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Electrocardiographic criteria for the diagnosis of abnormal hypertensive cardiac phenotypes

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This article compared the performance of 18 electrocardiographic (ECG) left ventricular hypertrophic (LVH) criteria and four P-wave indices for the diagnosis of echocardiographic (ECHO) LVH and left atrial enlargement (LAE), including the deepest S-wave amplitude added to the S-wave amplitude of lead V_4 (S_D+SV_4) and P-wave terminal force in lead V_1 ($PTFV_1$). A total of 152 middle-aged hypertensive patients without evident cardiovascular diseases (CVDs) were enrolled. The gold standard for the diagnosis of LVH and LAE was ECHO left ventricular mass index (LVMI) and largest left atrial volume index (LAVI). For the detection of LVH, Sokolow-Lyon voltage, Cornell voltage, Cornell product, S_D+SV_4, Manning, and R+S in any precordial lead had relatively higher sensitivity, especially S_D+SV_4 criteria. Their combination could further increase sensitivity (43% vs 29% [S_D+SV_4], P = 0.016). $PTFV_1$ was the only criterion that had significant diagnostic value for ECHO LAE (AUC, 0.68; 95% CI: 0.54-0.73, P = 0.008). For middle-aged hypertensive patients without evident cardiovascular diseases, S_D+SV_4 had the highest sensitivity for the diagnosis of LVH and the combination of several ECG LVH criteria might further increase sensitivity. $PTFV_1$ had significant diagnostic value for ECHO LAE.

1 | INTRODUCTION

Hypertension is known as a "cardiovascular syndrome," which is closely related to asymptomatic organ damage, such as left ventricular hypertrophy (LVH), left atrial enlargement (LAE), left ventricular diastolic dysfunction, and arterial stiffness. These subclinical organ damages are well-established predictors of cardiovascular events and all-cause mortality.[1,2] Echocardiography (ECHO) is the most important and noninvasive method for assessing cardiac structure and function. However, due to its high cost and strict requirement for examiners, its availability is far behind electrocardiographic (ECG), especially in rural communities. A great many of ECG LVH criteria and P-wave indices are existent to estimate the electrical remodeling in accordance with hypertensive heart disease.[3] The common problem with regard to these ECG criteria is their low sensitivity. Several ECG LVH criteria and P-wave indices are proved to be independently associated with cardiovascular events.[4,5] Given the lack of comprehensive evidences, our study aims to compare the diagnostic value of single and combined ECG criteria for ECHO LVH and LAE.

2 | METHODS

2.1 | Study population

During the period of September 2017 and January 2018, patients with hypertension aged between 30 and 65 years of age were enrolled from one urban community of Beijing. Those with secondary or suspected secondary hypertension were excluded from this study. Other exclusion criteria included patients with heart failure, left ventricular ejection fraction less than 50%, angina pectoris, myocardial infarction, percutaneous coronary intervention with stent or coronary artery bypass graft surgery, cardiovascular diseases, atrial fibrillation, left bundle branch block, cardiac valve diseases, cardiomyopathy, or pregnancy. This study was approved by institutional

TABLE 1 Definitions and thresholds of ECG LVH criteria and P-wave indices

ECG criteria	Definitions and cutoff values	References
ECG LVH criteria		
Sokolow-Lyon voltage	SV_1+RV_5/RV_6 ≥3.5 mV	19
Cornell voltage	$RaVL+SV_3$ ≥2.8 mV (male), ≥2.0 mV (female)	20
Cornell product	$(RaVL+SV_3)$×QRS duration (male), $(RaVL+SV_3+0.8)$×QRS duration (female): ≥244 mV × ms	21
S_D+SV_4	The deepest S-wave amplitude added to the S-wave amplitude of lead V_4 ≥ 2.8 mV (male), ≥2.3 mV (female)	12
Lewis	$R_I+S_{III}-R_{III}-S_I$>1.6 mV	22
Gubner-Ungerleider	R_I+S_{III}>2.5 mV	22
RI	>1.5 mV	3
RaVF	>2 mV	3
RaVL	>1.1 mV	19
RV5	>3.3 mV	23
RV6	>2.5 mV	23
RV6/RV5	>1.0	24
R+S in any limb lead	>1.9 mV	25
Manning	Manning (≥30 y): the sum of QRS amplitudes in lead aVF, V2, V6 >5.9 mV	26
SV1	>2.3 mV	23
SV2	>2.5 mV	27
R+S in any precordial lead	>3.5 mV	3
R in any precordial lead	>2.6 mV	28
ECG P-wave indices		
P-wave duration	P-wave duration in lead II ≥120 ms	29
$PTFV_1$	P-wave terminal force in lead V_1, namely the amplitude × duration of the negative terminal P wave in V_1 ≥4 mV × ms	30
P-wave dispersion	The largest P-wave duration minus the smallest ≥3.6 mV	31
P/PR	P-wave duration in lead II divided by PR interval (PR duration minus P-wave duration) >1.6	32

review committee of Fuwai hospital. All subjects provided written informed consent.

2.2 | Electrocardiography

Edan SE-301 multichannel electrocardiograph was used to acquire ECG waveform signal of 10 seconds. Automatic analyses were undertaken on SE-1515 ECG station software V1.3 equipped on the computer. The voltages and duration of all waves in each of the 12 leads were calculated as the average of the total circles in 10 seconds. The ECG LVH and left atrial abnormality criteria adopted in this study are listed in Table 1.

2.3 | Echocardiography

Echocardiography examinations were carried out with GE vivid E90 instrument, M5SC probe. The examinations were performed by one specially trained researcher and were analyzed off-line in EchoPAC 201 software. According to the American Society of Echocardiography, images of five consecutive cardiac circles from the parasternal long-axis view and apical four- and two-chamber views were stored.[7,8] End-diastolic interventricular septum (IVSd), posterior wall thickness (PWTd), and left ventricular internal diameter (LVIDd) were obtained by two-dimensional echocardiography-guided M-mode tracings. End-systolic left atrial anteroposterior dimension (LAAPDs) was measured from the two-dimensional view. Left atrial volumetric measurement was based on apical four- and two-chamber biplane method of disks. Mitral valve peak modal velocity in early (E) and late (A) diastole was acquired by using pulse wave Doppler with color flow imaging. Pulsed-wave tissue Doppler imaging early (e') and late (a') velocity at lateral and septal basal regions of mitral valve were also obtained. Left ventricular mass (LVM) was estimated by cube formula: $0.8 \times 1.04 \times [(IVSd+LVIDd+PWTd)^3 - LVIDd^3] + 0.$

6 g, and indexed to body surface area (LVMI). Left atrial volume was also indexed by body surface area (LAVI). Body surface area was calculated according to Stevenson formula: 0.0061 × Height (cm) + 0.0128 × Weight (kg) − 0.1529. The LVMI thresholds were 115 g/m^2 for male, 95 g/m^2 for female. The LAVI cutoff was 34 mL/m^2.

2.4 | Other measurements

A standard questionnaire was used to collect information about demographic characteristics, traditional risk factors, and medical history. Smoking and drinking included current and previous. Biochemical indices and office blood pressure were also measured. Blood pressure was measured three times after patients had seated for 5 minutes through a calibrated upper-arm electronic monitor HEM-7130, with 2 minutes apart between measurements. The average blood pressure values were analyzed in the study.

2.5 | Statistical analyses

Continuous variables were described as mean ± standard deviation and compared by using Student's *t* test. Normal distribution was assessed by Kolmogorov-Smirnov test. Categorical variables were expressed as number (percentage) and compared by chi-square test. Diagnostic value was evaluated by receiver operating characteristic method and compared by McNemar test. To determine the correlation coefficient, linear regression model was adopted. All analyses were carried on IBM SPSS statistics 22.0. A *P* value <0.05 was considered statistically significant.

TABLE 2 Demographic and clinical characteristics of study patients

Characteristic	Total	Male	Female	*P* value
N	152	44 (29%)	108 (71%)	
Age	58.1 ± 6.0	57.9 ± 7.2	58.2 ± 5.5	0.735
HTN duration (years)	9.7 ± 8.6	10.4 ± 9.1	9.5 ± 8.5	0.557
BMI (kg/m^2)	26.0 ± 3.2	26.0 ± 2.1	26.0 ± 3.5	0.963
Overweight (BMI ≥ 24)	86 (56.6%)	30 (68%)	56 (52%)	0.173
Obesity (BMI ≥ 28)	36 (24%)	8 (18%)	28 (26%)	
SBP (mm Hg)	128.8 ± 20.6	134.7 ± 15.6	126.5 ± 22.0	0.026
DBP (mm Hg)	79.8 ± 13.4	84.9 ± 10.5	77.7 ± 14.0	0.003
HR (beats/min)	75.5 ± 13.3	78.5 ± 10.8	74.2 ± 14.1	0.074
TC (mmol/L)	5.1 ± 1.0	4.6 ± 0.9	5.3 ± 1.0	0.003
HDL-C (mmol/L)	1.4 ± 0.3	1.2 ± 0.3	1.4 ± 0.3	0.001
LDL-C (mmol/L)	2.7 ± 0.9	2.2 ± 0.9	2.9 ± 0.8	0.002
TG (mmol/L)	1.8 ± 1.7	2.0 ± 2.5	1.8 ± 1.4	0.494
Smoking	28 (18.4%)	24 (54.5%)	4 (3.7%)	0.000
Drinking	31 (29.4%)	28 (63.6%)	3 (2.8%)	0.000
CCB	81(53.3%)	27 (61%)	54 (52%)	0.290
RAS inhibitors	57 (37.5%)	18 (41%)	39 (37%)	0.637
DM	28 (18.4%)	7 (16%)	21 (20%)	0.589
cfPWV (m/s)	8.5 ± 1.7	8.8 ± 1.9	8.4 ± 1.6	0.211
Elevated cfPWV	26 (17%)	8 (18%)	18 (17%)	0.860
LVMI (g/m^2)	80.4 ± 18.1	83.8 ± 22.6	79.1 ± 15.8	0.204
LVH	21 (14%)	5 (11%)	16 (15%)	0.570
LAAPDs (mm/s)	37.5 ± 4.2	39.0 ± 4.6	36.8 ± 3.8	0.007
LAVI (mL/m^2)	33.0 ± 7.6	33.2 ± 8.3	32.9 ± 7.4	0.815
LAE	61 (41%)	19 (44%)	42 (39%)	0.579
E/e'	9.0 ± 2.5	8.3 ± 2.3	9.3 ± 2.5	0.027

BMI, body mass index; CCB, calcium channel blocker; cfPWV, carotid-femoral pulse wave velocity; DBP, diastolic blood pressure; DM, diabetes mellitus; E/e', average mitral-to-peak early diastolic annular ratio; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; HTN, hypertension; LAAPDs, end-systolic left atrial anteroposterior dimension; LAE, left atrial enlargement; LAVI, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; RAS, renin-angiotensin system; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

TABLE 3 Performance of ECG LVH criteria for the diagnosis of ECHO LVH

ECG LVH criteria	AUC	*P* value	Sensitivity	95% CI	Specificity	95% CI	McNemar
SV_1+RV_5/RV_6	0.71 (0.59-0.83)	0.002	3/21 (14%)	3.8%, 37%	128/131 (98%)	93%, 99%	0.001
$RaVL+SV_3$	0.71 (0.58-0.84)	0.003	3/21 (14%)	3.8%, 37%	129/131 (98%)	94%, 99.7%	<0.0001
$(RaVL+SV_3) \times$ QRS duration	0.72 (0.59-0.85)	0.001	5/21 (24%)	9.1%, 47.5%	128/131 (98%)	93%, 99%	0.004
S_D+SV_4	0.71 (0.58-0.84)	0.002	6/21 (29%)	12.2%, 52%	120/131 (92%)	85%, 95.5%	0.557
RI+SIII-RIII-SI	0.44 (0.31-0.59)	0.44	2/21 (10%)	1.7%, 32%	123/131 (94%)	88%, 97%	0.052
RI+SIII	0.56 (0.43-0.68)	0.42	0/21 (0)	-	129/131 (98%)	-	-
RI	0.51 (0.37-0.64)	0.90	1/21 (5%)	0.2%, 26%	127/131 (97%)	92%, 99%	0.002
RaVF	0.58 (0.44-0.72)	0.25	0 (0)	-	131/131 (100%)	-	-
RaVL	0.61 (0.49-0.74)	0.10	1/21 (5%)	0.2%, 26%	127/131 (97%)	92%, 99%	0.002
RV5	0.63 (0.49-0.76)	0.07	1/21 (5%)	0.2%, 26%	131/131 (100%)	96%, 100%	0.000
RV6	0.62 (0.48-0.76)	0.08	2/21 (10%)	1.7%, 32%	131/131 (100%)	96%, 100%	0.000
RV6/RV5	0.50 (0.37-0.63)	0.97	1/21 (5%)	0.2%, 26%	130/131 (99%)	95%, 100%	0.000
R+S in any limb lead	0.67 (0.54-0.79)	0.016	0 (0)	-	130/131 (99%)	-	-
Manning	0.76 (0.65-0.86)	0.000	4/21 (19%)	6.3%, 43%	128/131 (98%)	93%, 99%	0.003
SV1	0.67 (0.54-0.81)	0.011	0 (0)	-	131/131 (100%)	-	-
SV2	0.71 (0.57-0.85)	0.003	1/21 (5%)	0.2%, 26%	130/131 (99%)	95%, 100%	0.000
R+S in any precordial lead	0.74 (0.63-0.84)	0.001	4/21 (19%)	6.3%, 43%	127/131 (97%)	92%, 99%	0.007
R in any precordial lead	0.63 (0.49-0.77)	0.053	4/21 (19%)	6.3%, 43%	126/131 (96%)	91%, 98.6%	0.017
Combination of two specific criteria[a]	-	-	8/21 (38%)	19%, 61%	119 /131 (91%)	84%, 95%	1.000
Combination of six specific criteria[b]	-	-	9/21 (43%)	22.6%, 65.6%	116/131 (88.5%)	81.5%, 93%	0.701
S_D+SV_4 vs Cornell P	-	-	-	-	-	-	0.035
Combination of two criteria vs S_D+SV_4	-	-	-	-	-	-	0.250
Combination of six criteria vs S_D+SV_4	-	-	-	-	-	-	0.016

[a]S_D+SV_4 or Cornell product criteria.
[b]Any of the six criteria, namely SV1+RV5/RV6, RaVL+SV3, (RaVL+SV3)×QRS duration, S_D+SV_4, Manning, R+S in any precordial lead.

3 | RESULTS

3.1 | Participant characteristics

We analyzed a total of 152 hypertensive patients with an average age of 58 years, 29% of whom were male subjects and 71% female subjects. The mean duration of hypertension was 10 years. The percentage of patients with obesity was 24%. Patients taking renin-angiotensin system blockers and calcium antagonists accounted for 37% and 53%, respectively. The proportion of patients with ECHO LVH and LAE was 14% and 41%. Between sexs, there was no significant difference in above characteristics. Other characteristics are also listed in Table 2.

3.2 | Diagnostic values of ECG LVH criteria and P-wave indices

The diagnostic values of 18 ECG LVH criteria using ECHO-LVMI-defined LVH as gold standard were estimated. The AUC analyses showed that with the exception of RI+SIII-RIII-SI, RI+SIII, RI, RaVF, RaVL, RV5, RV6, RV6/RV5, and R in any precordial lead, the other nine criteria had significant diagnostic values. Among these criteria, the sensitivity of S_D+SV_4 was the highest (29%; 95% CI: 12%, 52%), with no significant difference from LVMI criterion ($P = 0.557$). RI+SIII-RIII-SI, RI+SIII, RaVF, RaVL, and RV6/RV5 were not linearly associated with LVMI. After excluding patients with obesity, the results were similar. Further combining six criteria with relative high sensitivity, namely SV1+RV5/RV6, RaVL+SV3, (RaVL+SV3)×QRS duration, S_D+SV_4, Manning, and R+S in any precordial lead, the sensitivity was significantly improved in contrast to S_D+SV_4 (43% vs 29%, $P = 0.016$). Seen in Tables 3 and 4. Further analyses showed that when ECHO LVM was indexed to height[9,10] the main results were the same (data not shown).

The diagnostic values of P-wave indices for ECHO LVE were also calculated. $PTFV_1$ was the only criterion that had significant diagnostic value for ECHO LAE (AUC, 0.68; 95% CI: 0.54-0.73, $P = 0.008$), with sensitivity at 26% and specificity at 91%. The

TABLE 4 Correlation of ECG LVH criteria with ECHO LVMI using linear model

	LVMI		LVMI	
ECG LVH criteria	*β* value	*P* value	*β* value[a]	*P* value[a]
Sokolow-Lyon	0.339	0.000	0.345	0.000
Cornell voltage	0.347	0.000	0.278	0.003
Cornell product	0.322	0.000	0.232	0.012
S_D+SV_4	0.359	0.000	0.288	0.002
RI+SIII-RIII-SI	0.012	0.882	0.032	0.733
RI+SIII	0.094	0.251	0.113	0.225
RI	0.171	0.035	0.218	0.019
RaVF	0.063	0.444	0.093	0.320
RaVL	0.143	0.078	0.154	0.099
RV5	0.260	0.001	0.269	0.003
RV6	0.237	0.003	0.274	0.003
RV6/RV5	0.022	0.785	0.088	0.345
R+S in any limb lead	0.228	0.005	0.246	0.008
Manning	0.427	0.000	0.397	0.000
SV1	0.268	0.001	0.267	0.004
SV2	0.362	0.000	0.288	0.002
R+S in any precordial lead	0.439	0.000	0.375	0.000
R in any precordial lead	0.295	0.000	0.262	0.004

[a]Excluding those with obesity.

correlation between $PTFV_1$ and LAVI was significant ($P = 0.006$; Tables 5 and 6).

4 | DISCUSSION

It is a well-established fact that single ECG LVH criterion has low sensitivity and high specificity. Our study showed that nine among them, namely SV1+RV5/RV6, RaVL+SV3, (RaVL+SV3)×QRS duration, S_D+SV_4, Manning, R+S in any precordial lead, R+S in any limb lead, SV1, and SV2, had significant diagnostic value for ECHO LVH. However, the sensitivity of R+S in any limb lead, SV1, or SV2 was zero/5%. The present study also suggested that the sensitivity of S_D+SV_4 was the highest compared with other single criterion. S-wave amplitude in V3 and V4 was believed to reflect the depolarization of myocardium and epicardium, and change in accordance with chamber hypertrophy.[11] Peguero et al[12] recently discovered the new S_D+SV_4 criterion, with sensitivity of 62%. The sensitivity gap might be partly explained by the different ethnicity. Another article based on 668 Asian population also suggested that cutoffs of Cornell voltage and Sokolow-Lyon voltage derived from the westerns should be lowered due to the low sensitivity.[13] Our study showed that combining SV1+RV5/RV6, RaVL+SV3, (RaVL+SV3)×QRS duration, S_D+SV_4, Manning, and R+S in any precordial lead could significantly improve sensitivity. Many studies showed that ECG and ECHO LVH predict future adverse outcomes independently and complementarily.[10,14] Moreover, some studies suggested that combination of Cornell product and Sokolow-Lyon voltage increased sensitivity for the detection of LVH and coexistence of these two criteria further improved risk prediction for future cardiovascular events and all-cause mortality.[15] Previous studies usually adopted the most common ECG criteria, such as Cornell voltage/product or Sokolow-Lyon voltage, whereas in present study we analyzed 18 single established criteria. In particular, we only enrolled those noncomplicated hypertensive patients in their middle ages. On the other hand, many previous articles have demonstrated the low sensitivity and high specificity characteristic of ECG measurement. Therefore, parallel criteria could logically increase the diagnostic sensitivity. Because of the high prevalence of hypertension worldwide, plenty of articles explored the value of ECG for the detection of LVH and thus various criteria were found. Many guidelines underline the importance of ECG in the risk prediction of hypertensive patients. Our study suggested that sensitivity of ECG LVH criteria in middle-aged hypertensive patients might be improved by comparing and combining different ECG criteria. In rural areas with no expensive ECHO devices, ECG should be in full use in order to detect high-risk hypertensive patients.

P-wave indices, especially $PTFV_1$ abnormality, were demonstrated to increase the risk of atrial fibrillation and ischemic stroke.[4] Our study suggested that PTFV1 was the only criterion that had significant diagnostic value for ECHO LAE. One previous study also showed that the diagnostic value of PTFV1 for LAE might be better than other P-wave indices.[16] It is believed that left atrial remodeling precedes ventricular hypertrophy. Whether the relationship of PTFV1 with cardiovascular diseases is mediated by the anatomical-electrical remodeling of atria in the wake of hypertension is still uncovered. Either way, our study suggested that PTFV1 was a valuable diagnostic tool for anatomical LAE compared with other three

TABLE 5 Performance of ECG P-wave indices for the diagnosis of ECHO LAE

P-wave indices	AUC	*P* value	Sensitivity	Specificity	McNemar
P-wave duration	0.51 (0.42-0.60)	0.795	12/61 (20%)	68/88 (77%)	0.001
$PTFV_1$	0.68 (0.54-0.73)	0.008	16/61 (26%)	81/89 (91%)	<0.0001
P-wave dispersion	0.50 (0.40-0.59)	0.910	42/61 (69%)	32/89 (36%)	0.000
P/PR	0.56 (0.46-0.65)	0.220	46/61 (75%)	26/88 (30%)	0.000

P/PR, P-wave duration in lead II divided by PR interval; $PTFV_1$, P-wave terminal force in lead V1.

TABLE 6 Correlation of ECG P-wave indices with ECHO LAVI using linear model

P-wave indices	LAVI		LAVI	
	β value	*P* value	*β* value[a]	*P* value[a]
P duration	0.149	0.069	0.108	0.253
$PTFV_1$	0.224	0.006	0.284	0.002
P-wave dispersion	0.013	0.879	0.017	0.860
P/PR	0.174	0.034	0.158	0.092

LAVI, left atrial volume index; P/PR, P-wave duration in lead II divided by PR interval; $PTFV_1$, P-wave terminal force in lead V1.
[a]Excluding those with obesity.

P-wave indices. Future studies might further explore the progress and regress of ECG changes and discover profound electrical criteria that are closely related to cardiovascular diseases.

Several studies demonstrated that BMI could attenuate sensitivity of ECG LVH criteria.[17,18] To mitigate its effect, we further exclude patients with obesity from the analyses and the results were similar. However, our study had several limitations. First, even though our sample size fulfilled the requirement of the major statistical analyses, the number of patients with LVH was small. Second, our study used two-dimensional ECHO as gold standard for LVH and LAE, which could not totally represent the cardiac mass and volume despite their very high consistency.

In conclusion, our study suggested that in middle-aged hypertensive patients without obvious cardiovascular diseases, the combination of several ECG LVH criteria could further increase sensitivity. $PTFV_1$ was significantly associated with left atrial size.

CONFLICT OF INTEREST

There are no conflicts of interest.

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