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Usefulness of ECG Scoring in Screening for Chronic Thromboembolic Pulmonary Hypertension

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Abstract

Background : Patients with chronic thromboembolic pulmonary hypertension (CTEPH) lack specific symptoms in the early phase, and thus many patients are diagnosed after substantial disease progression, which may partly explain their poor prognoses. Although various therapeutic approaches (*i.e.,* disease modifying drugs, catheter intervention, and cardiac surgery) improve patient outcomes, the early diagnosis of CTEPH remains challenging. Therefore, the aim of the present study was to investigate the usefulness of electrocardiogram (ECG) for screening patients with CTEPH.

Methods : In a retrospective case-control study, 47 patients with CTEPH were analyzed at Tokyo Medical University Hospital between April 1, 2014 and June 30, 2019. These subjects were matched to 47 patients with chronic obstructive pulmonary disease (COPD) by age and sex (mean, 95% confidence interval [CI] = 63.0, 53.5-74.0 years ; women : 76%). The ECG score was calculated based on 6 items within the Clinical Survey Personal Form of the Intractable Disease Medical Research Foundation/Information Center for Intractable Diseases. The diagnostic value of ECG scores for CTEPH was assessed.

Results : Patients with CTEPH were more likely to have 5 individual ECG abnormalities compared with those with COPD ($p < 0.001$ for all). The diagnostic accuracy of ECG scores for CTEPH was excellent (area under the receiver operating characteristic curve, 95% CI = 0.90 [0.85-0.96]). An ECG score of 2 or more was able to identify both male and female CTEPH patients (sensitivity : 83.0% ; specificity : 78.7%).

Conclusion : Our results showed that ECG scores of 2 or more strongly suggest CTEPH. ECG may become a widely and readily available method for the screening of CTEPH in the future.

Background and objectives

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease that causes pulmonary hypertension (PH) owing to chronic stenosis or the occlusion of pulmonary arteries by an organic thrombus[1)2)]. In Japan, more than 300 patients are diagnosed as having CTEPH every year, according to the database of the Ministry of Health, Labor and Welfare, and the number of total cases is reported to be approximately 3,200 (25.2 per million)[3)]. However, patients with CTEPH have no distinctive symptoms. Specifically, the most frequent symptom is

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dyspnea on exertion, but this symptom is also seen in a variety of cardiac and lung diseases, such as chronic heart failure, ischemic heart disease, and chronic respiratory disease. Therefore, the diagnosis of CTEPH is often difficult. A prior study suggested that the mean time to diagnosis of CTEPH is 14 months[4]. However, patient prognosis worsens with the progression of CTEPH. In previous reports, the 5-year survival rate for patients with a mean pulmonary artery pressure (mPAP) of 40 mmHg or higher was reported to be 30%. Furthermore, a 5-year survival rate of only 10% was reported for patients with a mPAP of 50 mmHg or higher[5]. In recent years, pulmonary artery endarterectomy (PEA) has been established as the standard treatment for CTEPH[1)6-12)]. In addition, the efficacy of drug therapy and balloon pulmonary artery angioplasty for inoperable cases and patients with residual PH after PEA has been reported[13-23)]. Accumulating evidence support that these therapeutic interventions may improve the quality of life and prognosis of patients, and thus it is of paramount importance to diagnose CTEPH at an early phase of the disease course.

According to the national and international guidelines for CTEPH, the diagnosis of CTEPH is based on symptoms and physical findings, and if CTEPH is suspected, the first step in the diagnostic algorithm is to assess the presence of PH by echocardiography[10)24)]. However, echocardiography is a specialized test and is considered less versatile. The most common examinations to assess dyspnea in primary care are blood tests, chest X-ray, and electrocardiogram (ECG). Brain natriuretic peptide (BNP), a biomarker of heart failure, reflects the degree of left ventricular filling pressure. However, in patients with right heart failure associated with PH, such as CTEPH, increased plasma levels of BNP may be less suitable for screening for PH[25)]. In addition, chest X-ray may be less reliable for diagnosing CTEPH in many dyspneic patients[26)]. Although patients with mild PH may often have normal ECG waveforms, ECG has been reported to be able to detect increased right ventricular filling pressure associated with PH[27)]. Therefore, whether multiple scores of ECG analysis are useful for the screening of CTEPH requires further investigation.

In the present study, we analyzed whether ECG scores that capture characteristics particularly of right heart failure can be a screening test to diagnose CTEPH.

Subjects and methods

1. Study design and subjects

A total of 47 patients diagnosed with CTEPH based on the diagnostic criteria of the Foundation for Intractable Medical Research/Information Center for Intractable Diseases[28)] among patients aged 30 to 90 years who visited Tokyo Medical University Hospital between April 1, 2014 and June 30, 2019 were included as the CTEPH group. The controls were patients who visited Tokyo Medical University owing to shortness of breath and dyspnea similar to CTEPH, but who were diagnosed as having chronic obstructive pulmonary disease (COPD) based on the "Guidelines for the Diagnosis and Treatment of COPD"[30)] of the Japanese Respiratory Society. A total of 210 patients with a diagnosis of COPD for whom electrocardiography data was available were selected and matched to the CTEPH group by age (± 5 years) and sex. This study was approved by the Medical Ethics Review Committee of Tokyo Medical University (study approval number : T2019-0263). Informed consent was not obtained from the patients, but information about the study was disclosed and the opportunity to refuse was guaranteed.

2. Evaluation items

In the CTEPH group, data regarding age, sex, drug therapy, home oxygen therapy, right heart catheterization findings, World Health Organization Functional Classification of Pulmonary Hypertension (WHO-Fc)[31)] as severity assessment based on symptoms, the 6-minute walk test[32)] as exercise tolerance assessment, and ECG findings were collected at the patient's initial visit to Tokyo Medical University Hospital. In the COPD group, data was also collected regarding age, sex, and ECG findings at the time of the patient's initial visit to Tokyo Medical University Hospital, as well as staging data using paired standardized volume in 1 second (%FEV1) based on the "Guidelines for the Diagnosis and Treatment of COPD"[30)] of the Japan Respiratory Society.

2.1. The method of ECG scoring

Results of the first ECG test performed on the subjects (CTEPH group and COPD group) at Tokyo Medical University Hospital were used. CTEPH was diagnosed based on the total score of the ECG items, and the diagnostic ability of ECG for CTEPH was verified by the following methods. The presence of 6 ECG items (right axis deviation, right atrial load, $V_1R \geq 5$ mm or $R/S \geq 1$, $V_5S \geq 7$ mm or $R/S \leq 1$, negative T-wave from V_1 to V_3 leads, and atrial flutter/fibrillation) listed in the Clinical Survey Individual Form[28)] of the Intractable Disease Medical Research Foundation/Intractable Disease Information Center were evaluated. ECGs (12-lead) were recorded at a paper speed of 25 mm/sec, right-axis deviation was defined as QRS axis > 110° right atrial load as P-wave > 0.25 mV in the leads II, and right-axis deviation, was defined as $V_1R \geq 5$ mm or $R/S \geq 1$, $V_5S \geq 7$ mm or $R/S \leq 1$, and negative T-waves (V_1 to V_3) were interpreted as findings of right ventricular hypertrophy[33)34)]. ECGs were read by several cardiologists. The aforementioned ECG findings (6 items), the association between ECG score and CTEPH based on the total score of each item, and the diagnostic ability of ECG for

CTEPH were verified by the following methods.

Methods of analysis

1. Patient background

For summary statistics of patient background, continuous variables were expressed as median and interquartile range, and categorical variables as number of patients (%).

2. Association between ECG scores and right heart catheterization findings

The association between ECG scores and results of the first right heart catheterization performed within 6 months of the study mPAP and systolic right ventricular pressure sRVP) was analyzed by Pearson's correlation coefficient and the uncorrelated test.

3. Association between ECG scores and COPD stage

The association between ECG scores and COPD stage was assessed using the Kruskal–Wallis test.

4. Comparison of ECG scores between the CTEPH and COPD groups

The Wilcoxon rank sum test was used to test whether the distribution of ECG scores between the CTEPH and COPD groups differed.

5. Ability of ECG scores to diagnose CTEPH

Using a logistic regression model, the ability of ECG scores to distinguish between patients with CTEPH and those with COPD was evaluated. The interaction between ECG scores and diagnostic performance in patients of the same sex were analyzed, as in general, CTEPH patients are often women, whereas COPD patients are often men. The area under the curve (AUC) was used to evaluate the ability of CTEPH to be diagnosed by ECG scores. The conditional receiver operating characteristic (ROC) curve was determined by calculating the predicted risk from the ECG scores and covariate (i.e., sex), and the ROC curve was drawn using the predicted risk[35]. The optimal cutoff value of the ECG scores hence cannot be read directly from the conditional ROC curve. Therefore, the predicted risk by sex corresponding to each value of the ECG score was calculated from the logistic regression model, and a corresponding table was created. The optimal cutoff values for the ECG scores for men and women were then calculated using the corresponding tables, with the value of the predicted risk with the smallest distance from the upper left corner of the conditional ROC curve as the optimal cutoff value.

6. Other exploratory analyses

6–1. Comparison by item

The Fisher's direct probability test was used to test whether the frequency of each item was significantly different between the 2 groups.

6–2. Characteristics of patients with an ECG score of 1

Whether the applicable ECG items could distinguish diseases for patients with an ECG score of 1 in both groups was analyzed.

6–3. Overestimation of discriminative power

As the prediction model was created and evaluated using the same data set, there is a possibility that the prediction accuracy (AUC) was overestimated. Therefore, the AUC was recalculated using nlpred[40], which is a method that corrects for overestimation. A p–value less than 0.05 in the two–tailed test was considered to indicate a statistically significant difference for all analyses. Statistical analyses were performed using software R (version 4.1.0). The ROC curves and AUC calculations were performed using the pROC package.

Results

1. Patient background

The clinical characteristics of the 47 patients in the CTEPH group are shown in Table 1. The majority of the patients were women (76%), with a median age of 63 years (interquartile range : 53.5–74.0 years). Regarding adjuvant therapy, 91% of the patients were receiving anticoagulation therapy, 21% were receiving prostaglandin I2 formulations, 13% were receiving phosphodiesterase type 5 inhibitors, 17% were receiving endothelin receptor antagonists, and 78% were receiving home oxygen therapy. The number of patients in each class according to the criteria of WHO–Fc was as follows : class I, 0 ; class II, 19 ; class III, 22 ; class IV, 6 ; and the median 6–minute walk test result was 342.5 m. The median values of mPAP and sRVP as assessed by right heart catheterization were 42 and 72 mmHg, respectively.

The COPD group consisted of 76% women, with a median age of 64 years (quartile range : 53.5–73.5 years). Two patients were undergoing home oxygen therapy, and the stage distribution was as follows : stage I : 22 patients, stage II : 15 patients, stage III : 43 patients, and stage IV : 0 patients.

2. Association between ECG scores and right heart catheterization findings

A scatter plot of ECG scores and right heart catheterization measurements is shown in Fig. 1. The correlation coefficient between ECG score and mPAP value was 0.64 (95% confidence interval (CI) : 0.42–0.78), and that of sRVP value was 0.57 (95% CI : 0.34–0.74).

3. Association between ECG scores and COPD stage

ECG scores were not significantly associated with COPD stage ($p = 0.47$).

4. Comparison of ECG scores between the CTEPH and COPD groups

Fig. 2 shows that the distribution of ECG scores between the CTEPH and COPD groups was significantly different ($p < 0.001$), with scores ranging from 1 to 5 in

Table 1 Clinical characteristics of patients in the CTEPH and COPD groups ($n = 47$)

	CTEPH	COPD	p-value
Number of patients, *n*	47	47	NS
Age	63.0 (53.5-74.0)	63.0 (53.5-74.0)	NS
Women, *n* (%)	36 (76)	36 (76)	NS
Adjuvant therapy			
Medicine			
Anticoagulant, *n* (%)	43 (91)	—	
Prostaglandin I2, *n* (%)	10 (21)	—	
Phosphodiesterase inhibitor, *n* (%)	6 (13)	—	
Endothelin receptor antagonist, *n* (%)	8 (17)	—	
Home oxygen therapy, *n* (%)	21 (45)	2(5)	< 0.001
WHO-Fc I/II/III/IV, *n* (%)	0/19/22/6 (0/40/47/13)	—	
Stage (COPD) I/II/III/IV, *n* (%)	—	22/15/4/0 (54/36/10/0)	
6-minute walk test, m	343 (236-416)	—	
Right heart catheterization		—	
mPAP, mmHg	42.0 (30.3-48.0)	—	
sRVP, mmHg	72.0 (52.5-83.5)	—	

Continuous variables are expressed as the median (interquartile range).
For the 6-minute walk test of the CTEPH group, the n was 44 owing to missing data for 3 patients. For disease staging of the COPD group, the n was 37 owing to missing data for 10 patients.

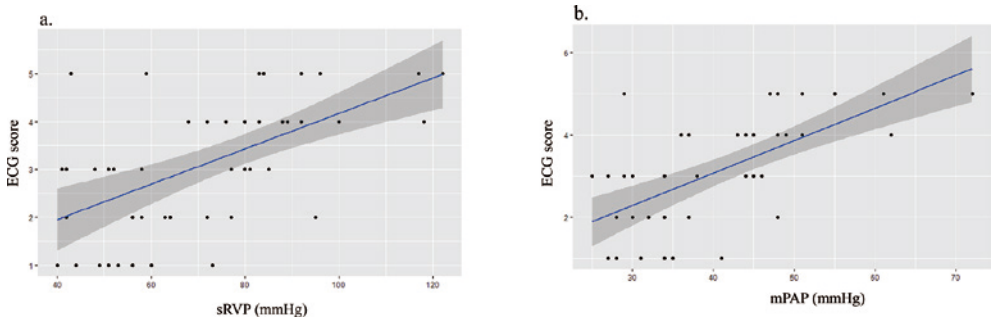

Fig. 1. Correlation between ECG scores and right heart catheterization measurements in the CTEPH group
a. Association between ECG scores and sRVP.
sRVP measurements and ECG scores. Straight lines are regression lines based on the least squares method, and 95% confidence bands are shown around the straight line.
b. Association between ECG scores and mPAP.
mPAP measurements and ECG scores. Straight lines are regression lines based on the least squares method, and 95% confidence bands are shown around the straight line.

the CTEPH group, and from 0 to 3 in the COPD group.

5. Efficacy of distinguishing CTEPH from COPD using ECG scores

Fig. 3 shows the conditional ROC curve of the ability to distinguish the CTEPH and COPD groups by ECG scores. The optimal cutoff value for the predicted risk in the conditional ROC curve was 0.30 (sensitivity : 83. 0% ; specificity : 78.7%), and there was no sex-associated difference in ECG scores to distinguish CTEPH from COPD.

6. Other exploratory analyses

6-1. Comparison of each ECG score item

Among all items of the ECG scores, right atrial overload was the most frequent, and atrial flutter/fibrillation was the least frequent in both the CTEPH and COPD groups (Table 2). Except for the presence of atrial fibrillation, patients with CTEPH were more likely to have all items of the ECG scores than those with COPD (Table 2).

6-2. Characteristics of patients with an ECG score of 1

In the CTEPH group, 17% of patients had an ECG score of 1, all of whom were found to have right atrial overload (Fig. 2). On the other hand, 30% of patients in the COPD group had an ECG score of 1 point, and a large number of these patients were found to have right atrial load.

6-3. Comparison of ECG score items

The AUC recalculated by overestimation nlpred[40]

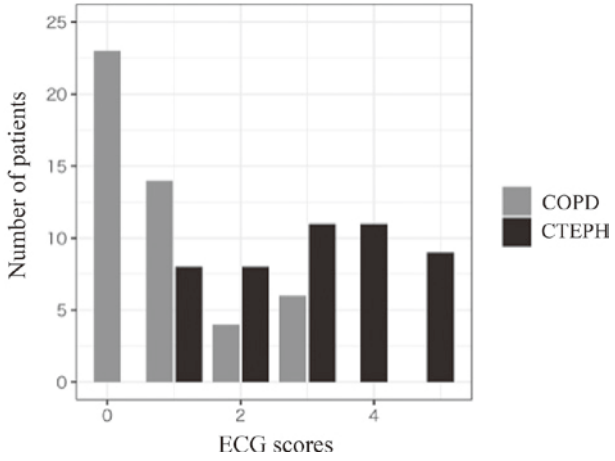

Fig. 2. Distribution of ECG scores in the CTEPH and COPD groups
Histogram of ECG scores of the CTEPH and COPD groups. ECG scores were statistically significantly different between the 2 groups ($p < 0.001$).

demonstrated a discriminatory power of 0.881 (95% CI : 0.821–0.941).

Discussion

Effective treatments for CTEPH has been established, and improves patient prognosis ; however, prompt therapeutic intervention may be a key to the more efficient management of patients with CTEPH. Therefore, it would be highly effective for general clinicians to screen for CTEPH based on simple and noninvasive ECG[36)37)]. Taken together, this is the first study to compare the ECG scores between patients with CTEPH and COPD, and to demonstrate high diagnostic accuracy for CTEPH using ECG scores.

Similar to CTEPH, in precapillary PH, in which the pathogenesis is primarily in the pulmonary arteries, the ECG waveform appears the pressure overload on the right ventricle and right atrium caused by the increased pulmonary artery pressure. In addition, chronic right ventricular load leads to right ventricular hypertrophy. That is, findings of right ventricular hypertrophy and

Corresponding Table

ECG score	Women	Men
0	0.08	0.06
1	0.27	0.17
2	0.63	0.39
3	0.88	0.67
4	0.97	0.86
5	0.99	0.95
6	1.00	0.98

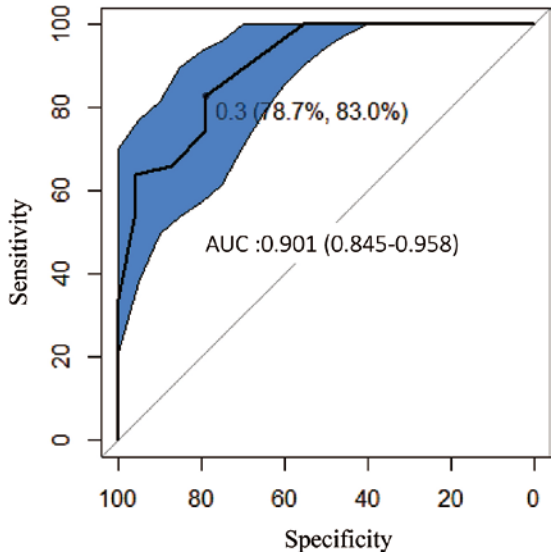

Fig. 3. Conditional ROC curve for ECG 6-item total score
The table on the left shows the predicted risk by logistic regression analysis for men and women, with a predicted risk of 0.3 on the ROC curve corresponding to an ECG score between 1 and 2 points. The optimal cutoff value (sensitivity : 83.0% ; specificity : 78.7%) for a positive diagnosis of CTEPH was 2 or more points for both men and women. The AUC was 0.901, with a 95% CI of 0.845% to 0.958%.

Table 2 Comparison of ECG items between the 2 groups

	CTEPH	COPD	*p*-value
Right axis deviation	25 (53%)	1 (2%)	< 0.001
P amplitude in II ≧ 0.25 mV	45 (96%)	17 (36%)	< 0.001
R in V1 ≧ 5 mm or R : S ratio in V1 ≧ 1	24 (51%)	5 (11%)	< 0.001
S in V5 ≧ 7 mm or R : S ratio in V5 ≦ 1	25 (53%)	9 (19%)	0.001
Negative T-wave in V1 through V3	25 (53%)	8 (17%)	< 0.001
Atrial flutter or atrial fibrillation	2 (4%)	0 (0%)	0.495

right atrial load on ECG may reflect increased mPAP and sRVP on right heart catheterization. In the present study, ECG scores significantly correlated with mPAP and sRVP values (Fig. 1), consistent with ECG changes in patients with PH in previous studies[33)34)38)]. ECG scores in CTEPH patients were significantly higher than in COPD patients (Fig. 2). Our results showed that it is possible to distinguish CTEPH from COPD using an ECG score of 2 or more in both men and women (Fig. 3). These findings suggest that, if a patient manifests with shortness of breath on exertion and has an ECG score of 2 or more, CTEPH should be considered. In the present study, the most common finding regarding ECG items in both groups was right atrial load when the ECG score was 1 point, suggesting that right atrial load alone may be less likely to distinguish between CTEPH and COPD. According to the 2002 Guidelines for the Evaluation of Results of Physical Examination and Posterior Guidance by the Japanese Society of Medical Checkups, right-axis deviation is Grade B (mild abnormality but no obstacle to daily life), right atrial load is Grade C (mild abnormality requiring lifestyle improvement or observation), and right ventricular enlargement, negative T-wave, and atrial fibrillation are Grade D (requiring further examination or treatment)[39)]. ECG findings indicative of right ventricular hypertrophy include QTc prolongation as well as the ECG items analyzed in this study[33)38)]. Sensitivity of the V1-3 lead negative T-wave (right ventricular strain), which was also analyzed in this study, has previously been reported to be as high as 78.8%[27)]. Negative T-waves were found in about half the CTEPH group (53%) and 17% of the COPD group, showing a significant difference in frequency (Table 2). Nevertheless, the fact that about half the CTEPH patients do not fall into this category suggests that it is difficult to distinguish between the 2 diseases based on negative T-wave findings alone. In this study, the number of patients with atrial flutter/fibrillation was small, and there was no significant difference between the 2 groups. However, atrial fibrillation was observed in 25% of patients with PH over a 5-year period, and was reported to cause hemodynamic deterioration owing to decreased cardiac output, so further investigation is warranted[40)]. One limitation of this study is that it was limited to CTEPH patients in Nice Classification Group 4, and further studies using clinical examination methods other than ECG are needed to differentiate CTEPH from other diseases that cause PH, such as idiopathic pulmonary arterial hypertension and lung lesions associated with collagen disease. It is also necessary to evaluate the ability to distinguish the diseases based on the sex and age distribution of the COPD and CTEPH groups. As the prediction model was created and evaluated using the same dataset, the prediction accuracy (AUC) may be overestimated. The AUC was 0.881 (95% CI : 0.821-0.941), which was not considered to be significantly different compared with the uncorrected AUC of 0.901 (95% CI : 0.845-0.958). Further studies for the external validation of ECG scores are hence required. ECG scores of the patients used in this study were those from the ECG performed at their initial visit to Tokyo Medical University Hospital ; therefore, the majority of patients with CTEPH had already undergone therapeutic interventions. In the CTEPH group, 17% of patients had a score of 1, but this is owing to the fact that a substantial number of patients show an improvement in symptoms upon therapeutic intervention compared with at the time of symptom onset. In addition, owing to the nature of university hospitals, there is a high possibility that patients with more severe symptoms were concentrated in the hospital, and hence there may be a discrepancy between the actual situation in primary care and the situation at our university hospital. On the other hand, the fact that 36% of patients in the COPD group had right atrial load may be owing to the high symptom severity of COPD patients being treated at a university hospital. This means that in primary care, the difference in ECG scores between COPD and CTEPH patients may be even greater. Another issue to be considered in older patients is the effects of other cardiovascular comorbidities on ECG. However, the ECG scoring presented in this study may provide clues to keeping CTEPH in mind in daily practice, and may have great potential for making accurate diagnoses.

Conclusion

ECG scoring was suggested to be useful as a screening method for CTEPH. When subjective symptoms that are suggestive of PH are confirmed, and 2 or more right heart overload findings are found on ECG, it is important to confirm the presence or absence of PH by echocardiography, leading to performing a thorough examination for CTEPH.

References

1) Kim NH, Delcroix M, Jenkins DP, Channick R, Dartevelle P, Jansa P, Lang I, Madani MM, Ogino H, Pengo V, Mayer E : Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol **62** : D92-99, 2013
2) Piazza G, Goldhaber SZ : Chronic thromboembolic pulmonary hypertension. N Engl J Med **364** : 351-360, 2011
3) The General Contact Point for Government Statistics (e-Stat) : Examples of Reports on Public Health Administration / Examples of Reports on Public Health Administration for the Year 2028 / Statistical Tables / Annual Reports. https://www.mhlw.go.jp/

toukei/list/36-19.html (accessed 30 August 2021).
4) Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Hamid AM, Jaïs X, Simonneau G, Chronic thromboembolic pulmonary hypertension (CTEPH) : results from an international prospective registry. Circulation **124** : 1973-1981, 2011
5) Riedel M, Stanek V, Widimsky J, Prerovsky I : Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. Chest **81** : 151-158, 1982
6) Ogino H, Ando M, Matsuda H, Minatoya K, Sasaki H, Nakanishi N, Kyotani S, Imanaka H, Kitamura S : Japanese single-center experience of surgery for chronic thromboembolic pulmonary hypertension. Ann Thorac Surg **82** : 630-636, 2006
7) Hoeper MM, Barberà JA, Channick RN, Hassoun PM, Lang IM, Manes A, Martinez FJ, Naeije R, Olschewski H, Pepke-Zaba J, Redfield MM, Robbins IM, Souza R, Torbicki A, McGoon M : Diagnosis, assessment, and treatment of non-pulmonary arterial-hypertension pulmonary hypertension. J Am Coll Cardiol **54** : S85-96, 2009
8) McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J : ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians ; American Thoracic Society, Inc. ; and the Pulmonary Hypertension Association. J Am Coll Cardiol **53** : 1573-1619, 2009
9) Mayer E, Jenkins D, Lindner J, D'Armini A, Kloek J, Meyns B, Ilkjaer LB, Klepetko W, Delcroix M, Lang I, Pepke-Zaba J, Simonneau G, Dartevelle, P : Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension : results from an international prospective registry. J Thorac Cardiovasc Surg **141** : 702-710, 2011
10) Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M : 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension : The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) : Endorsed by : Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantatio (ISHLT). Eur Heart J **37** : 67-119, 2016
11) Fukuda K, Date H, Doi S, Fukumoto Y, Fukushima N, Hatano M, Ito H, Kuwana M, Matsubara H, Momomura SI, Nishimura M, Ogino H, Satoh T, Shimokawa H, Yamauchi-Takihara K, Tatsumi K, Ishibashi-Ueda H, Yamada N, Yoshida S, Abe K, Ogawa A, Ogo T, Kasai T, Kataoka M, Kawakami T, Kogaki S, Nakamura M, Nakayama T, Nishizaki M, Sugimura K, Tanabe N, Tsujino I, Yao A, Akasaka T, Ando M, Kimura T, Kuriyama T, Nakanishi N, Nakanishi T, Tsutsui H : Guidelines for the Treatment of Pulmonary Hypertension (JCS 2017/JPCPHS 2017). CircJ **83** : 842-945, 2019
12) Tanabe N, Sugiura T, Tatsumi K : Recent progress in the diagnosis and management of chronic thromboembolic pulmonary hypertension. Respir Investig **51** : 134-146, 2013
13) Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ : Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation **103** : 10-13, 2001
14) Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H : Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv **5** : 748-755, 2012
15) Sugimura K, Fukumoto Y, Satoh K, Nochioka K, Miura Y, Aoki T, Tatebe S, Miyamichi-Yamamoto S, Shimokawa, H : Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension. Circ J **76** : 485-488, 2012
16) Taniguchi Y, Miyagawa K, Nakayama K, Kinutani H, Shinke T, Okada K, Okita Y, Hirata KI, Emoto N. Balloon pulmonary angioplasty : an additional treatmentoption to improve the prognosis of patients withchronic thromboembolic pulmonary hypertension. EuroIntervention **10** : 518-525, 2014
17) Aoki T, Sugimura K, Tatebe S, Miura M, Yamamoto S, Yaoita N, Suzuki H, Sato H, Kozu K, Konno R, Miyata S, Nochioka K, Satoh K, Shimokawa H : Comprehensive evaluation of the effectiveness and safety of balloon pulmonary angioplasty for inoperable chronic thrombo-embolic pulmonary hypertension : long-term effects and procedure-related complications. Eur Heart J **38** : 3152-3159, 2017
18) Ogawa A, Satoh T, Fukuda T, Sugimura K, Fukumoto Y, Emoto N, Yamada N, Yao A, Ando M, Ogino H, Tanabe N, Tsujino I, Hanaoka M, Minatoya K, Ito H, Matsubara H : Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension : Results of a Multicenter Registry. Circ Cardiovasc Qual Outcomes **10** : 2017

19) Kim NH, Delcroix M, Jais X, Madani MM, Matsubara Matsubara H, Mayer E, Ogo T, Tapson VF, Ghofrani HA, Jenkins DP : Chronic thromboembolic pulmonary hypertension. Eur Respir J **53** : 2019
20) Shimura N, Kataoka M, Inami T, Yanagisawa R, Ishiguro H, Kawakami T, Higuchi Y, Ando M, Fukuda K, Yoshino H, Satoh T : Additional percutaneous transluminal pulmonary angioplasty for residual or recurrent pulmonary hypertension after pulmonary endarterectomy. Int J Cardiol **183** : 138-142, 2015
21) Yanaka K, Nakayama K, Shinke T, Shinkura Y, Taniguchi Y, Kinutani H, Tamada N, Onishi H, Tsuboi Y, Satomi-Kobayashi S, Otake H, Tanaka H, Okita Y, Emoto N, Hirata KI : Sequential Hybrid Therapy With Pulmonary Endarterectomy and Additional Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension. J Am Heart Assoc **7** : 2018
22) Araszkiewicz A, Darocha S, Pietrasik A, Pietura R, Jankiewicz S, Banaszkiewicz M, Sławek-Szmyt S, Biederman A, Mularek-Kubzdela T, Lesiak M, Torbicki A, Kurzyna M : Balloon pulmonary angioplasty for the treatment of residual or recurrent pulmonary hypertension after pulmonary endarterectomy. Int J Cardiol **278** : 232-237, 2019
23) Ito R, Yamashita J, Sasaki Y, Ikeda S, Suzuki S, Murata N, Ogino H, Chikamori T : Efficacy and safety of balloon pulmonary angioplasty for residual pulmonary hypertension after pulmonary endarterectomy. Int J Cardiol : 2021.
24) Intractable Disease Policy Research Project "Research Group on Intractable Respiratory Disease and Pulmonary Hypertension" Japan Lung Association. Guideline for Chronic Thromboembolic Pulmonary Hypertension (CTEPH). http://jpcphs.org/pdf/guideline/cteph_guide line.pdf (accessed 30 August 2021).
25) European Heart Failure Guidelines 2016. European HeartJournal **37** : 2129-2200, 2016 doi : 10.1093/eurheartj/ehw128.
26) Sato S, Sugiura T, Tanabe N, Terada J, Sakao S, Kasahara Y, Takiguchi Y, Tatsumi K : Successful operative case of chronic thromboembolic pulmonary hypertension clinically diagnosed as bronchial asthma. Nihon Kokyuki Gakkai Zasshi **48** : 836-841, 2010
27) Bonderman D, Wexberg P, Martischnig AM, Heinzl H, Lang MB, Sadushi R, Skoro-Sajer N, Lang IM : A noninvasive algorithm to exclude pre-capillary pulmonary hypertension.
28) Intractable Diseases Information Center : Chronic thromboembolic pulmonary hypertension (Intractable disease 88). https://www.nanbyou.or.jp/entry/307
29) Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, Takahashi K, Nishimura K, Ishioka S, Aizawa H, Zaher C : COPD in Japan : the Nippon COPD Epidemiology study. Respirology **9** : 458-465, 2004
30) COPD Guideline 5th Edition prepared by the Japanese Respiratory Society Committee ed : COPD (Chronic Obstructive Pulmonary Disease) Diagnosis and Guidelines for the Diagnosis and Treatment of COPD 2018
31) Barst RJ, McGoon M, Torbicki A, Sitbon O, Krowka MJ, Olschewski H, Gaine S : Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol **43** : 40s-47s, 2004
32) McLaughlin VV, Badesch DB, Delcroix M, Fleming TR, Gaine SP, Galiè N, Gibbs JS, Kim NH, Oudiz RJ, Peacock A, Provencher S, Sitbon O, Tapson VF, Seeger, W : End points and clinical trial design in pulmonary arterial hypertension. J Am Coll Cardiol **54** : S97-107, 2009
33) Libby P, Zipes DP, Bonow RO, Mann DL, Tomaselli GF : Braunwald's Heart Disease : A Textbook of Cardiovascular Medicine. 11th Edn. Philadelphia, Elsevier Health, 2019
34) Hancock EW, Deal BJ, Mirvis DM, Okin P, Kligfield P, Gettes LS, Bailey JJ, Childers R, Gorgels A, Josephson M, Kors JA, Macfarlane P, Mason JW, Pahlm O, Rautaharju PM, Surawicz B, van Herpen G, Wagner GS, Wellens H : AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram : part V : electrocardiogram changes associated with cardiac chamber hypertrophy : a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology ; the American College of Cardiology Foundation ; and the Heart Rhythm Society : endorsed by the International Society for Computerized Electrocardiology. Circulation **119** : e251-261, 2009
35) Pepe MS, Fan J, Seymour CW : Estimating the receiver operating characteristic curve in studies that match controls to cases on covariates. Acad Radiol **20** : 863-873, 2013
36) Highland KB : Pulmonary arterial hypertension. Am J Med Sci **335** : 40-45, 2008
37) Sato S, Ogawa A, Sarashina T, Tsukuda S, Mizoguchi H, Miyaji K, Munemasa M, Matsubara H : Pulmonary hypertension in patients with pulmonary hypertension. Therapeutic Research **32** : 1250-1252, 2011
38) Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al : Primary pulmonary hypertension. A national prospective study. Ann Intern Med **107** : 216-223, 1987
39) Subcommittee on Guidelines for Human Health Checkup Results and Post-Guidance : Guidelines for the Evaluation of Human Health Checkup Results and Post-Qualification Guidance in Fiscal 2002
40) Olsson KM, Nickel NP, Tongers J, Hoeper MM : Atrial flutter and fibrillation in patients with pulmonary hypertension. Int J Cardiol **167** : 2300-2305, 2013

慢性血栓塞栓性肺高血圧症のスクリーニングにおける心電図スコアリングの有用性

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【要旨】（背景） 慢性血栓塞栓性肺高血圧症（chronic thromboembolic pulmonary hypertension : CTEPH）は特異的な症状に乏しく診断が困難であるため、重症化してから発見される症例が多く、予後不良とされていた。しかし近年では外科治療に加え、カテーテル治療や薬物療法が導入されており、予後が改善している。したがって、いかに初期段階で CTEPH を適切に診断できるかが、予後改善につながるといえる。本研究は、CTEPH の早期発見に、心電図検査がスクリーニング法として有用かを検討した。

（方法） 2014 年 4 月 1 日から 2019 年 6 月 30 日までに東京医科大学病院を受診した CTEPH 患者 47 名をケースとし、同様に呼吸困難を主訴として来院する慢性閉塞性肺疾患（chronic obstructive pulmonary disease : COPD）患者のうち、心電図検査が施行された患者をコントロールとするケースコントロール研究を実施した。コントロールは年齢と性別で CTEPH 群にマッチングさせた。難病医学研究財団／難病情報センターの臨床調査個人票に掲載されている心電図所見 6 項目について 2 群間で比較した。また、心電図 6 項目の合計点数（心電図スコア）と CTEPH との関連を、ロジスティック回帰モデルを用いて検証し、ROC 曲線（receiver operating characteristic curve）を用いて心電図スコアによる CTEPH の判別能を検証した。

（結果） 心電図 6 項目のいずれにおいても CTEPH 群における頻度が COPD 群に比べて有意に高かった。心電図スコアによる 2 群の判別性能を示す ROC 曲線の曲線下面積は 0.901 で 95% 信頼区間は 0.845-0.958 であった。また、男女共に 2 点以上を陽性と判定するのが最適カットオフ値であった。（感度 83.0%　特異度 78.7%）。

（結語） 心電図検査の右心負荷所見 2 項目以上の陽性所見が CTEPH のスクリーニングに有用である可能性が示唆された。

〈キーワード〉 慢性血栓塞栓性肺高血圧症、肺高血圧症、慢性閉塞性肺疾患、心電図検査、スクリーニング