$, Fig. 2).

Sensitivity. The Peguero-Lo Presti criterion had higher sensitivity compared to the Sokolow-Lyon voltage (51.9% [95% CI 45.4–58.3%] vs. 28.2% [95% CI 22.6–34.4%]; $p < 0.0001$), Cornell Voltage (35.3% [95% CI 29.2–41.7%]; $p < 0.0001$), Romhilt-Estes pointing system with the 5 points cutoff (RE5; 44.4% [95% CI 38–50.9%], $p = 0.042$) and similar sensitivity compare to the Romhilt-Estes pointing system with the 4 points cutoff (RE4; 54.4% [95% CI 47.8–60.8%], $p = 0.497$); all analyses using the McNemar's test for patients with LVH in the echocardiogram.

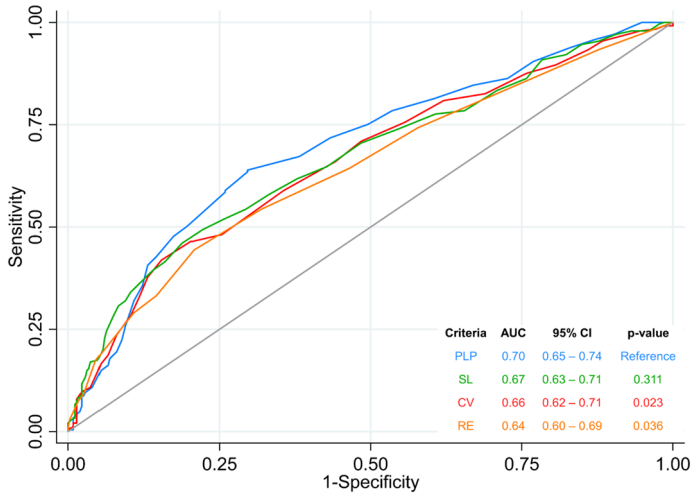

Figure 2. ROC curve and AUC for all ECG evaluated criteria. AUC of the ECG criteria, using the echocardiogram as the reference for LVH. All criteria were compared against the Peguero-Lo Presti criterion. *AUC* area under the curve; *CI* Confidence Interval; *Ref* reference.

LVH criteria	Reference: Echocardiogram					Reference: Peguero-Lo Presti	
	Sensitivity (95% CI)	Specificity (95% CI)	PPV (%)	NPV (%)	F1 Score (%)	McNemar test LVH[a] (comparing sensitivity)	McNemar test no LVH[b] (comparing specificity)
Sokolow-Lyon voltage	28.2 (22.6–34.4)	92.6 (89.3–95.1)	72.3	65.3	40.6	< 0.0001	< 0.0001
Cornell voltage	35.3 (29.2–41.7)	89.7 (86.1–92.7)	70.2	66.9	47.0	< 0.0001	< 0.0001
Peguero-Lo Presti	51.9 (45.4–58.3)	82.1 (77.6–85.9)	66.5	71.3	58.3	–	–
Romhilt Estes 4 points	54.4 (47.8–60.8)	68.1 (62.9–72.9)	53.9	68.5	54.1	0.497	< 0.001
Romhilt Estes 5 points	44.4 (38.0–50.9)	79.2 (74.6–83.3)	59.4	67.5	50.8	0.042	0.275

Table 2. Diagnostic performance of the ECG criteria. Comparison of the performance of the ECG criteria [a]McNemar test comparing other ECG criteria versus Peguero-Lo Presti in patient with LVH in echocardiogram; [b]McNemar test comparing other ECG criteria versus Peguero-Lo Presti in patient without LVH in the echocardiogram; [a] and [b] = $p < 0.05$ indicates lack of agreement. *CI* confidence interval; *NPV* negative predictive value; *PPV* positive predictive value.

Specificity. The specificity of the Peguero-Lo Presti criterion (82.1% [95% CI 77.6–85.9%]) was inferior to the Cornell Voltage and Sokolow-Lyon criteria (89.7% [95% CI 86.1–92.7%] and 92.6% [95% CI 89.3–95.1%], respectively, with $p < 0.0001$ for both comparisons using the McNemar's test for patients without LVH in the echocardiogram. The Peguero-Lo Presti criterion had higher specificity than the RE4 (68.1% [95% CI 62.9–72.9%], $p < 0.001$) and similar specificity compared to the RE5 (79.2% [95% CI 74.6–83.3%], $p = 0.275$).

Diagnostic performance. The Peguero-Lo Presti had the highest F1 score (58.3%), followed by the Romhilt-Estes 4 points cutoff (54.1%), the Romhilt-Estes 5 points cutoff (50.8%), the Cornell Voltage (47.0%) and finally the Sokolow-Lyon voltage (40.6%). Diagnostic performance of the ECG criteria is summarized in Table 2.

Combination of ECG criteria. The Peguero-Lo Presti criterion also had the highest sensitivity in combination of two (with RE4) or three criteria (with RE4 and Cornell Voltage or RE4 and Sokolow-Lyon) and overall F1 Score (combined with the Sokolow-Lyon and Cornell voltage criteria). Diagnostic performance of combined ECG criteria is summarized in the Supplementary Table S4.

Decision curve analysis. The Peguero-Lo Presti criterion had the best net benefit for most 20–60% threshold range as shown in Fig. 3a,b. For thresholds in-between 10 and 20% (low probability threshold scores, applicable to high resource settings, i.e., when physicians might tolerate more false positives ECGs to avoid missing LVH on echocardiogram), we found no/little clinical usefulness for all ECG criteria compared to ordering echocardiograms for all patients. For a probability threshold of 40%(moderate to high probability threshold scores, applicable to under-resourced settings, i.e., when physicians might tolerate fewer false positives to curb ordering of unnecessary echocardiograms) the Peguero-Lo Presti criterion would avoid nearly 20 exams (out of 100 screened patients) when compared to the hypothetical strategy of ordering echocardiogram for all patients. Also, when compared to all other ECG criteria for most 20–60% threshold range, the implementation of the

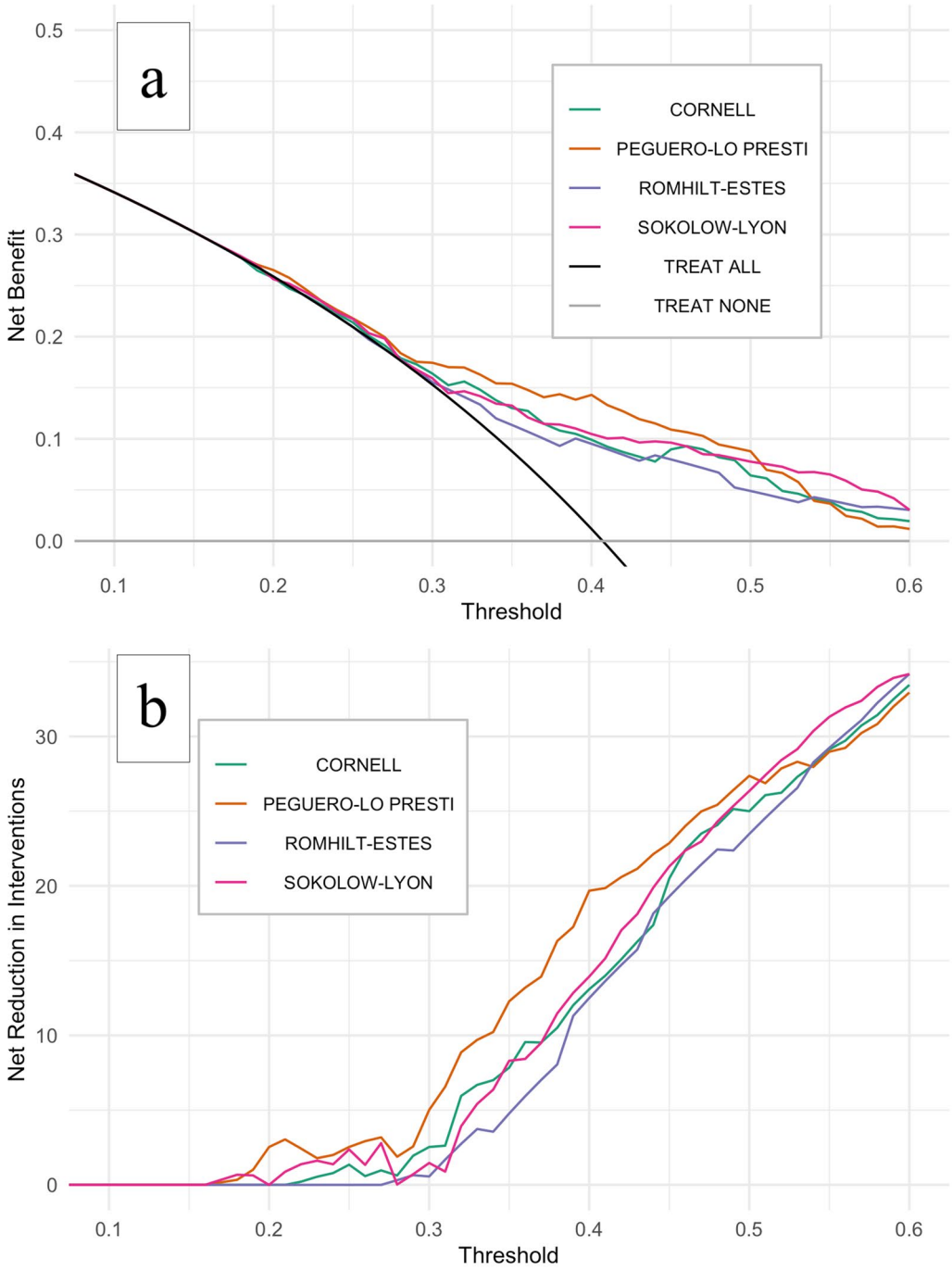

Figure 3. Decision curve analysis for the ECG criteria. Decision curve analysis showing the effect of ECG criteria on the detection of left ventricular hypertrophy as assessed by echocardiogram. Net benefit is plotted against the risk threshold at which the clinician would opt for ordering echocardiogram, compared to strategies of performing echocardiogram to all patients (black line) or none (grey line) (**a**). (**b**) Shows the net reduction in echocardiograms ordered by using different ECG criteria (as shown in the number of unnecessary echocardiograms avoided per 100 patients). Probability threshold range (0.1–0.6) reflect different relative values for harm (performing an echocardiogram in patients without LVH, i.e., false positives) and benefit (identifying a true positive) and were selected a priori to mimic both high (0.1–0.3) and under-resourced (0.3–0.6) theoretical clinical scenarios where elective echocardiogram availability and waiting times are supposed to vary.

Peguero-Lo Presti criterion would decrease the number of echocardiograms needed to diagnose one patient with echocardiographic LVH (true positive results) without missing additional patients with echocardiographic

LVH (false negative results). For illustrative purposes, the impact of screening 100 patients at-risk of LVH with each ECG criterion based on our dataset, using a 40% probability threshold, is pictured in Supplementary Fig. S2 and a direct comparison among all ECG criteria according to varying probability thresholds is summarized in the Supplementary Table S5.

Discussion

The development of accurate ECG criteria for LVH is an unmet need in Cardiology, especially in the elderly, where very few data are available. In this study, we demonstrated that the PLP had superior performance when compared to the other ECG criteria using the AUC, the F1 score and the decision curve analysis. To the best of our knowledge, we report three new comparisons for the first time: the first between the recently proposed Peguero-Lo Presti criterion and traditional ECG criteria in the elderly, an age group systematic underrepresented in other cohorts. Second, we compared the Peguero-Lo Presti versus the Romhilt-Estes scoring system (that unlike the other criteria, considers more than only the QRS complex voltage for LVH diagnosis). Third, we used the decision curve analysis to help clinicians use a selective strategy to perform echocardiogram in patients at risk of LVH.

After the original publication of the Peguero-Lo Presti criterion several other groups compared the sensitivity of the novel electrocardiographic criterion with other ECG criteria with conflicting results[32,38–45]. The PLP criterion also predicted LVH in another cohort of patients with aortic stenosis[46] and mortality in a clustered probability sample of the general population[5]. Also, in a cohort of apparently healthy individuals[47], the specificity of the PLP criterion seemed to be higher in older rather than young individuals. We believe our results add relevant findings: the Peguero-Lo Presti criterion had the highest discriminative performance compared to all other criteria, as assessed by the AUC and the F1 score. We also have shown that, despite previous concerns about its generalizability in certain populations not properly represented in the original publication[39], the Peguero-Lo Presti criterion can be used in elderly patients with the proposed cut-offs, having an improved sensitivity compared to other voltage criteria and similar sensitivity to the more complex and laborious Rohmilt-Estes scoring system.

Despite the higher sensitivity of the Peguero Lo–Presti criterion, it would not be suitable as a screening test in our population, because near 1 out of 2 patients with LVH would be missed—even in a population from a tertiary center with high prevalence of disease, where sensitivity is probably overestimated due to the spectrum effect[48]. An alternative approach that deserves further exploration to overcome this ECG limitation is to combine different criteria[49,50], aiming to increase sensitivity and helping surpass the historical inability of the ECG to rule out LVH[51]. Indeed, findings from our exploratory analysis suggests that combination of ECG criteria using the Peguero-Lo Presti criterion increased sensitivity and performance (F1 score) of the ECG.

As the optimal strategy to screen for LVH in patients at risk is still to be determined[7], the decision curve analysis suggested that the Peguero-Lo Presti criterion might have a role in guiding treatment decisions. The Peguero-Lo Presti provided the best net benefit for most tested thresholds and, compared to other ECG criteria, could optimize the use of echocardiography—a need in low-resource areas, where the waiting time for an elective scheduled echocardiogram can last up to 540 days[52]. As a low-cost, ubiquitous and easily accessible test, the ECG is theoretically the perfect tool for both diagnosis and follow-up of LVH worldwide.

Study limitations. This was a retrospective single-center study and several limitations bear acknowledgement. First, the gold standard for LVH diagnosis was the two-dimensional echocardiogram that is known to be an operator-dependent test and inferior to MRI[53]. Second, we could not adjust the Sokolow-Lyon voltage product according to body mass index as proposed by Rider and colleagues[54]. Third, since mortality and other long-term cardiovascular endpoints were not available, we could not test the hypothesis that ECG-based LVH assessed by the Peguero-Lo Presti (named electrical LVH) has prognostic implications besides anatomic-based LVH—as both ECG-LVH and echocardiographic LVH may provide prognostic information[55]. Fourth, because we excluded patients with bundle branch blocks, pacemaker and atrial fibrillation, our findings cannot be extrapolated to these groups. Fifth, even though Brazil is a highly ethnically diverse country, ethnic background was not routinely accessed and extrapolations of our findings to certain populations must be done with caution. Finally, our population is representative of a tertiary center with a high burden of cardiovascular disease, which may limit generalizability to the general population. Despite these limitations, we consider that our method is aligned with current clinical practice, where echocardiogram is the most frequently method to assess for LVH and the ECG criteria is rarely adjusted for body habitus. Also, our methodology was very similar to the original publication of the Peguero-Lo Presti criterion[23].

Conclusion

Compared to other ECG criteria, the Peguero-Lo Presti criterion had the best diagnostic performance in elderly patients and can potentially be used to guide a selective approach to echocardiogram ordering in low-resource settings. The sensitivity of this criterion, however, remains low and far from what would be expected as a screening tool. Further investigation—possibly by combining different ECG criteria—is needed to fill this long-standing knowledge gap in Cardiology, especially in patients with advanced age, systematically excluded and underrepresented in clinical research.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

C.A.M.T., M.F. and N.S. planned the study and primarily wrote the manuscript. L.C.G. did the primary statistical analysis, and with M.E.F. contributed to methodology, writing and editing. E.M.P. and F.L.N. did data acquisition and contributed to writing and editing. C.A.P., L.A.H. and W.J.F. helped conceive the original idea of the study and supervised the findings of the work to the final written manuscript. All the authors reviewed and approved the final version of the manuscript.

Competing interests

Michael E. Farkouh: research grants from Amgen, Novartis and Novo Nordisk; the other authors declare no competing interests.

Additional information

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Supplementary Information

Supplementary Table S1. The Romhilt and Estes Scoring System.

1. Voltage Criteria	R or S wave in limb leads ≥ 2mV	3 Points
	S wave in V1, V2 or V3 ≥3mV	
	R wave in V4, V5 ou V6 ≥3mV	
2. ST/T morphology with strain pattern	Without digitalis	3 Points
	With digitalis	1 Point
3. QRS axis deviation ≥ -30º		2 Points
4. QRS duration ≥0.09seg		1 Point
5. Left Atrial Abnormality	P terminal force in V1≥0.1mV and duration ≥40msec	3 Points
6. Intrinsicoid Deflection in V5 or V6 ≥ 40msec		1 Point

Sum of points used for calculation of the Romhilt-Estes criterion. Intrinsicoid Deflection (or R-wave peak time) is measured from the onset of the QRS complex to the peak of the R wave). A value of 4 points is termed LVH as probable and ≥5 points as definite.

Supplementary Table S2. The STARD 2015 checklist

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	1
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	2-3
	4	Study objectives and hypotheses	3
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	4-6
Participants	**6**	Eligibility criteria	4 and Figure 1
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	4
	8	Where and when potentially eligible participants were identified (setting, location and dates)	4
	9	Whether participants formed a consecutive, random or convenience series	4
Test methods	**10a**	Index test, in sufficient detail to allow replication	6
	10b	Reference standard, in sufficient detail to allow replication	6
	11	Rationale for choosing the reference standard (if alternatives exist)	6
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	4
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	4
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	4
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	4
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	6
	15	How indeterminate index test or reference standard results were handled	6

Section & Topic	No	Item	Reported on page #
	16	How missing data on the index test and reference standard were handled	6-7
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	6-7
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Figure 1
	20	Baseline demographic and clinical characteristics of participants	Table 1
	21a	Distribution of severity of disease in those with the target condition	Table 1
	21b	Distribution of alternative diagnoses in those without the target condition	Table 1
	22	Time interval and any clinical interventions between index test and reference standard	Table 1
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 3
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 3
	25	Any adverse events from performing the index test or the reference standard	N/A
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	11-12
	27	Implications for practice, including the intended use and clinical role of the index test	10-12
OTHER INFORMATION			
	28	Registration number and name of registry	N/A
	29	Where the full study protocol can be accessed	N/A
	30	Sources of funding and other support; role of funders	1

Abbreviations: **N/A** = not applicable

Supplementary Table S3. Echocardiographic parameters

Echocardiographic parameters	Non-LVH patients (n=351)	LVH patients (n=241)	P value
Ejection fraction (%)	60.59 ± 8.54	54.88 ± 13.07	<0.001
Left ventricular mass index (g/m^2)	84.10 ± 14.95	130.45 ± 26.11	<0.001
RWT	0.40 ± 0.06	0.43 ± 0.10	<0.001
Left Atrium diameter (mm)	39.14 ± 5.87	43.10 ± 5.98	<0.001
Interventricular septal diameter (mm)	9.45 ± 1.27	11.34 ± 1.81	<0.001
Posterior wall diameter (mm)	8.96 ± 1.11	10.51 ± 1.48	<0.001
Left ventricular end- diastolic diameter (mm)	46.92 ± 5.19	52.70 ± 7.16	<0.001
Left ventricular end-systolic diameter (mm)	31.33 ± 5.13	36.95 ± 8.42	<0.001
Moderate or severe aortic stenosis	23 (6.6%)	59 (24.5%)	<0.001
Moderate or severe mitral regurgitation	34 (9.7%)	47 (19.5%)	0.001
Moderate or severe aortic regurgitation	4 (1.1%)	31 (12.9%)	<0.001

Echocardiographic parameters of cohort, according to the left ventricular hypertrophy status evaluated by echocardiography. Values are mean ± standard deviation or n (%). Abbreviations: **RWT** = Relative wall thickness (no unit).

Supplementary Table S4. Diagnostic performance of combined ECG Criteria

ECG combination criteria		Sensitivity (95% CI)	Specificity (95% CI)	PPV (%)	NPV (%)	F1 Score (%)
Any two criteria	CV / SL	50.2 (44.0-56.4)	84.9 (81.2-88.9)	69.5	71.3	58.3
	CV / PLP	55.2 (49.2-61.4)	80.1(75.8-84.2)	65.5	72.2	59.9
	CV / RE4	64.3 (57.7-70.5)	65.5 (60.4-70.6)	56.2	72.8	60.0
	CV / RE5	58.5 (51.8-64.7)	74.4 (69.5-78.9)	61.0	72.3	59.8
	SL / PLP	60.6 (54.1-66.8)	78.6 (74.2-83.2)	66.1	74.4	63.2
	SL / RE4	58.5 (52.3-64.7)	65.2 (60.4-70.4)	53.6	69.6	56.0
	SL / RE5	50.2 (44.1-56.2)	75.8 (71.2-80.2)	58.7	68.9	54.1
	PLP / RE4	69.3 (63.5-75.2)	60.4 (55.0-65.6)	54.6	74.1	61.1
	PLP / RE5	64.3 (57.9-70.2)	68.7 (65.2-73.7)	58.5	73.7	61.3
Any three criteria	CV / SL / PLP	63.5 (57.3-69.2)	76.6 (72.2-80.9)	65.1	75.4	64.3
	CV / SL / RE4	67.2 (61.1-73.8)	63.0 (57.8-68.2)	55.5	73.7	60.8
	CV / SL / RE5	63.1 (56.5-69.1)	71.5 (66.7-75.9)	60.3	73.8	61.7
	CV / PLP / RE4	71.4 (65.5-77.0)	59.3 (54.2-64.6)	54.6	75.1	61.9
	CV / PLP / RE5	67.2 (61.5-72.7)	67.0 (62.0-71.9)	58.3	74.8	62.4
	SL / PLP / RE4	71.4 (65.0-76.8)	58.7 (53.3-64.1)	54.3	74.9	61.7
	SL / PLP / RE5	67.2 (61.2-73.3)	66.7 (62.0-71.2)	58.1	74.8	62.3
Any criteria		73.4 (67.6-78.7)	57.6 (52.4-62.7)	54.3	75.9	62.3

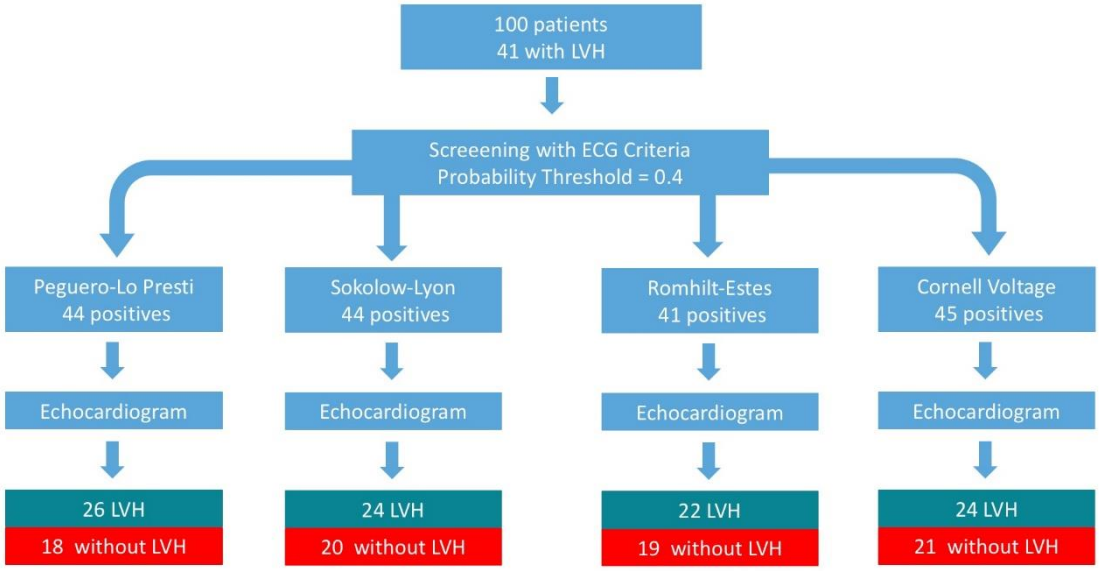
Comparison of the diagnostic performance of combined ECG criteria. Abbreviations: **CI** = Confidence Interval; **CV** = Cornell Voltage; **PLP** = Peguero-Lo Presti; **RE4** = Romhilt-Estes 4-points cutoff; **RE5** = Romhilt-Estes 5-points cutoff; **SL** = Sokolow-Lyon; **NPV** = Negative Predictive Value; **PPV** = Positive Predictive Value.

Supplementary Table S5. Direct comparisons of the ECG criteria using different probability thresholds.

ECG Criteria	Probability Threshold	Echocardiogram		Echocardiographic LVH	
		Performed	Not performed	Recognized	Missed
Peguero-Lo Presti	10%	1000	0	407	0
	20%	975	25	407	0
	30%	742	276	344	63
	40%	435	565	260	147
	50%	243	757	165	242
	60%	113	887	73	334
Sokolow-Lyon	10%	1000	0	407	0
	20%	968	32	399	8
	30%	760	240	339	68
	40%	434	566	236	171
	50%	220	780	149	258
	60%	115	885	81	326
Romhilt-Estes	10%	1000	0	407	0
	20%	1000	0	407	0
	30%	645	355	302	105
	40%	410	590	222	185
	50%	221	779	135	272
	60%	98	902	71	336
Cornell Voltage	10%	1000	0	407	0
	20%	988	12	404	3
	30%	806	194	357	50
	40%	451	549	239	168
	50%	203	797	133	274
	60%	100	900	67	340

Numbers are given per 1000 patients screened with each ECG criterion. For each probability threshold and ECG criteria, numbers of patients that would perform or not an echocardiogram if the ECG criterion was positive are shown (Echocardiogram column), calculated according to varying thresholds. Also, numbers of true positives (LVH confirmed by the echocardiogram) and false negatives (echocardiographic LVH missed by the ECG) are shown according to ECG criteria and probability thresholds. Probability thresholds were selected *a priori* to mimic both high (0.1-0.3) and under-resourced (0.3-0.6) theoretical clinical scenarios where elective echocardiogram availability and waiting times are supposed to vary. Abbreviations: **ECG**: Electrocardiogram; **LVH** = Left Ventricular Hypertrophy.

Supplementary Figure 1. Impact of screening 100 patients at-risk of LVH with each ECG criterion



Step by step illustrative impact of screening 100 patients using a 40% probability threshold. First, 100 patients (41 with LVH) are screened with each ECG criterion. If the ECG criterion is positive, then an echocardiogram is performed to confirm or rebut the ECG finding. After the echocardiogram, patients are classified in true positives (echocardiographic LVH) or false positives (without echocardiographic LVH). Abbreviations: **ECG**: Electrocardiogram; **LVH** = Left Ventricular Hypertrophy.

ANEXO 2

BMC Cardiovascular Disorders

RESEARCH

Open Access

Usefulness of ECG criteria to rule out left ventricular hypertrophy in older individuals with true left bundle branch block: an observational study

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Abstract

Background: Advanced age is associated with both left bundle branch block (LBBB) and hypertension and the usefulness of ECG criteria to detect left ventricular hypertrophy (LVH) in patients with LBBB is still unclear. The diagnostic performance and clinical applicability of ECG-based LVH criteria in patients with LBBB defined by stricter ECG criteria is unknown. The aim of this study was to compare diagnostic accuracy and clinical utility of ECG criteria in patients with advanced age and strict LBBB criteria.

Methods: Retrospective single-center study conducted from Jan/2017 to Mar/2018. Patients undergoing both ECG and echocardiogram examinations were included. Ten criteria for ECG-based LVH were compared using LVH defined by the echocardiogram as the gold standard. Sensitivity, specificity, predictive values, likelihood ratios, AUC, and the Brier score were used to compare diagnostic performance and a decision curve analysis was performed.

Results: From 4621 screened patients, 68 were included, median age was 78.4 years, (IQR 73.3–83.4), 73.5% with hypertension. All ECG criteria failed to provide accurate discrimination of LVH with AUC range between 0.54 and 0.67, and no ECG criteria had a balanced tradeoff between sensitivity and specificity. No ECG criteria consistently improved the net benefit compared to the strategy of performing routine echocardiogram in all patients in the decision curve analysis within the 10–60% probability threshold range.

Conclusion: ECG-based criteria for LVH in patients with advanced age and true LBBB lack diagnostic accuracy or clinical usefulness and should not be routinely assessed.

Keywords: Hypertension, Electrocardiography, Left bundle branch block, Elderly

Introduction

Left ventricular hypertrophy (LVH) is an ultimate consequence of long-standing hypertension and is associated with all-cause mortality [1]. In patients receiving antihypertensive therapy, the improvement of LVH, as evaluated by the electrocardiogram (ECG), is associated with improved cardiovascular prognosis [2, 3]. Accordingly, current clinical practice guidelines recommend using the

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ECG as part of the routine assessment of patients with hypertension at baseline and during follow-up [4].

Abnormal depolarization of the left ventricle due to left bundle branch block (LBBB) may compromise the electrocardiographic diagnose of LVH because the LVH diagnostic criteria were developed and validated in patients without conduction disturbances [5]. More recent studies that evaluated ECG diagnostic performance in patients with LBBB, were heterogeneous and had a wide range of sensitivities due to the inclusion of different populations, use of multiple cut-offs, and distinct criteria [6], creating barriers for implementation into clinical practice. In fact, some authors even consider that the electrocardiographic diagnosis of LVH should not be applied in those with LBBB [7]. The lack of universally accepted standards to distinguish true LBBB from conduction delay [8] adds even more complexity to this topic.

Advanced age is associated with hypertension and LBBB [9–11], and the number of patients with both conditions is expected to grow progressively in the next years because of the overall aging population. Validating or developing new accurate ECG criteria for LVH in this population can have relevant and immediate clinical applicability. We aim to evaluate the diagnostic accuracy of the traditional ECG-based LVH criteria in patients with LBBB and the clinical usefulness of using a selective strategy to guide echocardiogram orders.

Methods

Population

We retrospectively collected data from patients ≥ 70 years old (as of March/31/2018) evaluated at a tertiary care teaching hospital in Sao Paulo, Brazil. From January/2017 to March/2018, all outpatients and inpatients in non-critical care units patients who underwent a 12-lead ECG and echocardiogram from January/2017 to March/2018 were deemed eligible. Exclusion criteria were time between ECG and echocardiogram greater than 180 days, ECG images that could not be retrieved, only ECG images available from the ICU and ECG with lead changes or missing leads. ECG tracings were then inspected to exclude patients with ventricular pacemaker, non-sinus rhythm, advanced atrioventricular block or QRS with non-LBBB morphology (Fig. 1).

ECG analysis

Standard 12-lead ECGs were acquired at 10 mm/mV calibration and speed of 25 mm/s. Two physicians (CAMT and EMP) independently screened all tracings for LBBB, using the strict definition proposed by Strauss et al. (available in the Additional file 1: Table S1). As the LBBB identified by the ECG can represent conduction disease, left ventricle myocardial disease or a combination of both, the stricter LBBB criteria proposed by Strauss identify only those with true conduction disease and were developed aiming to predict who would better respond to cardiac resynchronization therapy (CRT) [12]. In cases of discordance between the examiners, the tracings were reviewed together with an experienced cardiologist (CAP) and the classification was defined based on consensus. Two cardiologists (NS and MF), blinded to echocardiogram and clinical data, calculated the following LVH criteria in all ECGs with LBBB: Peguero-Lo Presti, Cornell voltage, Cornell Voltage duration, SV2 plus SV3, R wave in avL, R wave product in avL, Sokolow-Lyon, Sokolow-Lyon product, Dalfó criteria and Gubner-Ungerleider (Additional file 1: Table S2). In case of discordances, a third cardiologist also revised the ECG tracings (CAMT).

Echocardiographic analysis

Echocardiograms were used as the gold-standard method to diagnose LVH. All echocardiograms were performed at our institution according to international guidelines [12]. Left Ventricular Mass was calculated using the Devereux formula: left ventricular mass (g) = 0,80 × 1,04 [(septal thickness + internal diameter + posterior wall thickness)^3 − (internal diameter)^3] + 0.6 g[13], and indexed by the Body Surface Area (BSA), calculated by the Dubois Formula (BSA = 0.007184 × height (m)$^{0.725}$ × weight (kg)$^{0.425}$, with LVH defined as > 95 g/m^2 in females and > 115 g/m^2 male subjects.

Clinical data

Epidemiological data from all patients were retrieved from the electronic medical record: anthropometric data (height, weight, body mass index), age in years (at the day of echocardiogram exam), comorbidities as diagnosed by the attending physician (hypertension, diabetes, coronary artery disease, prior myocardial infarction, coronary artery bypass graft surgery, prior percutaneous coronary intervention, atrial fibrillation, peripheral artery disease, chronic obstructive pulmonary disease), medications prescribed (beta-blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptors blockers (ARB), hydralazine/nitrate). Vital signs were obtained through chart review (blood pressure and heart rate).

Statistical analysis

Clinical and echocardiographic characteristics were summarized as median and interquartile range or proportions, based on LVH status in the echocardiogram. The rank sum test was used for comparing continuous variables between groups and the Fisher exact test for categorical variables. For each ECG criterion, sensitivity,

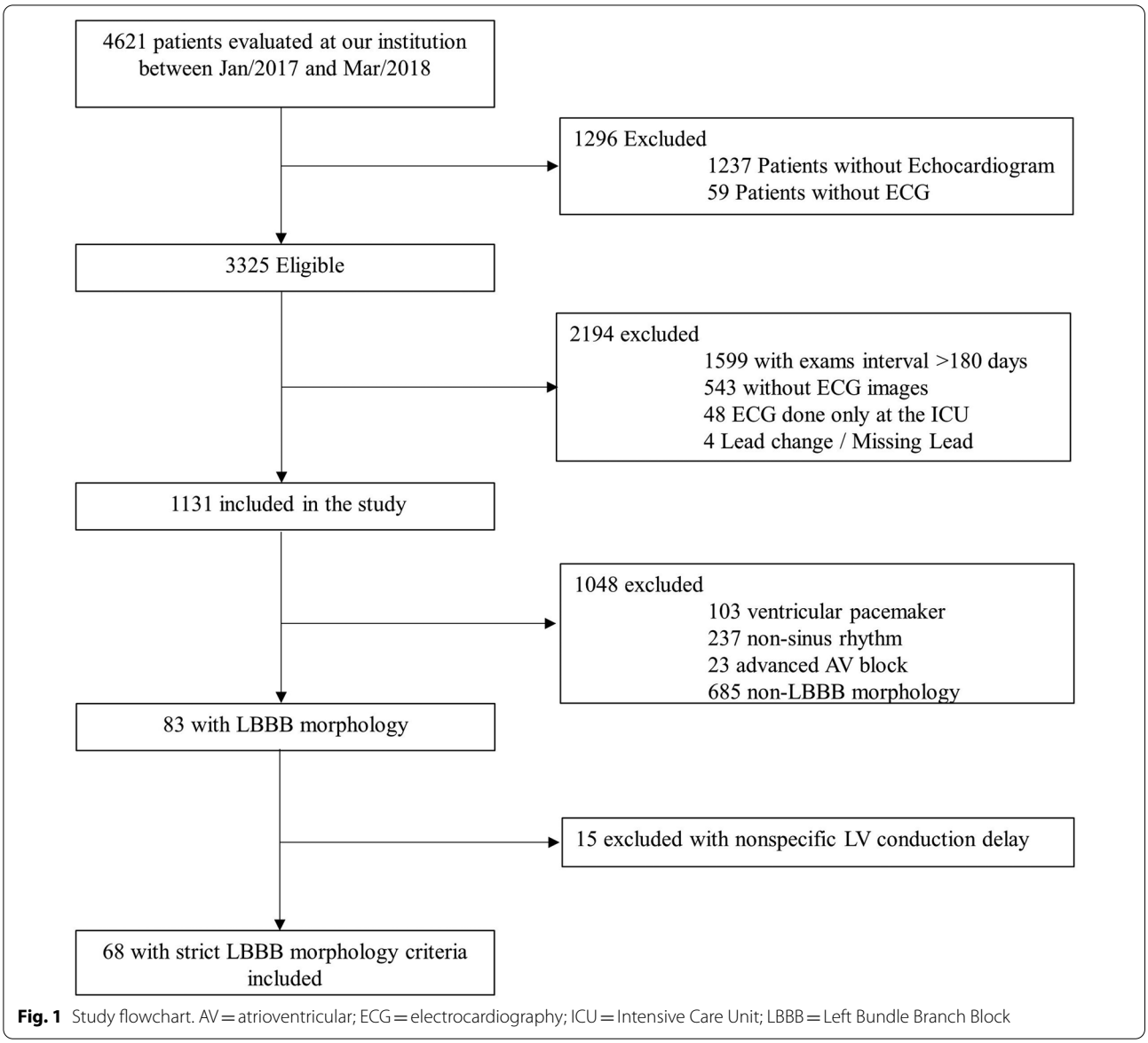

Fig. 1 Study flowchart. AV = atrioventricular; ECG = electrocardiography; ICU = Intensive Care Unit; LBBB = Left Bundle Branch Block

specificity, positive and negative predictive values, and likelihood ratios were calculated using the echocardiogram as the gold standard. Pearson correlation coefficients between ECG criteria and left ventricular mass index were calculated using the ECG criteria as continuous variables. Discriminative performance of the ECG criteria was calculated according to the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. The Brier Score was calculated as a measure of overall performance, defined as the mean squared difference between the observed (Echo-LVH) and predicted outcome (ECG-LVH, for each ECG criteria). The Brier Score ranges from 0 to 1 with lower values being indicative of better overall performance.

We used a decision curve analysis framework to assess how each ECG criterion would impact clinical practice. In brief, the net-benefit for each ECG criterion was calculated by subtracting the proportion of false positives from the true positives, weighted by the relative harm of a false positive and a false negative result. Each score was then compared to strategies of ordering echocardiogram for all or none, by subtracting the estimated net-benefit of ordering-all strategy from the respective criteria. This method considers how many false positives cases the physician is willing to treat to avoid not treating a false negative patient. In our case, this can be translated as how many echocardiograms without LVH the physician is willing to accept to avoid not recognizing one

echocardiogram with LVH, which could guide the physician's decision on echocardiogram orders. The threshold probabilities were selected a priori with a large threshold range (0.1–0.6) to mirror different resource settings. Detailed explanation of the decision curve analysis can be found elsewhere [13]. Our manuscript was based in the 2015 Standards for Reporting Diagnostic Accuracy Studies (STARD), available in the Additional file 1: Table S3. A two-sided $p < 0.05$ was considered statistically significant. Statistical analysis was performed using the R software, version 3.6.2 (R Project for Statistical Computing).

Results

Characteristics of the study population

As outlined in Fig. 1, after screening 4621 patients, 68 patients with LBBB criteria were included, of whom 46 (67.6%) had LVH based on the echocardiogram. The median age was 78.4 years (IQR 73.3–83.4), most were female (n = 38, 55.9%), and hypertension was the most common chronic disease (n = 50, 73.5%); followed by coronary artery disease (n = 32, 47.1%) and dyslipidemia (n = 27, 39.7%). The median time interval between the ECG and the echocardiogram was 14 days (IQR 1.0–43.3). Patients with LVH were older and predominantly male. Demographic data of the population is summarized in Table 1. As expected, echocardiographic diagnosis of LVH was associated with distinct echocardiographic parameters: lower ejection fraction (46.5% versus 59.5%, $p = 0.027$), higher left ventricular mass index (141.0 versus 97.5 g/m^2, $p < 0.001$), increased left atrium diameter (46.0 versus 38.0 mm, $p < 0.001$), left ventricular end-diastolic diameter (57.5 versus 48.0 mm, $p = 0.001$), and left ventricular end-systolic diameter (43.5 versus 34.0 mm, $p = 0.004$), as shown in Table 2.

Diagnostic performance of the ECG criteria

Sensitivity, specificity, predictive values and likelihood ratios The standard cut-offs of the ECG criteria had a wide range of sensitivities (26.1–100%) and specificities (0–81.8%) (Table 3). No single ECG criterion had a

Table 1 Demographic data

Demographic data	All patients (n = 68)	LVH patients (n = 46)	Non-LVH patients (n = 22)	*P* value
Age (years)	78.4 (73.3–83.4)	78.7 (74.5–79.9)	76.2 (71.6–80.6)	0.018
Female	38 (55.9%)	19 (41.3%)	19 (86.4%)	<0.001
BMI (kg/m^2)	25.3 (23–8–27.8)	24.8 (22.9–27.7)	26.0 (24.2–27.7)	0.235
SBP (mmHg)	120.0 (110.0–140.0)	120.0 (110.0–132.0)	121.0 (112.5–140.0)	0.256
DBP (mmHg)	71.5(60.0–80.0)	70.0 (60.0–80.0)	80.0 (71.5–80.0)	0.033
Heart rate (bpm)	67.0 (57.0–77.0)	69.0 (55.5–77.8)	65.0 (59.0–73.8)	0.854
Hypertension	50 (73.5%)	33 (71.7%)	17 (77.3%)	0.772
Type 2 diabetes	19 (27.9%)	10 (21.7%)	9 (40.9%)	0.148
Dyslipidemia	27 (39.7%)	18 (39.1%)	9 (40.9%)	1.000
Paroxysmal atrial fibrillation	11 (16.2%)	9 (19.6%)	2 (9.1%)	0.482
Coronary artery disease	32 (47.1%)	19 (41.3%)	13 (59.1%)	0.201
Previous myocardial infarction	17 (25.0%)	11 (23.9%)	6 (27.3%)	0.772
Previous CABG	14 (20.6%)	7 (15.2%)	7 (31.8%)	0.198
Previous PCI	18 (26.5%)	12 (26.1%)	6 (27.3%)	1.000
Peripheral artery disease	6 (8.8%)	4 (8.7%)	2 (9.1%)	1.000
Chronic obstructive pulmonary disease	8 (11.8%)	6 (13.0%)	2 (9.1%)	1.000
Medication use				
ACEi	31 (45.6%)	20 (43.5%)	11 (50.0%)	0.795
ARBs	19 (27.9%)	13 (28.3%)	6 (27.3%)	1.000
CCBs	14 (20.6%)	8 (17.4%)	6 (27.3%)	0.356
Beta blocker	47 (69.1%)	33 (71.7%)	14 (63.76%)	0.579
Hydralazine/Nitrate	11 (16.2%)	8 (17.4%)	3 (13.6%)	1.000
Diuretic	44 (64.7%)	28 (60.9%)	16 (72.7%)	0.421
Days between echocardiogram and ECG	14 (1.0–43.3)	13.5(1.0–42.8)	14 (3.3–47.8)	0.506

Demographic data of the cohort, according to the left ventricular hypertrophy status evaluated by echocardiography. Values are median and interquartile range or n (%)

ACEi: = Angiotensin-Converting Enzyme inhibitors; ARBs = Angiotensin Receptor blockers; BMI = Body Mass Index; CABG = Coronary Artery Bypass Graft; CCBs = Calcium Channel Blockers; DBP = Diastolic Blood Pressure; PCI = Percutaneous Coronary Intervention; SBP = Systolic Blood Pressure

Table 2 Echocardiographic parameters

Echocardiographic parameters	LVH patients (n = 46)	Non-LVH patients (n = 22)	*P* value
Ejection fraction (%)	46.5 (30.0–60.8)	59.5 (40.3–65.8)	0.027
Left ventricular mass index (g/m^2)	141.0 (117.8–173.5)	97.5 (86.5–108.5)	< 0.001
Relative wall thickness (no unit)	0.37 (0.30–0.44)	0.41 (0.33–0.45)	< 0.306
Left Atrium diameter (mm)	46.0 (42.0–49.0)	38.0 (36.0–43.0)	< 0.001
Interventricular septal diameter (mm)	10.5 (9.3–10.7)	10.0 (9.0–11.0)	0.085
Posterior wall diameter (mm)	10.0 (9.0–11.0)	10.0 (9.0–10.0)	0.088
Left ventricular end- diastolic diameter (mm)	57.5 (50.0–65.8)	48.0 (47.0–55.8)	0.001
Left ventricular end-systolic diameter (mm)	43.5 (33.8–55.5)	34.0 (31.3–37.8)	0.004
Moderate or severe aortic stenosis	9 (19.6%)	2 (9.1%)	0.482
Moderate or severe mitral regurgitation	11 (23.9%)	1 (4.5%)	0.086
Moderate or severe aortic regurgitation	4 (8.7%)	1 (4.5%)	1.000

Echocardiographic parameters of cohort, according to the left ventricular hypertrophy status evaluated by echocardiography. Values are median and interquartile range or n (%)

Table 3 Clinical utility of the ECG criteria

ECG criteria	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	LR+ (95% CI)	NPV (%) (95% CI)	LR− (95% CI)
Peguero-Lo Presti	96.0 (88.6–100)	9.1 (0–22.7)	68.8 (57.2–79.0)	1.05 (0.93–1.24)	50.0 (0–100)	0.48 (0–1.86)
Cornell voltage	87.0 (76.0–96.1)	27.3 (8.0–47.4)	71.4 (59.3–83.7)	1.2 (0.92–1.67)	50.0 (22.2–78.6)	0.48 (0.1–1.46)
Cornell VDP	100 (NA)	9.1 (0–22.2)	69.7 (58.2–80.0)	1.10 (1.00–1.28)	100 (NA)	0 (NA)
SV2 + SV3	39.1 (26.1–53.8)	59.1 (36.9–79.2)	66.7 (50.0–84.4)	0.96 (0.50–2.15)	31.7 (17.5–46.5)	1.03 (0.70–1.70)
R aVL	26.1 (13.3–38.7)	81.8 (63.2–95.7)	75.0 (50.0–93.8)	0.96 (0.50–2.15)	34.6 (21.6–48.2)	0.90 (0.69–1.19)
R aVL VDP	67.4 (53.2–80.0)	54.6 (33.3–76.2)	75.6 (61.1–88.4)	1.48 (0.92–2.69)	44.4 (26.1–65.2)	0.60 (0.31–1.08)
Sokolow-Lyon	26.1 (13.7–41.3)	81.8 (63.0–95.7)	75.0 (50.1–94.7)	1.43 (0.53–6.13)	34.6 (22.2–47.9)	0.90 (0.70–1.23)
Sokolow-Lyon VDP	60.9 (46.5–73.5)	50.0 (29.2–71.4)	71.8 (56.4–85.4)	1.22 (0.73–2.18)	37.9 (20.7–54.6)	0.78 (0.46–1.40)
Gubner-Ungerleider	82.6 (70.6–93.2)	18.2 (63.2–95.7)	67.9 (55.8–79.3	1.01 (0.79–1.32)	33.3 (6.7–62.5)	0.96 (0.32–4.24)
Dalfó	95.7 (88.9–100)	0 (NA)	66.7 (55.9–78.5)	0.96 (0.89–1.00)	NA	NA

Diagnostic performance of all the ECG criteria in patients with left bundle branch block, using the echocardiogram based left ventricular hypertrophy as the gold-standard

CI = Confidence Interval; LR+ = positive likelihood ration; LR− = negative likelihood ratio; NA = non applicable; NPV = Negative Predictive Value; PPV = Positive Predictive Value; R aVL = R wave in lead aVL; SV2 + SV3 = sum of the S wave in V2 plus V3; VDP = voltage-duration product

good balance for both indices. The Peguero-Lo Presti and the Cornell Voltage Duration Product criteria had high sensitivity, but low specificity (sensitivity 100%, specificity 9.1% and sensitivity 97.8%, specificity 27.3%, respectively), whereas the Sokolow-Lyon and R wave in lead avL criteria had high specificity but low sensitivity (specificity 81.8%, sensitivity 26.1% and specificity 81.8%, sensitivity 26.1%, respectively). Nominally, the highest positive likelihood ratio was observed for R avL (1.48) and the lowest negative likelihood ratio for Cornell Voltage Duration Product. Overall, the R avL voltage duration product had the highest positive predictive value (75.6%) and the Cornell Voltage Duration Product the highest negative predictive value (100%).

Discriminative power assessed by the area under the curve (AUC) and overall performance according to the Brier score Discrimination of all ECG criteria was poor. The AUC ranged between 0.53 and 0.67 and the Brier score from 0.20 to 0.22. The AUC of the Cornell Voltage duration product was numerically higher than the other criteria (0.67, 95% CI 0.53–0.79) (Table 4).

Correlation between ECG criteria and left ventricular mass index Moderate correlation (0.39–0.53) was observed for all ECG criteria. Figure 2 summarizes the correlation coefficients between the left ventricular mass index and ECG criteria.

Decision curve analysis For all the tested threshold probabilities (10–60%) we found little to no clinical

Table 4 Area under the receiver operating characteristic curve (AUC) and brier score for all ECG criteria

ECG criteria	AUC (95% CI)	Brier score
Peguero-Lo Presti	0.59 (0.45–0.72)	0.21
Cornell Voltage	0.55 (0.40–0.68)	0.22
Cornell VDP	0.67 (0.53–0.79)	0.20
SV2 + SV3	0.53 (0.38–0.68)	0.22
R aVL	0.62 (0.46–0.76)	0.21
R aVL VDP	0.64 (0.49–0.78)	0.21
Sokolow-Lyon	0.54 (0.39–0.69)	0.22
Sokolow-Lyon VDP	0.57 (0.42–0.72)	0.22
Gubner-Ungerleider	0.54 (0.42–0.72)	0.22
Dalfó	0.55 (0.39–0.69)	0.22

AUC and Brier Score for the ECG criteria using the echocardiogram based left ventricular hypertrophy as the gold-standard

CI = Confidence Interval; R aVL = R wave in lead aVL; SV2 + SV3 = sum of the S wave in V2 plus V3; VDP = voltage-duration product

benefit of utilizing ECG criteria compared to a strategy of ordering echocardiograms for all patients (Fig. 3).

Discussion

Our study had three main findings: first, the poor diagnostic performance of traditional ECG criteria in patients with strict criteria for LBBB; second, the low diagnostic accuracy of the recently proposed Peguero-Lo Presti criteria in patients with LBBB and third, the lack of clinical usefulness of the ECG criteria as a screening method for deciding on the need for an echocardiogram.

As expected, LBBB poises a challenging issue for ECG screening tests because it is associated with a high prevalence of LVH (over 40% in the literature [14–16] and 68% in our cohort). High pre-test probability of disease consequently demands a criterion to have an exceptionally low negative likelihood ratio to exclude the diagnosis. For instance, even though the Cornell Voltage Duration Product captured all patients with LVH, with a sensitivity of 100%, specificity was very low (9.1%), nearly classifying every patient as with ECG-based LVH, thus not useful as tool to discriminate/identify those with LVH. None of the other ECG scores and respective cut-offs tested had a negative predictive value (NPV) over 80% and therefore were unable to adequately rule-out LVH. One could alter criteria cut-offs; however, the analysis of the decision curve showed little to no clinical benefit in using these scores even when accounting for a wide range of thresholds.

These results question the usefulness of the LVH electrocardiographic criteria in patient with LBBB. Although some reports have yielded high sensitivity [17–21], especially when using a computer-assisted diagnostic system [6], other groups have also questioned the use of ECG-based LVH criteria in patients with LBBB [7]. Previous studies testing ECG-based LVH criteria in patients with LBBB were performed prior to the development of the stricter LBBB criteria, and likely enrolled a more heterogeneous population, mixing conduction disease with LVH or LV dilation. This limitation could have artificially improved the LVH diagnostic performance of the ECG.

Our highly selective approach identified a more homogenous group of patients with true conduction disease where ECG-based criteria were unsuitable to diagnose echocardiographic LVH. Because conventional LBBB criteria on the ECG represents a complex interplay between conduction system and LV muscle disease, applying ECG criteria to recognize mainly muscle disease (LVH) in those with established conduction disease (strict LBBB criteria) might lead to many false positives—as observed by the low positive likelihood ratios found in our study. Indeed, our results from the correlation coefficients between the ECG criteria and left ventricular mass support this hypothesis as well, where correlation coefficients were consistently weak/moderate for all studied ECG criteria.

Our findings also inform practice. The 2018 AHA/ACCF/HRS guidelines recommend that patients diagnosed with new LBBB should undergo screening with echocardiogram [22]. However, the approach for patients at risk for LVH and a baseline echocardiogram without LVH is still uncertain. Because of the long waiting time for echocardiogram in low- and middle-income countries [23], alternatives for LVH assessment are needed, as LVH might influence treatment decisions [24]. ECGs can be performed at a low cost and repeated on a regular basis [23], helping clinicians to identify patients who have evolving changes and are at high risk of adverse outcomes earlier. This approach can shorten echocardiogram waiting times for those deemed high risk and create an earlier therapeutic window for intervention. Nevertheless, based on our findings, the ECG criteria we tested are not reliable to guide selective screening of patients for LVH when LBBB is present, and, therefore, routine assessment of LVH based on ECG criteria should not be performed.

Study limitations

This was a retrospective single-center study with inherent limitations that warrant acknowledgment. First, despite screening more than 4,000 patients, our final sample size is small, which mirrors the prevalence of LBBB. Second, we excluded patients with atrial fibrillation and other non-sinus rhythms to minimize differences between QRS voltage measurements and caution is needed when attempting to extrapolate our findings to these patients. Third, as our study was performed using a single ECG analysis, we have not evaluated if evolving changes in

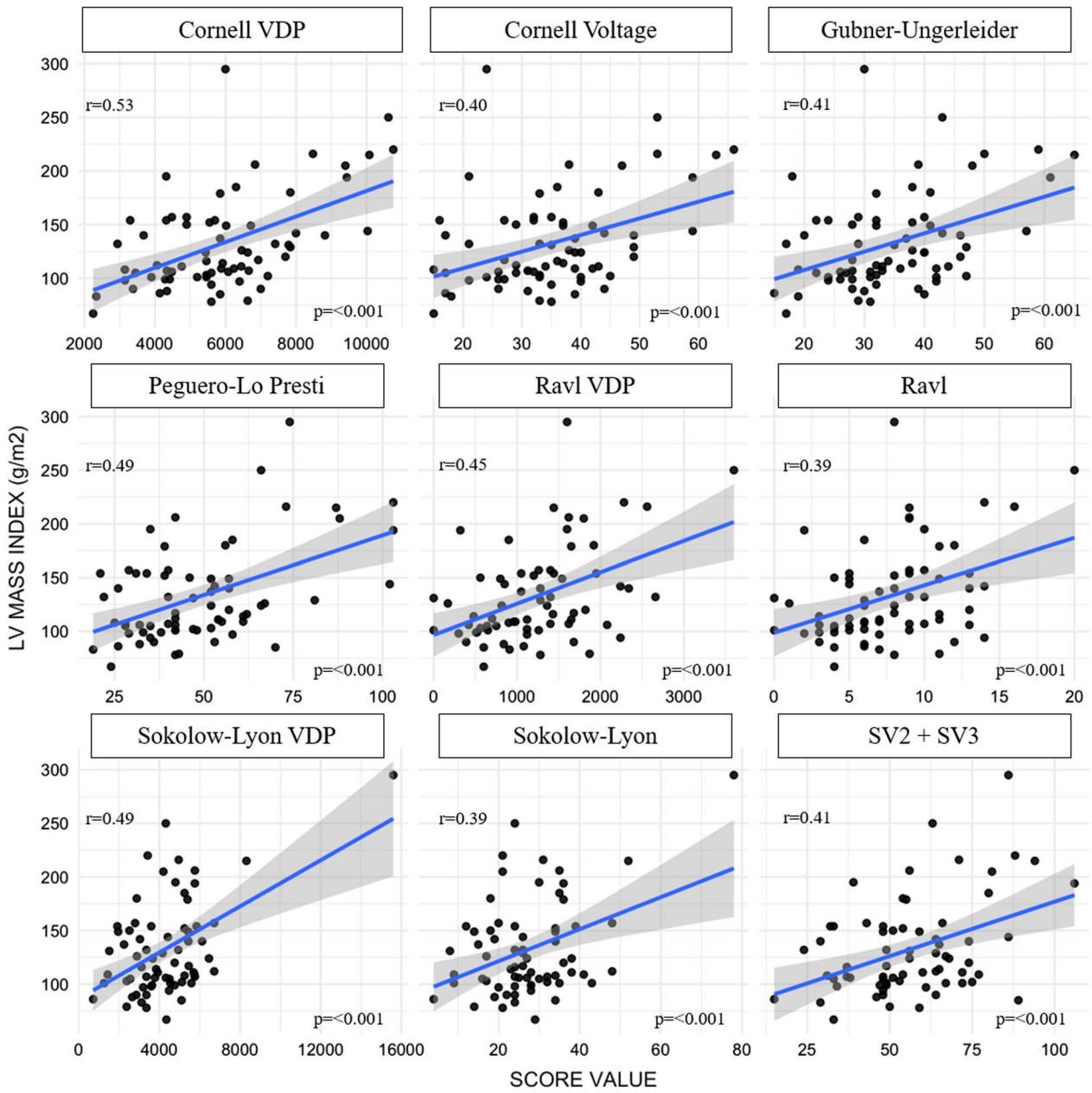

Fig. 2 Correlation between ECG criteria and left ventricular mass index. LV = left ventricular; R aVL = R wave in lead aVL; SV2 + SV3 = sum of the S wave in V2 plus V3; VDP = voltage-duration product

ECG criteria over time might have a role in the diagnosis or follow-up of ECG-based LVH. Fourth, our study did not address if ECG-based LVH (named electrical LVH) might provide prognostic information even in the absence of LVH as assessed by echocardiogram (named anatomic LVH) in patients with LBBB, as long-term outcomes were not available [25]. Finally, our population is representative of a tertiary cardiovascular reference center, where there is a high burden of cardiovascular disease, and the generalization of our findings to primary and secondary care settings may be limited.

Conclusion

Our findings suggest no role for routine use of traditional LVH electrocardiographic criteria in patients with LBBB, neither for screening of LVH nor for guiding a selective approach to ordering echocardiograms.

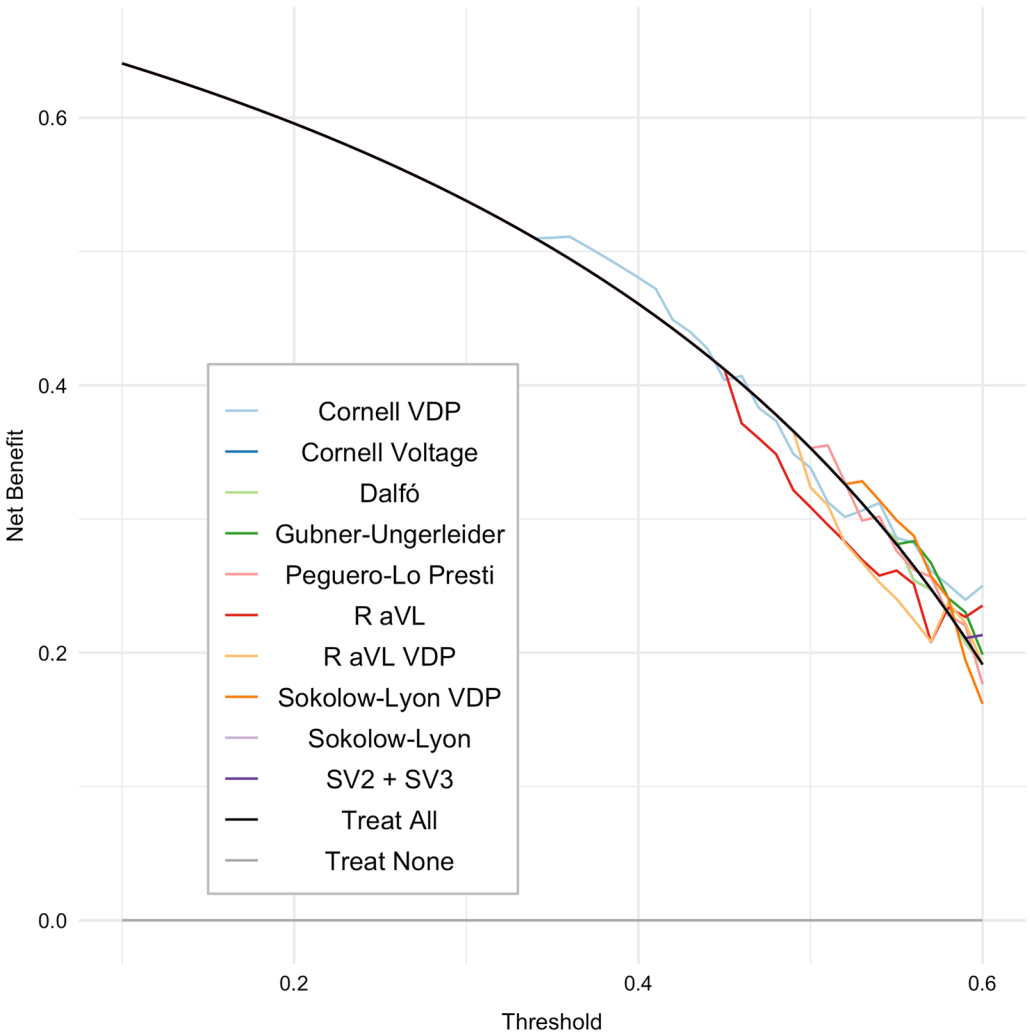

Fig. 3 Decision curve analysis for the ECG criteria. Decision curve analysis of the ECG criteria for the detection of left ventricular hypertrophy as assessed by the echocardiogram. For different risk thresholds for which the clinician would opt to order an echocardiogram, the net benefit of each ECG criteria is plotted compared against strategies of echocardiogram to all patients (black line) or none (grey line). CI = Confidence Interval; R aVL = R wave in lead aVL; SV2 + SV3 = sum of the S wave in V2 plus V3; VDP = voltage-duration product

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-021-02332-8.

Additional file 1. Supplementary Tables S1–S3.

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Authors' contributions
CAMT and NS planned the study and primarily wrote the manuscript. FLN did the primary statistical analysis and contributed to writing and editing. LCG and MEF contributed to methodology, writing and editing. EMHP and MF did data acquisition and contributed to writing and editing. CAP, LAH and WJF helped conceive the original idea of the study and supervised the findings of the work to the final written manuscript. All the authors reviewed and approved the final version of the manuscript.

Funding
None.

Availability of data and materials
The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Hospital das Clínicas, Medicine School, University of São Paulo, Brazil (Protocol Number 3.210.301, Project Number 08797119.1.0000.0068 on 03/20/2019) and the need for individual signed informed consent was waived. We declare that all methods were performed in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
Caio de Assis Moura Tavares: none; Nelson Samesima: none; Felippe Lazar Neto: none; Ludhmila Abrahão Hajjar: none; Lucas C. Godoy: none; Eduardo Messias Hirano Padrão: none; Mirella Facin: none; Wilson Jacob Filho: none; Michael E. Farkouh: research grants from Amgen, Novartis and Novo Nordisk; Carlos Alberto Pastore: none.

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Publisher's Note

Additional file 1

1- Additional file 1: Table S1
2- Additional file 1: Table S2
3- Additional file 1: Table S3
4- References

Additional file 1: Table S1. ECG criteria for LBBB as proposed by Strauss et al(1) and updated in 2018(2).

ECG criteria	Description
QRS duration	≥140 msec for males ≥130 msec for females
Morphologic criteria for right-sided leads (V1, V2)	QS or rS in V1 and V2
Mid-QRS notching or slurring[a]	≥2 leads including I, avL, V1, V2, V5 or V6

ECG features of stricter left bundle branch block criteria as proposed by Strauss. LBBB is diagnosed when all three criteria are fulfilled. [a] = defined as notches or slurs that starts 40 msec after the beginning of the QRS complex and before 50% of the QRS width.

Additional file 1: Table S2. ECG criteria and cut-offs for left ventricular hypertrophy in patients with Left Bundle Branch Block

Criteria	Formula	Threshold	Reference
Peguero-Lo Presti	Deepest S wave + S_{V4}	≥2.8mV males ≥2.3mV females	(3)
Cornell Voltage	$R_{avL} + S_{V3}$	≥2.8mV males ≥2.0mV females	(4)
Cornell Voltage duration product	Males: $(R_{aVL}+S_{V3})$ *QRS duration Females: $(R_{aVL}+S_{V3}+0.6$ mV) *QRS duration	>244 mV * msec	(5)
SV2 + SV3	$S_{V2} + S_{V3}$	>6.0mV	(6)
R aVL	R_{aVL}	≥1.1mV	(7)
R aVL duration product	R_{aVL}*QRS duration	>103 mV * msec	(8)
Sokolow-Lyon	S_{V1} + Tallest R wave (V5 or V6)	≥3.5mV	(7)
Sokolow-Lyon product	S_{V1} + Tallest R wave (V5 or V6)*QRS duration	>367.4 mV* msec males >322.4 mV *msec females	(5)
Gubner-Ungerleider	$R_I + S_{III}$	>2.5mV	(9)
Dalfó	$R_{aVL} + S_{V3}$	>1.6mV males > 1.4mV females	(10)

Additional file 1: Table S3. The STARD 2015 guidelines checklist

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	N/A
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	Figure 1 / page 5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Figure 1 / page 5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Figure 1 / page 5
	9	Whether participants formed a consecutive, random or convenience series	Figure 1 / page 5
Test methods	**10a**	Index test, in sufficient detail to allow replication	6
	10b	Reference standard, in sufficient detail to allow replication	6
	11	Rationale for choosing the reference standard (if alternatives exist)	6
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Supplementary table S2
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Supplementary table S2
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	5
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	5
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	6 and 7

Section & Topic	No	Item	Reported on page #
	15	How indeterminate index test or reference standard results were handled	N/A
	16	How missing data on the index test and reference standard were handled	N/A
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	N/A
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Figure 1
	20	Baseline demographic and clinical characteristics of participants	Table 1
	21a	Distribution of severity of disease in those with the target condition	Tables 1 and 2
	21b	Distribution of alternative diagnoses in those without the target condition	N/A
	22	Time interval and any clinical interventions between index test and reference standard	Table 1
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Tables 3 and 4
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Tables 3 and 4
	25	Any adverse events from performing the index test or the reference standard	N/A
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	11
	27	Implications for practice, including the intended use and clinical role of the index test	11
OTHER INFORMATION			
	28	Registration number and name of registry	N/A
	29	Where the full study protocol can be accessed	N/A
	30	Sources of funding and other support; role of funders	11

Abbreviations: **N/A** = not applicable

Additional file 1: References

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ANEXO 3

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação de critérios eletrocardiográficos para detecção da hipertrofia ventricular esquerda em pacientes acima dos 70 anos.

Pesquisador: Ludhmila Abrahão Hajjar

Área Temática:

Versão: 1

CAAE: 08797119.1.0000.0068

Instituição Proponente: Hospital das Clínicas da Faculdade de Medicina da USP

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.210.301

Apresentação do Projeto:

A Hipertrofia Ventricular Esquerda (HVE) é um preditor independente para mortalidade e morbidade cardiovascular em pacientes hipertensos tanto na população geral como em indivíduos muito idosos . O eletrocardiograma (ECG) de 12 derivações tem papel fundamental para detecção da HVE: é o exame recomendado a ser realizado de rotina em todos os pacientes hipertensos tanto pelas diretrizes brasileira, europeia e americana , dada sua grande disponibilidade, acessibilidade, baixo custo e valor prognóstico estabelecido. O ECG pode ainda servir de ferramenta para aumentar a precisão do risco cardiovascular quando adicionado aos scores de risco cardiovasculares. A definição de HVE pelo ECG, no entanto, apresenta algumas limitações: a) o grande número de critérios eletrocardiográficos para definição de HVE ; b) a baixa sensibilidade (4-48%) dos critérios quando comparados a exames de imagem e c) influência de fatores extra cardíacos na detecção dos vetores elétricos da ativação e repolarização ventricular como tamanho do corpo, tecido adiposo, derrame pericárdico, tecido pulmonar, a distância do centro de massa do ventrículo esquerdo para a parede torácica, além da variabilidade diária do eletrocardiograma de um mesmo indivíduo. Existem poucos estudos que testaram a acurácia dos critérios diagnósticos em uma população de idosos. No entanto, a detecção de HVE através do ECG permanece um fator independente de doença cardiovascular nessa subpopulação e é a principal ferramenta diagnóstica utilizada pelos clínicos para detecção de HVE em todo o mundo. Um novo critério para a detecção de sobrecarga ventricular esquerda foi recentemente proposto. O Critério

de Peguero-Lo Presti realiza a soma da onda S mais profunda nas 12 derivações com a onda S em V4, sendo a soma maior do que 2.3mV para mulheres e 2.8mV para homens considerada diagnóstica de HVE. O critério de Peguero LoPresti também se mostrou eficaz em detectar HVE em pacientes com Estenose Aórtica. Dados de países com perfil socioeconômico semelhante ao Brasil – Índia e China, estimam a prevalência de HAS em 65%-70% com as novas diretrizes. A acurácia do ECG, um exame facilmente acessível, barato e de baixa complexidade é fundamental para a detecção de HVE – visto sua aplicação praticamente universal em todos os serviços de saúde: primários, secundários, terciários ou quaternários. Ressalta-se que o diagnóstico HVE tem implicações prognósticas, terapêuticas e fundamentais para o seguimento, que são independentes dos valores pressóricos, associado ao aumento da expectativa de vida, no Brasil e no mundo - haverá um aumento concomitante de doenças cardiovasculares que podem causar hipertrofia ventricular como Hipertensão Arterial Sistêmica e Doenças Valvares , a pesquisa para validação de novos critérios eletrocardiográficos que detectem hipertrofia ventricular esquerda através de um teste não -invasivo, acessível, de fácil aplicação, boa reprodutibilidade , de baixo custo é fundamental.

Objetivo da Pesquisa:

Objetivo Primário:Calcular a área sob a curva, sensibilidade e especificidade de cada critério diagnóstico eletrocardiográfico (Peguero-Lo Presti, Romhilt-Estes,
Sokolow-Lyon e Cornell) sendo a definição de HVE dada pelo índice de massa no Ecocardiograma Transtorácico, com os cortes de 95g/m2 para mulheres e 115g/m2 para homens.

Objetivo Secundário: 1) Avaliar a acurácia diagnóstico de HVE por cada um dos critérios eletrocardiográficos de hipertrofia de acordo com o tipo de remodelamento ventricular esquerdo determinado pelo Ecocardiograma Transtorácico ;2) Análises de subgrupos: avaliar se cada um dos subgrupos altera significantemente a sensibilidade e especifidade de cada critério eletrocardiográfico quando comparado ao ecocardiograma transtorácico: tipo de valvopatia, presença ou não de hipertensão pulmonar pelo ecocardiograma transtorácica, IMC, Peso, Altura, número de medicações anti-hipertensivas;3) Avaliar a aplicação de critérios de SVE para pacientes em ritmo sinusal com Bloqueio de Ramo Esquerdo e Bloqueio de Ramo Direito e ritmo de marcapasso ventricular; 4) Comparar a variabilidade Interobservador entre cada um dos métodos eletrocardiográficos analisados; 5) Avaliar a sensibilidade e especificidade dos critérios eletrocardiográficos para pacientes com fibrilação, flutter e taquicardia atrial; 6) Avaliação de sensibilidade e especificidade do eletrocardiograma para detecção de HVE de acordo com o intervalo de tempo transcorrido entre o eletrocardiograma e o ecocardiograma.

Avaliação dos Riscos e Benefícios:

Riscos:Por tratar-se de ensaio retrospectivo onde não está previsto qualquer tipo de intervenção ao paciente, não são esperados riscos associados ao estudo. Benefícios:Esperamos encontrar o melhor método de diagnóstico da hipertrofia ventricular esquerda, por meio do exame de eletrocardiograma.

Comentários e Considerações sobre a Pesquisa:

Coorte retrospectiva em prontuários de pacientes atendidos no Instituto do Coração de 01/01/2017 até 01/03/2018 e idade acima de 70 anos.Pacientes com ecocardiograma e eletrocardiograma realizados com intervalo de 6 meses entre os exames serão incluídos na análise após verificação dos critérios de exclusão de acordo com o desenho do estudo.Dados fornecidos pelo SIM evidenciaram que no período avaliado 4617 pacientes com idade acima de 70 anos foram atendidos na instituição. Destes, 3320 pacientes realizaram ecocardiograma transtorácico e eletrocardiograma, sendo que 1762 realizaram o exame com intervalo de tempo menor que 6 meses.Dispensa de TCLE, dentro dos critérios.

Considerações sobre os Termos de apresentação obrigatória:

Adequados

Conclusões ou Pendências e Lista de Inadequações:

Sem pendências éticas.

Considerações Finais a critério do CEP:

Em conformidade com a Resolução CNS nº 466/12 – cabe ao pesquisador: a) desenvolver o projeto conforme delineado; b) elaborar e apresentar relatórios parciais e final; c)apresentar dados solicitados pelo CEP, a qualquer momento; d) manter em arquivo sob sua guarda, por 5 anos da pesquisa, contendo fichas individuais e todos os demais documentos recomendados pelo CEP; e) encaminhar os resultados para publicação, com os devidos créditos aos pesquisadores associados e ao pessoal técnico participante do projeto; f) justificar perante ao CEP interrupção do projeto ou a não publicação dos resultados.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1244375.pdf	27/02/2019 18:02:30		Aceito
Outros	Justificativa_dispensa_Termo_Estudo	27/02/2019	Elaine Lagonegro	Aceito

Outros	_ECG_aluno_Caio_Tavares.pdf	18:02:14	Santana Martinho	Aceito
Outros	Declaracao_de_nao_custos_Estudo_ECG_aluno_Caio_Tavares.pdf	27/02/2019 18:02:01	Elaine Lagonegro Santana Martinho	Aceito
Outros	Cronograma_Estudo_ECG_aluno_Caio_tavares.pdf	27/02/2019 18:01:41	Elaine Lagonegro Santana Martinho	Aceito
Projeto Detalhado / Brochura Investigador	projeto_caio_revisado_pos.docx	27/02/2019 18:01:06	Elaine Lagonegro Santana Martinho	Aceito
Outros	Carta_de_compromisso_doutorado_Estudo_ECG_aluno_Caio_Tavares.pdf	27/02/2019 17:59:33	Elaine Lagonegro Santana Martinho	Aceito
Outros	sgp_assinado.pdf	27/02/2019 17:59:20	Elaine Lagonegro Santana Martinho	Aceito
Folha de Rosto	fr_pb_assinada.pdf	27/02/2019 17:58:56	Elaine Lagonegro Santana Martinho	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 20 de Março de 2019

Assinado por:
ALFREDO JOSE MANSUR
(Coordenador(a))