CLINICAL STUDY

Deeper S Wave in Lead V5 and Broader Extent of T Wave Inversions in the Precordial Leads are Clinically Useful Electrocardiographic Parameters for Predicting Pulmonary Hypertension

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Summary

Electrocardiography (ECG) is used to screen for pulmonary hypertension (PH). However, it is unclear which parameters of ECG are the most useful for screening.

ECG parameters related to right ventricular hypertrophy criteria were examined in 145 ECGs of subjects who were suspected to have PH and underwent right heart catheterization (RHC) (age 58.4 ± 17.5 years, 112 women, mean pulmonary arterial pressure [MPAP] 35.4 ± 13.3 mmHg). Based on the results of RHC, 108 subjects had PH (56 pulmonary arterial hypertension [PAH] and 52 chronic thromboembolic pulmonary hypertension [CTEPH]).

Fourteen of 17 ECG parameters in the present study were significantly associated with PH on univariate analysis. On multivariable logistic regression analysis, S wave depth in lead V5 (odds ratio [OR] 1.25, 95% confidence interval [CI] 1.10-1.47) and depth of T wave inversion in lead V4 (OR 1.21, 95% CI 1.03-1.46) were independent predictors of MPAP ≥ 25 mmHg, and the cut-off values determined by receiver operating characteristic curve analyses were 0.42 mV and -0.28 mV, respectively.

In conclusion, a deeper S wave in lead V5 and the presence of a wider extent of negative T waves in the precordial leads may be clinically simple and useful ECG parameters for screening for PH.

Pulmonary hypertension (PH) causes pressure overload of the right ventricle (RV) with RV hypertrophy and dilatation, leading to right heart failure and premature death. Despite recent advances in management, the prognosis of PH patients is still poor, with a 3-year survival rate of 67%.[1] Given that over 50% of the pulmonary microcirculation must be obstructed before resting pulmonary arterial pressure (PAP) rises,[2] a delayed diagnosis of PH fails to detect the disease during a stage when it can be successfully treated and this leads to a poor prognosis. Early detection of PH is crucial to improve the outcome; therefore, simple and widely used diagnostic tests are required to detect PH. Several biochemical markers for PH have been explored, but a specific marker has not been established.[3-5] Right heart catheterization (RHC) is required for the definitive diagnosis of PH (mean pulmonary arterial pressure (MPAP) ≥ 25 mmHg at rest);[6] however, RHC is inappropriate for screening because of its invasiveness.

Electrocardiography (ECG) is a widely available screening test. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline recommends non-invasive screening tests including ECG, chest X-ray, and echocardiography before performing an invasive definitive diagnostic test such as RHC.[6] Currently, the ECG criteria for right ventricular hypertrophy (RVH) are used to screen for PH. Twenty-one criteria for RVH have been advocated by the AHA, ACCF, and the Heart Rhythm Society (HRS).[7] However, the prevalence of ECG criteria for RVH in PH patients is not very high. Naamani, *et al*. reported that the prevalence of ECG criteria for RVH in PH patients was only 1.1-13.5%.[8] Kopec, *et al*. reported that the prevalence of ECG criteria for RVH in idiopathic pulmonary arterial hypertension (IPAH) patients was 6.7-75%.[9] Thus, the ECG criteria may not have sufficient sensitivity to serve as an effective screening tool for PH, especially mild PH.[10] In addition, some complex criteria are required for the measurements and calculations of several ECG parameters, which implies that making a judgment based on simply viewing an ECG

Table I. ECG Parameters

Parameters
Axis
P wave in lead II
P wave in lead III
P wave in lead aVF
ST depression in lead II
ST depression in lead III
ST depression in lead aVF
QRS duration
QTc duration
R wave in lead V1
S wave in lead V1
R wave in lead V5
S wave in lead V5
Negative T wave in lead V1
Negative T wave in lead V2
Negative T wave in lead V3
Negative T wave in lead V4

is not easy.

PH is associated with various conditions, such as connective tissue diseases, congenital heart diseases, portal hypertension, left heart diseases, lung diseases, and pulmonary thromboembolism; therefore, a multidisciplinary approach to its diagnosis is needed. However, physicians in various departments including cardiology, pulmonology, rheumatology, and hepatology, are required to make a diagnosis of PH, though some of them may not be familiar with reading ECGs. Therefore, it is clinically important to identify simple and sensitive ECG parameters predicting MPAP ≥ 25 mmHg in order to proceed with further examinations. In the present study, the aim was to examine which ECG parameters are clinically useful for screening for PH.

Methods

Patient charts were reviewed retrospectively, and 145 ECGs of subjects who underwent RHC from January 2006 to July 2015 at the Nagasaki University Hospital were included. Patients with left heart failure, pulmonary disease, and chronic kidney disease on hemodialysis were excluded to avoid their effects on the ECG. There were 108 ECGs of patients with PH (56 pulmonary arterial hypertension [PAH] and 52 chronic thromboembolism pulmonary hypertension [CTEPH]) and 37 ECGs of patients without PH. The PAH patients included the following: 35 idiopathic PAH, 15 connective tissue disease-associated, 2 congenital heart disease-associated, and 4 portal hypertension-associated PAH. This study complied with the Declaration of Helsinki with regard to investigations in humans, and the Ethics Committee of Nagasaki University Hospital approved the protocol. All patients provided their written, informed consent before RHC.

Twelve-lead ECGs were performed in the resting supine position. The ECG calibration was 25 mm/s and 10 mm/mV. No patients had a pacemaker. ECGs were analyzed within 1 month before or after RHC. A total of 17 ECG parameters, which included relatively simple and

easily measurable parameters related to the RVH criteria[7] and had been reported to be associated with PH[11-17] were selected (Table I). The amplitude of the P, R, S, and T waves, QTc and QRS complex durations, the QRS axis, and the ST level at the J-point were measured by a cardiologist who was blinded to the subjects' clinical conditions. These parameters were measured using an ECG data management system, EFS-8800 Viewer (Fukuda Denshi Co. Ltd., Tokyo, Japan), or manually on appropriately magnified ECGs. Intraobserver reliability was assessed by intraclass correlation coefficients (ICCs) with 10 randomly selected ECGs on 2 separate occasions. ICCs ranged from 0.792 to 0.989, which means high reliability (substantial, almost perfect).[18] For the measurements of ST depression and negative T waves, the amplitude of a depressed ST level and the maximum depth of a negative T wave from baseline were considered positive values. Patients with right/left bundle branch block and arrhythmias were excluded from the analysis in this study.

On RHC, hemodynamic data including right atrial pressure, right ventricular pressure, PAP, pulmonary arterial wedge pressure (PAWP), cardiac output, and cardiac index were recorded at end expiration. Pulmonary vascular resistance (PVR: dyne·sec·cm^{-5}) was calculated using the formula: PVR = (MPAP - mean PAWP)/cardiac output × 80. A definitive diagnosis of PH was made on RHC as MPAP ≥ 25 mmHg. All PH patients in this study had a mean PAWP < 15 mmHg.

Statistical analysis was performed with JMP 10.0.2 (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as means ± standard deviation. Prevalence was calculated by the proportion of patients with the ECG parameters among the total number of patients. The predictive ability of ECG parameters for MPAP ≥ 25 mmHg was estimated by univariate and multivariable logistic regression analyses. The goodness of fit was calculated by the Hosmer-Lemeshow test to evaluate the models. The P value was calculated using the likelihood ratio test to evaluate the variables. The odds ratio (OR) and 95% confidence interval (95% CI) of each parameter, except for axis, were corrected to 0.1 or 0.01 units. Significant parameters indicating PH were determined using multivariable logistic regression analysis. Parameters with $P < 0.05$ on univariate analyses were selected based on their clinical importance when parameters had strong correlations with each other to avoid any problems of multicollinearity and entered into the multivariable analysis. For ECG parameters that were found to be significantly related to PH, receiver operating characteristic (ROC) curve analyses were performed to evaluate their diagnostic ability based on the area under the curve (AUC). Then, the cut-off value, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using Youden's Index. The significance level was set at $P < 0.05$.

Results

The characteristics of the subjects are summarized in Table II. The mean age of all subjects was 58.4 ± 17.5 years. On RHC, MPAP, mean PAWP, cardiac output, and

PVR were 35.4 ± 13.3 mmHg, 8.0 ± 3.6 mmHg, 4.5 ± 1.9 L/minute, and 565.9 ± 370.1 dyne·sec·cm^{-5}, respectively. The average 6-minute walking distance was 360.4 m.

Univariate logistic regression analyses of ECG parameters in all subjects showed that 14 ECG parameters were significant predictors of MPAP ≥ 25 mmHg (Table III). Multivariable logistic regression analysis identified the depth of the S wave in lead V5 (OR 1.25, 95% CI 1.10-1.47, *P* < 0.001) and the negative T wave in lead V4 (OR 1.21, 95% CI 1.03-1.46, *P* = 0.018) as significant and independent predictors of MPAP ≥ 25 mmHg (Table III). On ROC analysis, the AUCs of the S wave in lead V5 and the negative T wave in lead V4 were 0.75 (95% CI 0.65-0.83) and 0.76 (95% CI 0.66-0.84), respectively. The cut-off values of these parameters were 0.42 mV (sensitivity 73.0%, specificity 68.5%, PPV 88.1%, and NPV

44.3%) and -0.28 mV (sensitivity 69.2%, specificity 75.7%, PPV 89.2%, and NPV 45.2%), respectively (Table IV).

In PAH patients, the amplitude of the R wave in lead V5, the depth of the S wave in lead V5, and the depth of the negative T wave in lead V4 were significant and independent predictors of MPAP ≥ 25 mmHg on multivariable logistic regression analysis. The ORs of these parameters were 0.86 (95% CI 0.72-1.00), 1.27 (95% CI 1.08-1.57), and 1.53 (95% CI 1.24-1.99), respectively (Table V).

In CTEPH patients, multivariable logistic regression analysis showed that the depth of the S wave in lead V5 (OR 1.19, 95%CI 1.02-1.43) and the depth of the negative T wave in lead V1 (OR 1.88, 95% CI 1.29-2.99) were significant and independent predictors (Table VI).

Table VII shows the cut-off value, AUC, sensitivity, specificity, PPV, and NPV of each ECG parameter in PAH and CTEPH patients on the ROC analyses. The depth of the S wave in lead V5 had a similar cut-off value with a similar diagnostic accuracy in both groups. In addition, the depth of the negative T wave in lead V4 of PAH patients and lead V1 of CTEPH patients had slightly higher diagnostic accuracy than the depth of the S wave in lead V5.

Table II.   Patient Characteristics

Variables	Mean ± SD
With PH:Without PH	108:37
PAH:CTEPH	56:52
Sex (male:female)	33:112
Age (years)	58.4 ± 17.5
Body mass index (kg/m^2)	23.1 ± 3.9
Right heart catheterization data	
Mean pulmonary artery pressure (mmHg)	35.4 ± 13.3
Mean pulmonary arterial wedge pressure (mmHg)	8.0 ± 3.6
Cardiac output (L/minute)	4.5 ± 1.9
Pulmonary vascular resistance (dynes·sec·cm^{-5})	565.9 ± 370.1
Laboratory data	
Red blood cell (×10^4/μL)	470.0 ± 322.9
Hemoglobin (g/dL)	13.3 ± 1.9
Platelet (×10^4/μL)	19.4 ± 6.6
Uric acid (mg/dL)	5.7 ± 1.5
NT-proBNP (pg/mL)	481.7 ± 729.2
Exercise test	
6 minutes walking distance (m)	360.4 ± 115.1

PH indicates pulmonary hypertension; PAH, pulmonary arterial hypertension; BUN, blood urea nitrogen; and NT-pro BNP, N-terminal pro-brain natriuretic peptide.

Discussion

In the present study, a deep S wave in lead V5 (more than 0.42 mV) was an independent predictor of PH in the entire group. The presence of a negative T wave in the precordial leads was also an independent predictor of MPAP ≥ 25 mmHg.

Several studies have shown the correlations between ECG parameters and PH. Wokhlu, *et al*. reported that a P wave in lead II of 0.12 mV corresponded to MPAP of 25 mmHg with a sensitivity of 73% and a specificity of 67% in 23 patients with scleroderma.[19] Sun, *et al*. reported that prolonged QRS duration (QRS ≥ 120 ms) was an independent predictor of mortality in idiopathic PAH patients. Although prolonged QRS duration was associated with right ventricular diameter and right atrial diameter on

Table III.   Univariate and Multivariable Logistic Regression Analyses of ECG Parameters for Predicting MPAP ≥ 25 mmHg

	Univariate analysis		Multivariable analysis	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Axis, per 1°	1.01 (1.00-1.02)	0.002		
P wave in lead II, per 0.1 mV	2.10 (1.12-4.31)	0.019		
P wave in lead aVF, per 0.1 mV	1.94 (1.02-4.07)	0.028		
ST depression in lead II, per 0.01 mV	1.12 (1.04-1.21)	< 0.001		
ST depression in lead III, per 0.01 mV	1.12 (1.04-1.20)	0.002		
ST depression in lead aVF, per 0.01 mV	1.14 (1.05-1.25)	< 0.001		
QTc duration, per 0.01 sec	1.20 (1.04-1.41)	0.011		
R wave in lead V1, 0.1 mV	1.23 (1.08-1.43)	< 0.001		
R wave in lead V5, 0.1 mV	0.91 (0.83-0.99)	0.022		
S wave in lead V5, 0.1 mV	1.35 (1.18-1.59)	< 0.001	1.25 (1.10-1.47)	< 0.001
Negative T wave in lead V1, per 0.1 mV	1.55 (1.23-2.00)	< 0.001		
Negative T wave in lead V2, per 0.1 mV	1.32 (1.16-1.54)	< 0.001		
Negative T wave in lead V3, per 0.1 mV	1.40 (1.21-1.66)	< 0.001		
Negative T wave in lead V4, per 0.1 mV	1.42 (1.21-1.72)	< 0.001	1.21 (1.03-1.46)	0.018

Table IV. Accuracy, Sensitivity, and Specificity of the Cut-Off Values of ECG Parameters for Predicting MPAP ≥ 25 mmHg

	Cut-off value	AUC	95% CI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
S wave in lead V5 (mV)	0.42	0.75	0.65-0.83	73.0	68.5	88.1	44.3
Negative T wave in lead V4 (mV)	-0.28	0.76	0.66-0.84	69.2	75.7	89.2	45.2

AUC indicates area under curve; and CI, confidence interval.

Table V. Univariate and Multivariable Logistic Regression Analyses of ECG Parameters for Predicting MPAP ≥ 25 mmHg in PAH Patients

	Univariate analysis		Multivariable analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Axis, per 1°	1.02 (1.01-1.03)	0.003		
P wave in lead II, per 0.1 mV	2.53 (1.32-5.45)	0.004		
P wave in lead aVF, per 0.1 mV	2.12 (1.05-4.72)	0.037		
ST depression in lead II, per 0.01 mV	1.13 (1.04-1.24)	< 0.001		
ST depression in lead III, per 0.01 mV	1.10 (1.02-1.18)	0.009		
ST depression in lead aVF, per 0.01 mV	1.13 (1.04-1.24)	< 0.001		
R wave in lead V1, 0.1 mV	1.17 (1.00-1.40)	0.043		
S wave in lead V1, 0.1 mV	0.93 (0.84-1.00)	0.040		
R wave in lead V5, 0.1 mV	0.88 (0.78-0.97)	0.013	0.86 (0.72-1.00)	0.047
S wave in lead V5, 0.1 mV	1.34 (1.16-1.59)	< 0.001	1.27 (1.08-1.57)	0.003
Negative T wave in lead V1, per 0.1 mV	1.30 (1.01-1.71)	0.041		
Negative T wave in lead V2, per 0.1 mV	1.25 (1.09-1.46)	< 0.001		
Negative T wave in lead V3, per 0.1 mV	1.38 (1.19-1.65)	< 0.001		
Negative T wave in lead V4, per 0.1 mV	1.55 (1.28-1.96)	< 0.001	1.53 (1.24-1.99)	< 0.001

Table VI. Univariate and Multivariable Logistic Regression Analyses of ECG Parameters for Predicting MPAP ≥ 25 mmHg in CTEPH Patients

	Univariate analysis		Multivariable analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Axis, per 1°	1.02 (1.01-1.04)	0.001		
P wave in lead II, per 0.1 mV	1.10 (1.01-1.22)	0.014		
P wave in lead III, per 0.1 mV	1.16 (1.06-1.29)	0.001		
P wave in lead aVF, per 0.1 mV	1.19 (1.06-1.36)	< 0.001		
QTc duration, per 0.01 sec	1.25 (1.06-1.50)	0.009		
R wave in lead V1, 0.1 mV	1.31 (1.13-1.54)	< 0.001		
S wave in lead V5, 0.1 mV	1.35 (1.15-1.62)	< 0.001	1.19 (1.02-1.43)	0.027
Negative T wave in lead V1, per 0.1 mV	2.24 (1.58-3.48)	< 0.0001	1.88 (1.29-2.99)	< 0.001
Negative T wave in lead V2, per 0.1 mV	1.50 (1.25-1.87)	< 0.0001		
Negative T wave in lead V3, per 0.1 mV	1.41 (1.18-1.74)	< 0.0001		
Negative T wave in lead V4, per 0.1 mV	1.29 (1.09-1.59)	0.0003		

Table VII. Accuracy, Sensitivity, and Specificity of the Cut-Off Values of ECG Parameters for Predicting MPAP ≥ 25 mmHg in PAH and CTEPH Patients

	Cut-off value	AUC	95%CI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PAH patient							
R wave in lead V5 (mV)	1.05	0.65	0.52-0.75	42.6	86.1	80.0	47.1
S wave in lead V5 (mV)	0.42	0.75	0.64-0.84	67.9	73.0	79.2	60.0
Negative T wave in lead V4 (mV)	-0.27	0.81	0.71-0.89	80.0	75.7	83.0	70.0
CTEPH patients							
S wave in lead V5 (mV)	0.43	0.75	0.63-0.84	69.2	73.0	78.3	62.8
Negative T wave in lead V1 (mV)	0.13	0.81	0.71-0.89	75.0	75.7	81.3	68.3

AUC indicates area under curve; and CI, confidence interval.

echocardiography, it was not associated with tricuspid valve regurgitation velocity on echocardiography, which correlated with systolic PAP on RHC.[20]

Focusing on R and S wave amplitudes, a previous study demonstrated that R wave in lead I ≤ 2 mm, S wave in lead V1 ≤ 2 mm, R/S ratio in lead V1 ≥ 1, R/S ratio in
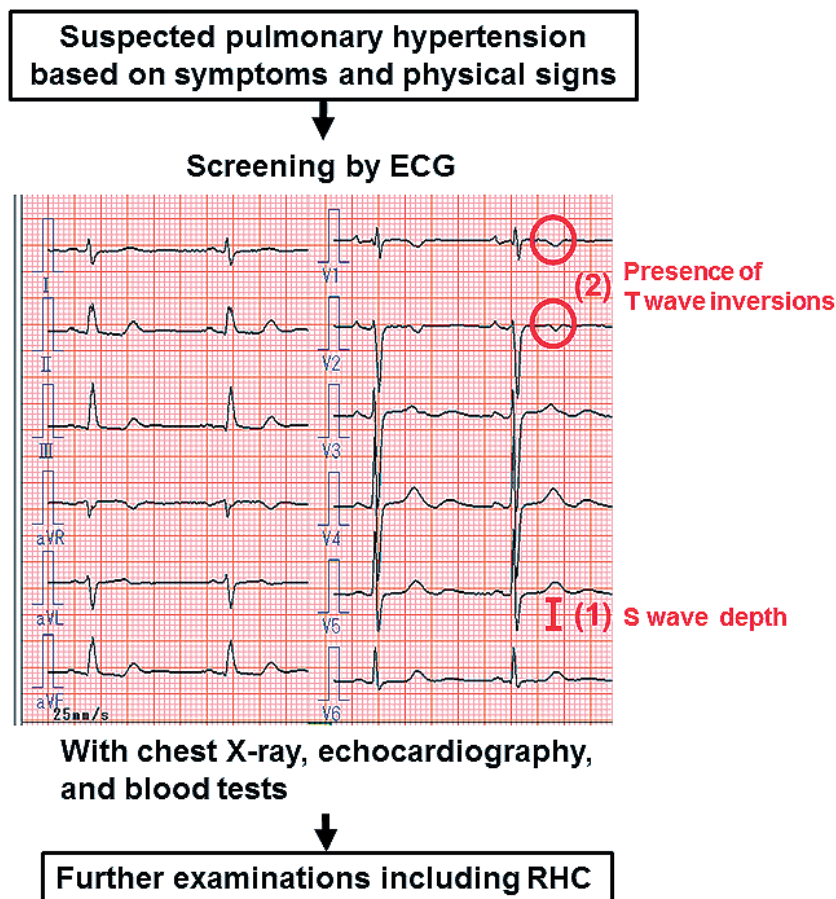
Figure. A flow chart for PH diagnosis using the electrocardiogram (ECG). If the patient is suspected to have pulmonary hypertension based on symptoms and physical signs, ECG screening is then performed. When looking at the ECG, first, whether the depth of the S wave is more than around 5 mm with a calibration of 1 mV/10 mm is checked (1). Second, whether the presence of T wave inversion extends beyond lead V3 in the precordial leads is checked (2). The screening is performed together with chest X-ray, echocardiography, and blood tests. These findings then help decide whether further examinations, including right heart catheterization (RHC), are required.

lead V6 ≤ 1, QRS axis ≥ 110°, and qR in V1 had superior PPVs for PH.[8] Kopec, *et al*. also demonstrated that an R wave in lead V1 had the best correlation with RVH among the ECG voltage criteria because V1 is the closest lead to the RV.[9] Given that an R/S ratio ≥ 1 in lead V1 is observed in only 1% of patients as a normal variant,[21] these findings suggest that a higher R wave in lead V1 is a useful parameter for detecting PH or RVH. In contrast, the QRS amplitude of lead V5, but not V1, was identified as an independent predictor of PH in the present study. In the former study, the amplitude of the QRS complex in lead V5 was not included among the analyzed parameters, and the PH definition was based on echocardiography but not RHC. The latter study demonstrated the associations between ECG parameters and RVH assessed by magnetic resonance imaging, unlike the present study that measured hemodynamics by RHC. Few studies have reported the correlation between the QRS amplitude in lead V5 and PAP measured by RHC, as in the present study. In the normal heart, the more muscular LV produces depolarization current flowing toward the lateral leads (V5, 6);

therefore, the changes of LV depolarization and location may be reflected in these leads. An echocardiographic study showed that LV torsion, the maximal difference between the apical and basal rotation during systole, was decreased in PH patients,[22] which suggested depression of the depolarization current flow to the LV. Additionally, RV enlargement caused by RV overload changes the relative location of the LV toward the posterior. This may influence the changes of the QRS complex in lead V5. Chronic RV pressure overload affects the terminal depolarization of the QRS vector, the S wave.[23] Thus, the S wave in lead V5 may be more sensitive for detecting PH than the other ECG parameters.

The present study also demonstrated that the presence of negative T waves in the precordial leads had the highest PPV for detecting PH in both groups and the entire group. It is well-known that T wave inversions in the precordial leads are clinically observed in various conditions, such as coronary artery disease, acute pulmonary embolism, and healthy women. In patients with acute pulmonary embolism, a systematic review and meta-analysis

showed that the presence of inverted T waves in leads V1-V4 was an ECG finding to predict hemodynamic collapse and death within 30 days after onset.[24] Furthermore, an increasing number of leads with T wave inversion was related to a higher mortality rate and a higher frequency of complications.[25,26] A possible mechanism of T wave inversion is acute cor pulmonale with rapid right ventricular pressure overload and right ventricular enlargement, although it is not completely understood. In 44 patients with CTEPH, Lewzcuk, et al. reported that a negative T wave in the precordial V1-V5 leads was most commonly observed (45.4%) as an ECG sign of right ventricular overload, and the sensitivity and specificity for detecting MPAP > 30 mmHg were 48.0% and 95.0%, respectively.[27] The extent of T wave inversion in the precordial leads differed between PAH and CTEPH patients in the present study. Polanowski, et al.[28] showed that dynamic coupling between the RV and pulmonary arteries is more disturbed in CTEPH than in PAH, despite similar levels of PAP. This may cause RV strain,[29] resulting in T wave inversion in the precordial leads. However, the reason is uncertain. An increasing number of leads with negative T waves in the precordial leads increased the specificity for detecting PH in the entire group of this study (data not shown). Thus, a wider extent of T wave inversion in the precordial leads could be associated with a greater RV overload.

The clinical implications of ECG parameters to predict PH were as follows. When glancing at an ECG of a patient with suspected PH, we first checked whether S wave depth is more than around 5 mm with calibration of 1 mV/10 mm, based on the results of the multivariable analysis in the entire group and its cut-off value of 0.42 mV. Second, whether T wave inversion extends beyond lead V3 in the precordial leads was checked. Because the cut-off value of T wave inversion in lead V4 was -0.28 mV, the T wave was almost flat in lead V3, indicating that the T wave changed from negative to positive around lead V4 in the precordial leads. A flow chart of PH diagnosis based on the clinical implications suggested by the present study is shown in the Figure. We suggest checking these two parameters as an easy and simple screening test for predicting MPAP ≥ 25 mmHg and if positive, then proceeding to further examinations including RHC. The patients who meet current RVH criteria could have a higher MPAP, and, of course, should undergo further examinations.

The present study has several limitations. First, because this was a retrospective study in only our hospital, potential selection and information bias could not be avoided. Second, the etiology of PH was limited to PAH and CTEPH. The reason for this was that the distinction between these two conditions was not easy to discern clinically during screening for these diseases, and no significant differences in ECG findings between these two conditions have been reported.[30-32] The results from this study may not be applied to PH of other etiologies, such as acute pulmonary thromboembolism and secondary to left heart failure and pulmonary disease. Third, 28.3% of PAH patients had taken pulmonary vasodilators including endothelin receptor antagonists and phosphodiesterase V

inhibitors, which may have affected the results. Fourth, disease duration may have some effects on the ECG findings. This was not included in the present analysis, because the exact onset time could not be identified. Finally, arrhythmias such as premature atrial/ventricular contractions, atrial fibrillation, and atrioventricular block were not examined.

In conclusion, a deeper S wave in lead V5 and a wider extent of T wave inversions in the precordial leads can be clinically simple and useful ECG parameters for screening for MPAP ≥ 25 mmHg. This may lead to earlier diagnosis and treatment of PH.

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Disclosures

Conflicts of interest: The authors have no conflicts of interest to disclose.

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