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【 ORIGINAL ARTICLE 】

Electrocardiographic Criteria of Right Ventricular Hypertrophy in Patients with Chronic Thromboembolic Pulmonary Hypertension after Balloon Pulmonary Angioplasty

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Abstract:

Objective Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive disease that leads to right-sided heart failure with electrocardiographic abnormalities. There are only a few reports about the effects of balloon pulmonary angioplasty for CTEPH on the electrocardiographic criteria of right ventricular hypertrophy. To determine the effect of balloon angioplasty on electrocardiography in patients with CTEPH.

Methods We evaluated electrocardiograms in 19 patients (mean age, 64±10 years) who underwent balloon pulmonary angioplasty.

Results We compared the hemodynamic parameters after balloon pulmonary angioplasty. The mean pulmonary artery pressure was decreased ($p<0.001$), and the cardiac index was increased ($p=0.025$) after balloon pulmonary angioplasty. The level of brain natriuretic peptide was decreased ($p=0.001$) after balloon pulmonary angioplasty ($p<0.001$). We applied 15 criteria for right ventricular hypertrophy to the patients, according to the American Heart Association recommendations of the electrocardiogram, after balloon pulmonary angioplasty. Among the criteria, the numbers of patients who met the criteria of deep S in V_6 ($p=0.005$) and max R in $V_{1, 2}$+max S in I, aV_L-S in V_1 ($p=0.046$) were significantly decreased after balloon pulmonary angioplasty. The mean numbers regarding the right ventricular hypertrophic criteria in each patient were significantly decreased after balloon pulmonary angioplasty (4.8±2.6 to 3.1±2.5, $p=0.003$).

Conclusion In addition to improvement in hemodynamics, improvement in right ventricular hypertrophy was also observed using the electrocardiographic criteria in patients with CTEPH after balloon pulmonary angioplasty, suggesting that we should pay more attention to these changes.

Key words: chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, electrocardiogram, right ventricular hypertrophy

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease that causes progressive hypoxemia and right heart failure. Pulmonary endarterectomy has been established as an effective treatment for operable CTEPH (1), while inoperable CTEPH is treated by balloon pulmonary angioplasty and pulmonary vasodilators (2-5).

Pulmonary vasodilators improve exercise tolerance but insufficiently reduce the mean pulmonary artery pressure in patients with CTEPH (5). Balloon pulmonary angioplasty

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significantly improves the symptoms and prognosis in patients with CTEPH (4, 6, 7). Several modalities, including echocardiography, magnetic resonance imaging, and single-photon emission computed tomography, in addition to right heart catheterization as the golden standard examination for pulmonary hypertension, have been used to evaluate the effectiveness of balloon pulmonary angioplasty in CTEPH (8-10). The 12-lead electrocardiogram is the simplest, most widely available diagnostic tool for cardiovascular diseases. Electrocardiogram is useful for the diagnosis of right ventricular hypertrophy and for evaluating the survival rate in patients with pulmonary hypertension (11-14). There have only been a few reports about the influence of balloon pulmonary angioplasty on electrocardiogram findings. Therefore, we investigated the electrocardiographic criteria of right ventricular hypertrophy after balloon pulmonary angioplasty in patients with CTEPH.

Materials and Methods

Twenty-two consecutive patients with CTEPH who underwent balloon pulmonary angioplasty between September 2012 and March 2018 at Fukushima Medical University Hospital were enrolled. Three patients died during this period, so we ultimately included the other 19 patients as successful cases in this study. The baseline data of age, sex, body mass index, World Health Organization (WHO) functional class, medical history, laboratory data, echocardiographic data, current medications, and hemodynamic data by cardiac catheterization were collected at the time of enrollment in this study. The WHO functional class, levels of brain natriuretic peptide, and hemodynamics were also measured before and after balloon pulmonary angioplasty.

This study was approved by the institutional ethics committee of Fukushima Medical University. Written informed consent was provided by all patients.

Electrocardiogram

Twelve-lead electrocardiograms were recorded with patients in the supine position at a paper speed of 25 mm/s and with a sensitivity of 1 mV=10 mm before and after balloon pulmonary angioplasty. Electrocardiograms were evaluated by an expert cardiologist. The QTc interval was calculated using the Bazett formula ($QTc = QT/\sqrt{RR}$). Left axis deviation was defined as a QRS axis between −30° and −90°, and right axis deviation was defined as a QRS axis between +90° and +180° (15). The criteria associated with right ventricular hypertrophy were measured according to the American Heart Association recommendations of the electrocardiogram: tall R in V_1>6 mm; increased R:S ratio in V_1>1.0; deep S in V_5>10 mm; deep S in V_6>3 mm; tall R in aV_R>4 mm; small S in V_1<2 mm; small R in $V_{5, 6}$<3 mm; reduced R:S ratio in V_5<0.75; reduced R:S ratio in V_6<0.4; reduced R:S in V_5 to R:S in V_1<0.04; (R1+SIII)-(SI+RIII) <15 mm; max R in $V_{1, 2}$+max S in I, aV_L-S in V_1>6 mm; R in V_1 +S in $V_{5, 6}$>10.5 mm; R peak in V_1>0.035 s; and QR in V_1 present (16).

Echocardiography

Echocardiography was performed by an experienced echocardiographer using the standard techniques (17). The echocardiographic criteria investigated included the left ventricular diastolic diameter and tricuspid regurgitation peak gradient. The left ventricular ejection fraction was measured using the modified biplane Simpson's method. The right ventricular wall thickness was measured in the subcostal view using two-dimensional imaging (18).

Right heart catheterization and balloon pulmonary angioplasty

Right heart catheterization was performed using a 6- or 7-Fr Swan-Ganz catheter. In balloon pulmonary angioplasty, we used a plastic jacket wire to penetrate the obstructive lesions and then replaced it with a conventional guide wire using a micro catheter to avoid peripheral perforation before obstruction by intravascular ultrasound and balloon expansion. The optimal balloon size was determined after measuring the vessel diameter by intravascular ultrasound. The endpoints of ballooning were an improvement in the blood flow by intravascular ultrasound with color Doppler or pulmonary venous return confirmed by angiography. In each session, the vessels from a maximum of two branches selected from only one side of the lung were treated. Patients were hospitalized and underwent balloon pulmonary angioplasty several times to finally achieve a mean pulmonary artery pressure <30 mmHg. The interval of each session was generally two to four weeks.

Statistical analyses

Data were analyzed using the Statistical Package for Social Sciences version 25 software program (SPSS, Chicago, USA). Continuous data are expressed as the mean±standard deviation, and skewed data are presented as the median and interquartile range. Categorical variables are expressed as numbers and percentages. The statistical significance of differences was analyzed using Student's *t*-test for parametric continuous variables and the Mann-Whitney U-test for nonparametric continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test. The paired samples were analyzed using the paired *t*-test for parametric continuous variables and Wilcoxon's signed rank test for nonparametric continuous variables. Correlations were analyzed using a Spearman's correlation analysis for variables. A p value of <0.05 was considered statistically significant.

Results

Table 1 shows the baseline characteristics of 19 patients in this study. The mean number of balloon pulmonary angioplasty sessions was 4.8. We analyzed the parameters to assess the severity of CTEPH before and after the last ses-

sion of balloon pulmonary angioplasty. As shown in Table 2, the brain natriuretic peptide level (p=0.001), right ventricular wall thickness (p=0.025), and mean pulmonary artery pressure (p<0.001) were decreased, while the cardiac index (p=0.025) was increased after balloon pulmonary angioplasty. The WHO functional class was improved after balloon pulmonary angioplasty (p<0.001). During the follow-up period (mean period, 1,284±650 days), all 19 patients survived.

We applied 15 criteria for right ventricular hypertrophy to the patients before and after balloon pulmonary angioplasty. The mean period from the first balloon pulmonary angioplasty to the electrocardiogram after the last balloon pulmonary angioplasty was 378±348 days. As shown in Table 3, the mean numbers of right ventricular hypertrophy criteria in each patient were significantly decreased after balloon pulmonary angioplasty from 4.8±2.6 to 3.1±2.5 (p=0.003). The heart rate (p=0.004) and the number of patients who met the criteria for right axis deviation (p=0.014), deep S in V_6 (p=0.005), and max R in $V_{1, 2}$+max S in I, aV_L-S in V_1 (p=0.046) were significantly decreased after balloon pulmonary angioplasty. The number of patients who met the criteria for normal axis deviation was significantly increased after balloon pulmonary angioplasty (p=0.014). A representative electrocardiogram is shown in Figure. These data suggest that right ventricular hypertrophy was improved after balloon pulmonary angioplasty.

Table 4 shows the correlations between hemodynamics and the mean numbers of right ventricular hypertrophic criteria met by each patient. The mean numbers of right ventricular hypertrophic criteria met by each patient were significantly correlated with the cardiac index (r=−0.496, p=0.036) but not with the mean pulmonary artery pressure (r=0.172, p=0.481).

Table 1. Baseline Characteristics.

	n=19
Age, years	64±10
Male	4 (21%)
BMI, kg/m^2	23±4
Hypertension	10 (53%)
Diabetes mellitus	4 (21%)
Laboratory data	
eGFR, mL/min/1.73 m^2	63±11
Echocardiography	
LVDd, mm	36±5
LVEF, %	66±8
TRPG, mmHg	76±25
Oral medication	
Pulmonary vasodilators	17 (90%)
Number of BPA sessions	4.4±2.3

Values are mean±SD.

BMI: body mass index, eGFR: estimated glomerular filtration rate, IQR: interquartile range, LVDd: left ventricular diastolic diameter, LVEF: left ventricular ejection fraction, TRPG: tricuspid regurgitation peak gradient, BPA: balloon pulmonary angioplasty

Discussion

The present study showed improvement in right ventricular hypertrophy according to the electrocardiographic criteria in patients with CTEPH, reflecting a reduced right ventricular pressure overload after balloon pulmonary angioplasty. CTEPH is a progressive disorder associated with poor clinical outcomes (19, 20). A previous study reported that balloon pulmonary angioplasty was able to improve the long-term prognosis in CTEPH patients, with many having improved symptoms and hemodynamics (6). However, no study has applied electrocardiographic criteria of right ventricular hypertrophy in CTEPH after balloon pulmonary angioplasty. This study is the first to evaluate balloon pulmonary angioplasty while using the electrocardiographic criteria for right ventricular hypertrophy in CTEPH patients.

The 12-lead electrocardiogram is the simplest and most widely available type of clinical diagnostic test. Electrocardiographic abnormalities can be a predictor of death in pulmonary hypertension (12-14). In pulmonary hypertension patients, it has been reported that changes in the R wave and the presence of qR in lead V_1 predict the sur-

Table 2. Changes in Severity of CTEPH.

	Before BPA	After BPA	p value
WHO class, I/II/III/IV	0/3/16/0	6/13/0/0	<0.001
BNP, pg/mL*	169 (47-495)	28 (13-71)	0.001
Echocardiography			
RV wall thickness, mm	5.9±1.0	5.4±0.8	0.025
Hemodynamics			
Mean PAP, mmHg	45±8	28±7	<0.001
Mean PCWP, mmHg	10±5	9±4	0.567
Cardiac index, L/min/m^2	2.4±0.8	2.8±0.8	0.025

Values are mean±SD, *median (IQR), or number.

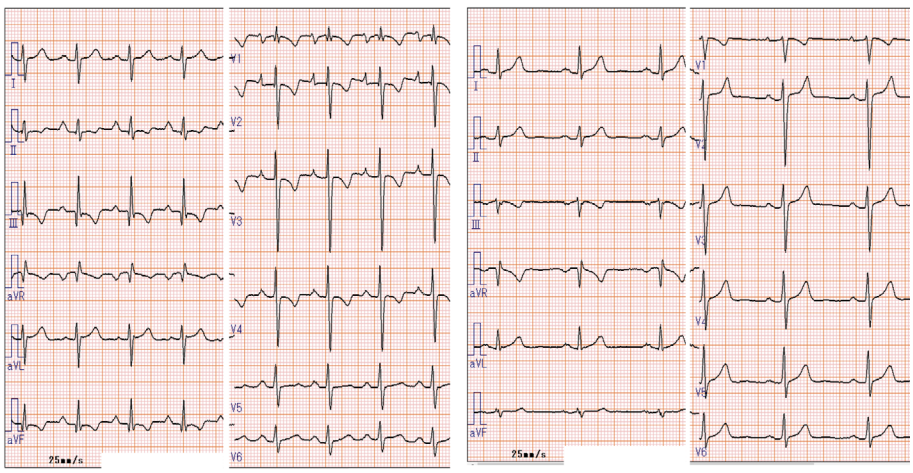
CTEPH: chronic thromboembolism pulmonary hypertension, WHO: World Health Organization, BNP: brain natriuretic peptide, IQR: interquartile range, PAP: pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, RV: right ventricular

Table 3. Electrocardiographic Findings.

	Before BPA	After BPA	p value
Heart rate, bpm	83±12	73±14	0.004
QTc, ms	447±31	436±24	0.102
Axis			
Normal axis deviation	8 (36)	14 (64)	0.014
Left axis deviation	0 (0)	0 (0)	-
Right axis deviation	11 (58)	5 (31)	0.014
Electrocardiographic RVH criteria			
Tall R V_1	10 (53)	6 (32)	0.102
Increased R:S ratio V_1	9 (47)	7 (37)	0.157
Deep S V_5	4 (21)	2 (11)	0.317
Deep S V_6	10 (53)	2 (11)	0.005
Tall R in aV_R	2 (11)	1 (5)	0.317
Small S V_1	5 (26)	3 (16)	0.414
Small R $V_{5, 6}$	0 (0)	1 (5)	0.317
Reduced R:S ratio V_5	2 (11)	0 (0)	0.157
Reduced R:S ratio V_6	0 (0)	0 (0)	-
Reduced R:S V_5 to R:S V_1	0 (0)	0 (0)	-
(R1+SIII)-(SI+RIII)	17 (90)	17 (90)	1.000
Max R $V_{1, 2}$+max SI, aV_L-SV_1	12 (63)	8 (42)	0.046
RV_1+$SV_{5, 6}$	11 (58)	6 (32)	0.096
R peak V_1 (QRS duration<0.12 s)	5 (26)	3 (16)	0.414
QR V_1	4 (21)	2 (11)	0.317
Mean numbers of RVH criteria in each patient	4.8±2.6	3.1±2.5	0.003

Values are mean±SD, number (%).

RVH: right ventricular hypertrophic



a. b.

Figure. Representative electrocardiograms in a patient with chronic thromboembolic pulmonary hypertension. (a) The electrocardiogram before balloon pulmonary angioplasty shows deep S in V_6, tall R in aV_R, small S in V_1, (R1+SIII)-(SI+RIII), max R in $V_{1, 2}$+max SI in aV_L-S in V_1, and R in V_1+S in $V_{5, 6}$ among the criteria of right ventricular hypertrophy. (b) The electrocardiogram after balloon pulmonary angioplasty shows only (R1+SIII)-(SI+RIII) among the criteria of right ventricular hypertrophy.

vival (12, 14). R/S >1 or qR in V_1 among various electrocardiographic parameters may be the most sensitive predictor for pulmonary hypertension-associated right ventricular dysfunction and the therapeutic response to pulmonary hypertension vasodilators (21, 22). Electrocardiograms of CTEPH patients change after pulmonary endarterectomy, reflecting right ventricular hemodynamic overload (23). There have only been a few reports on the changes in electrocardio-

Table 4. Correlation between Mean Numbers of Right Ventricular Hypertrophic Criteria Met by Each Patient and Hemodynamics.

	r	p value
Mean pulmonary artery pressure	0.172	0.481
Cardiac index	-0.496	0.036

grams after balloon pulmonary angioplasty. Only one report described the electrocardiographic changes after balloon pulmonary angioplasty and implied that R in V_1+S in V_5 is associated with a better functional status at follow-up (24). In the present study, we revealed changes in several right ventricular hypertrophic criteria for electrocardiograms after balloon pulmonary angioplasty, which were in accordance with a significant decrease in the right ventricular wall thickness. The right ventricular function is a significant prognostic factor in CTEPH (8). Electrocardiographic changes observed after balloon pulmonary angioplasty were correlated with the improvement of hemodynamics (24). Based on the present findings, a decrease in the mean number of right ventricular hypertrophic criteria might well reflect right ventricular remodeling after balloon pulmonary angioplasty.

In this study, the number of patients who met the criteria for deep S in V_6 or max R in $V_{1, 2}$+max S in I, aV_L-S in V_1 was significantly decreased after balloon pulmonary angioplasty. The number of patients who had an increased R:S ratio in lead V_1 was not significantly changed after balloon pulmonary angioplasty. Among the criteria of right ventricular hypertrophy, we should take care in interpreting the correlation of deep S in V_6 or max R in $V_{1, 2}$+max S in I, aV_L-S in V_1 after balloon pulmonary angioplasty with remodeling of the right ventricle.

This study has several limitations. First, the number of subjects was relatively small, so larger prospective studies will be necessary in order to assess changes in electrocardiograms and the correlation between the electrocardiographic findings and hemodynamics. Second, many patients were treated with pulmonary vasodilators, and the improvement in the WHO functional status, hemodynamics, and resultant electrocardiograms was caused by not only balloon pulmonary angioplasty but also pulmonary vasodilators.

In conclusion, balloon pulmonary angioplasty improved symptoms, hemodynamics, and remodeling of the right ventricle in patients with CTEPH. Applying electrocardiographic criteria may be a simple and easy way to evaluate right ventricular hypertrophy after balloon pulmonary angioplasty.

The authors state that they have no Conflict of Interest (COI).

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