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Prolonged QRS duration as a predictor of right ventricular dysfunction after balloon pulmonary angioplasty☆

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ABSTRACT

Background: Balloon pulmonary angioplasty (BPA) has shown beneficial effects for chronic thromboembolic pulmonary hypertension (CTEPH). However, previous studies have shown less cardiac output improvement and symptoms remaining after BPA, implying poor right ventricular (RV) function recovery. Therefore, we investigated the residual RV dysfunction after BPA to reveal risk factors, clinical effects, and possible underlying histopathological mechanisms.

Methods and results: We investigated 61 consecutive CTEPH patients who underwent cardiovascular magnetic resonance before and 3 and 12 months after BPA series. Residual dysfunction (RD) of RV was defined as RV end-diastolic volume index >100 ml/m^2 or RV ejection fraction (EF) <45% at 12-month follow-up. Patients were divided into RD (44%) and normalized dysfunction (ND) (56%) groups.

Compared with the ND group, the RD group had significantly worse World Health Organization (WHO) functional class at follow-up. No significant hemodynamic differences were observed between the groups. On multivariable logistic regression analysis, male sex (odds ratio [OR] 12.5, $p = 0.004$) and prolonged QRS duration (OR 1.08, $p = 0.029$) were independently associated with residual RV dysfunction. Additionally, RV histopathology in 11 CTEPH autopsy cases showed that QRS duration was correlated with RV fibrosis area.

Conclusions: Relatively high percentage (44%) of residual RV dysfunction with worse WHO functional class was observed in CTEPH patients even after BPA. Prolonged QRS duration may predict poor recovery in RV function after BPA.

1. Introduction

Right ventricular (RV) function is a major determinant of symptoms, functional capacity, and prognosis in pulmonary hypertension (PH) [1,2]. Chronic pressure and volume overload of RV in PH induce RV remodeling and dysfunction, resulting in exercise limitations, renal and liver dysfunction, arrhythmias, acute heart failure, and sudden cardiac death. Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening disease characterized by high pulmonary vascular resistance due to organized thrombi and leads to progressive right heart failure and death if untreated [3].

Pulmonary endarterectomy (PEA) is the gold standard for the treatment of CTEPH [4,5]. While PEA improves CTEPH prognosis, previous studies have indicated that RV dysfunction is improved but not normalized after PEA [6,7]. In the United Kingdom national PEA cohort

Abbreviations: BNP, brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CAF, collagen area fraction; CI, confidence interval; CMR, cardiovascular magnetic resonance; CTEPH, chronic thromboembolic pulmonary hypertension; ECG, electrocardiography; EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; LV, left ventricle; ND, normalized dysfunction; OR, odds ratio; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RD, residual dysfunction; RHC, right heart catheterization; ROC, receiver operating characteristics; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization functional class.

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(n = 880), 82 of the patients who survived surgery died during the follow-up period (4.3 ± 3.6 years) and 29 of these deaths were caused by RV failure [8]. Residual RV dysfunction after PEA might be multifactorial, resulting not only from afterload burden, but also from myocardial injury caused by deep hypothermic circulatory arrest during surgery.

Recently, we and others reported that balloon pulmonary angioplasty (BPA) could improve symptoms, hemodynamics, exercise capacity, and prognosis of patients with CTEPH in a less invasive manner than PEA [9–11]. Our previous pilot study, which composed of small number of patients and short-term follow-up, revealed that BPA induced RV reverse remodeling by ameliorating hemodynamics in patients with inoperable CTEPH [12]. However, the extent of RV reversibility varied among individuals. Moreover, previous studies showed limited improvement in cardiac output and symptoms remaining in long-term after BPA [13]. Thus, the present study focused on the variability of RV response, and we aimed to clarify the frequency, clinical characteristics, and predictors of residual RV dysfunction following BPA in patients with CTEPH in larger and longer follow-up cohort using cardiovascular magnetic resonance (CMR) imaging.

2. Methods

2.1. Study design and subjects

We retrospectively investigated 61 consecutive patients for whom quantitative cardiovascular magnetic resonance (CMR) imaging was obtained before and 3 and 12 months after the final BPA between August 2012 and January 2017 to evaluate the prevalence, clinical characteristics, and predictors of residual RV dysfunction. All patients complained of dyspnea on effort that was more severe than World Health Organization functional class (WHO-FC) II. CTEPH was diagnosed according to the WHO guideline at Nice in 2013 [14]. PEA operability was determined by the CTEPH multidisciplinary team at the National Cerebral and Cardiovascular Centre, Suita, Osaka, Japan, which comprised cardiologists specializing in CTEPH, radiologists, BPA interventionists, and PEA surgeons. Patients who underwent BPA due to residual PH after PEA were excluded from this study. The BPA procedure has been described previously (Supplementary material S1) [9]. We selected the target vessels on the basis of pulmonary digital subtraction angiography and cone-beam computed tomography/area-detector computed tomography [15]. We selectively introduced a 6-French multipurpose guiding catheter (Mach1 Peripheral MP; Boston Scientific, Natick, MA, USA). After passing a 0.014-inch guide wire (Cruse; Asahi Intecc, Tokyo, Japan) through the targeted lesion, we inflated the balloons (IKAZUCHI PAD; Kaneka, Osaka, Japan) until the indentation disappeared. The appropriate balloon size (ranging from 2.0 to 6.0 mm) was determined based on the targeted vessel diameter. Treatment during the first session was limited to one to two segments in one lobe to prevent severe reperfusion pulmonary edema after BPA. BPA was repeated until mean pulmonary arterial pressure (PAP) of <30 mm Hg was achieved in a stepwise manner. This study complies with the principles of the Declaration of Helsinki and was approved by the institutional ethics committee. All patients provided written informed consent.

2.2. Data collection

We collected data from the patients' medical records, including demographic profile, previous medical history, baseline characteristics, medical treatment, and procedures. All patients were followed up at 3 and 12 months after the final BPA, and underwent examinations, including the brain natriuretic peptide (BNP) test, chest radiography, electrocardiography (ECG), 6-minute walk distance (6MWD) test, trans-thoracic echocardiography, right heart catheterization, and simultaneous CMR recording. The mean pulmonary capillary wedge pressure, PAP, right atrial pressure, cardiac output, and pulmonary vascular resistance (PVR) were measured using right heart catheterization (RHC). Cardiac output was determined using the Fick method and corrected for body surface area.

2.3. CMR imaging and volumetric analysis

CMR imaging was performed with a standardized clinical protocol on a 1.5-T system (Magneton Sonata; Siemens, Erlangen, Germany) [12]. Cine imaging was acquired using a true-FLISP sequence (echo time 1.3 ms, repetition time 2.6 ms, flip angle 60°, slice thickness 8 mm, gap width 2 mm, in-plane resolution 4.17 × 2.73 mm) with multiple breath-holds in contiguous short-axis and trans-axial slices that encompassed both ventricles and three standard long-axis slices. Prospective ECG gating was performed using the R-wave as a trigger. To quantify the RV end-diastolic volume (RVEDV), RV end-systolic volume (RVESV), RV stroke volume, and RV ejection fraction (EF), two experienced radiologists manually traced the RV endocardial and epicardial contours in the end-systolic and end-diastolic frames of trans-axial slices using dedicated software (Argus; Siemens Erlangen, Germany). Left ventricular (LV) volumes were determined in the same manner but using short-axis slices. All cardiac volumes and masses were corrected for body surface area. CMR has shown good reproducibility for LV and RV volumes and functions [16,17].

2.4. Definitions of RV dysfunction

Residual RV dysfunction following BPA was defined as RVEDVI of >100 ml/m^2 or RVEF of <45%, based on previous studies [12,18]. We divided the patients into two groups according to the CMR findings at 12-month follow-up (Supplementary material S2): residual dysfunction (RD) and normalized dysfunction (ND) groups.

2.5. Histopathological analysis

To clarify the underlying mechanisms of prediction for residual RV dysfunction, we performed RV histopathological analysis in a series of 11 CTEPH autopsy cases (female 82%, median age 61 [interquartile range 51–64]) at our center. Myocardial collagen accumulation was semi-quantitatively measured in Masson's trichrome-stained sections, as described previously in our laboratory [19,20]. Briefly, photomicrographs of a transverse section of mid-ventricular RV were taken at 20× magnification. We randomly selected 10 images from each of 3 segments (anterior, lateral, and posterior wall), avoiding the sub-endocardial area. Collagen area fraction (CAF) was calculated as the ratio of the total blue-stained area to the whole myocardial area using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

2.6. Statistical analysis

Data were presented as mean ± SD, median with interquartile range, or percentage. The Student's *t*-test was used for between-group comparison of continuous variables with a normal distribution, and the Mann-Whitney *U* test was used for comparison of skewed continuous or discrete variables. Nominal variables were compared using the chi-squared test. The paired *t*-test was used to compare clinical RHC and CMR data between baseline and follow-up. The Wilcoxon singed-rank test was applied to evaluate change in WHO-FC from baseline to follow-up. To evaluate the influence of various factors on residual RV dysfunction, univariable and multivariable logistic regression models were employed. The receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive accuracy. The Pearson's correlation analysis was performed to estimate correlations between QRS duration and RV parameters including RVEDVI, RVEF, and RV CAF. A two-tailed p value < 0.05 was considered to indicate a significant difference. All analyses were performed using SPSS software version 24.0 (IBM Corp., Armonk, NY, USA) and R version 3.1.2 (R Development Core Team; http://www.r-project.org/).

3. Results

3.1. Baseline clinical characteristics

The baseline clinical characteristics of the patients are summarized in Table 1. In the cohort, 44 patients were female, the median age was 69 (interquartile range 61–77) years, and the mean BNP level was 133 ± 154 pg/ml. WHO-FC II, III, and IV were observed in 23%, 72%, and 5% of the patients, respectively. PH-specific drugs were used in 72% of the patients.

3.2. BPA effects on clinical, hemodynamic, and CMR parameters

A series of BPA (mean 4.9 ± 1.8 sessions per patients) was performed, with a median duration of 25 (interquartile range 15–67) months from symptom onset to the procedure. As shown in Table 2, BPA significantly improved WHO-FC, 6MWD, and BNP level. BPA decreased mean PAP from 39 ± 9 to 22 ± 5 mm Hg ($p < 0.001$) and PVR from 10.3 ± 4.3 to 4.4 ± 1.8 Wood Units ($p < 0.001$) and increased cardiac index from 2.3 ± 0.6 to 2.6 ± 0.6 l/min/m^2 ($p < 0.001$). CMR imaging indicated that BPA significantly reduced RVEDVI from 113 ± 45 to 75 ± 17 ml/m^2 ($p < 0.001$) and RV end-systolic volume index (ESVI) from 75 ± 38 to 41 ± 14 ml/m^2 ($p < 0.001$), with concomitant improvement in RVEF from 36 ± 9 to 46 ± 8% ($p < 0.001$). RVEDVI reduced gradually over a year, whereas RVEF improved within 3 months after BPA series (Supplementary material S3).

3.3. Comparison of clinical parameters between the RD and ND groups

On CMR examination, RV dysfunction remained in 27 patients (RD group, 44%), while it was normalized in 34 patients (ND group, 56%) at 12-month follow-up after BPA series. We compared the baseline clinical characteristics between the two groups (Table 1) and found no significant differences in age, body mass index, history of comorbidity, history of smoking, WHO-FC, 6MWD, or cardiothoracic ratio on chest

Table 1
Baseline clinical characteristics.

Variables	Total (n = 61)	RD group (n = 27)	ND group (n = 34)	p value
Age at BPA (years, IQR)	69 (61–77)	66 (53–78)	71 (64–76)	0.323
Female/male (n, %)	44 (72%)/17 (28%)	12 (44%)/15 (56%)	32 (94%)/2 (6%)	<0.001
Body mass index (kg/m^2, SD)	22 ± 3	21 ± 3	22 ± 3	0.190
Comorbidity				
Hypertension (n, %)	25 (41%)	10 (37%)	15 (44%)	0.580
Dyslipidemia (n, %)	21 (34%)	8 (30%)	13 (38%)	0.486
Diabetes mellitus (n, %)	4 (7%)	2 (7%)	2 (6%)	0.813
Stroke (n, %)	1 (2%)	1 (4%)	0 (0%)	0.262
Malignancy (n, %)	7 (12%)	2 (7%)	5 (15%)	0.378
Smoking (n, %)	19 (31%)	11 (41%)	8 (24%)	0.153
Clinical parameters				
WHO-FC II/III/IV (n)	14/44/3	7/19/1	7/25/2	0.565
Six-minute walk distance (m, SD)	390 ± 108	415 ± 114	370 ± 100	0.126
B-type natriuretic peptide (pg/ml, SD)	133 ± 154	197 ± 200	85 ± 79	0.004
Cardio thoracic ratio on chest radiography (%, SD)	52 ± 6	52 ± 7	53 ± 5	0.973
ECG parameters				
PR duration (ms)	168 ± 23	174 ± 25	164 ± 19	0,091
P wave amplitude in II (uV)	211 ± 62	215 ± 68	208 ± 56	0.671
QRS duration (ms)	103 ± 17	111 ± 20	96 ± 9	<0.001
QRS axis (degree)	75 ± 47	83 ± 52	69 ± 42	0.271
R/S ration >1 in V1 (n, %)	24 (39%)	15 (56%)	9 (26%)	0.021
S wave amplitude in V5 (uV)	810 ± 419	889 ± 409	747 ± 422	0.190
Right bundle branch block (n, %)	9 (15%)	5 (19%)	4 (12%)	0.494
QT duration (ms)	444 ± 27	449 ± 34	440 ± 20	0.214
Medication				
PH specific therapy (n, %)	44 (72%)	22 (82%)	22 (65%)	0.150
Endothelin receptor antagonist (n, %)	11 (18%)	7 (26%)	4 (12%)	0.156
Soluble guanylate cyclase stimulator (n, %)	19 (31%)	7 (26%)	12 (35%)	0.436
Phosphodiesterase type-5 inhibitor (n, %)	6 (10%)	2 (7%)	4 (12%)	0.573
Oral prostacyclin agonist (n, %)	26 (43%)	14 (52%)	12 (35%)	0.198
Intravenous epoprostenol (n, %)	0 (0%)	0 (0%)	0 (0%)	NA
BPA				
Duration from onset to BPA (months, IQR)	25 (15–67)	46 (19–88)	20 (13–51)	0.042
Total BPA sessions (number, SD)	4.9 ± 1.8	5.3 ± 1.8	4.6 ± 1.8	0.127

Continuous values are expressed as mean ± SD or median (IQR). Categorical values are expressed as number and percentages; n indicates the number of patients. BPA, balloon pulmonary angioplasty; ECG, electrocardiography; IQR, interquartile range; PH, pulmonary hypertension; SD, standard deviation; WHO-FC, world health organization functional class.

radiography. The RD group had a higher proportion of male patients and R/S ration >1 in V1, and higher BNP level, more prolonged QRS duration, and longer treatment duration from onset to BPA than the ND group (male, 56% vs. 6%, p < 0.001; R/S ration > 1, 56% vs. 26%, p = 0.021; BNP level, 197 ± 200 vs. 85 ± 79 pg/mL, p = 0.004; QRS duration, 111 ± 20 vs. 96 ± 9 ms, p < 0.001; treatment duration, 46 [19–88] vs. 20 [13–51] months). PH specific drugs were used comparably in both groups.

Table 2
BPA effect on clinical and hemodynamic parameters and CMR findings.

Variables	Total (n = 61)			RD group (n = 27)		ND group (n = 34)		Between-group comparison	
	Before	After	p-Value	Before	After	Before	After	Before p value	After p value
Clinical data									
WHO-FC I/II/III/IV (n)	0/14/44/3	12/36/13/0	<0.001	0/7/19/1	3/16/8/0	0/7/25/2	9/21/4/0	0.565	0.042
BNP level (pg/ml)	133 ± 154	33 ± 32	<0.001	197 ± 200	33 ± 39	85 ± 79	42 ± 25	0.004	0.987
RHC data									
Heart rate (beats/min)	73 ± 14	67 ± 11	0.001	73 ± 16	66 ± 9	73 ± 14	69 ± 12	0.839	0.295
Mean RAP (mm Hg)	3.2 ± 2.1	2.3 ± 1.5	0.003	3.0 ± 2.0	2.0 ± 1.3	3.3 ± 2.2	2.4 ± 1.7	0.685	0.265
Systolic PAP (mm Hg)	71 ± 18	42 ± 10	<0.001	72 ± 17	42 ± 11	71 ± 20	41 ± 10	0.890	0.732
Diastolic PAP (mm Hg)	22 ± 5	13 ± 4	<0.001	22 ± 6	14 ± 4	23 ± 7	13 ± 4	0.487	0.557
Mean PAP (mm Hg)	39 ± 9	22 ± 5	<0.001	39 ± 8	22 ± 5	39 ± 9	22 ± 5	0.820	0.844
SaO_2 (%)	90 ± 5	94 ± 3	<0.001	90 ± 5	94 ± 3	89 ± 4	94 ± 3	0.358	0.226
SvO_2 (%)	62 ± 8	70 ± 6	<0.001	61 ± 8	70 ± 4	64 ± 7	70 ± 6	0.246	0.983
Cardiac Index (l/min/m^2)	2.3 ± 0.6	2.6 ± 0.6	<0.001	2.2 ± 0.6	2.6 ± 0.5	2.3 ± 0.6	2.6 ± 0.7	0.391	0.916
PVR (Wood unit)	10.3 ± 4.3	4.4 ± 1.8	<0.001	10.0 ± 4.5	4.2 ± 1.6	10.4 ± 4.3	4.5 ± 2.0	0.789	0.477
CMR findings									
RVEDVI (ml/m^2)	113 ± 45	75 ± 17	<0.001	132 ± 53	81 ± 19	99 ± 30	70 ± 13	0.003	0.012
RVESVI (ml/m^2)	75 ± 38	41 ± 14	<0.001	92 ± 44	50 ± 14	61 ± 24	34 ± 7	0.001	<0.001
RVEF (%)	36 ± 9	46 ± 8	<0.001	32 ± 8	39 ± 6	39 ± 8	51 ± 4	<0.001	<0.001
LVEDVI (ml/m^2)	64 ± 15	48 ± 14	<0.001	67 ± 16	53 ± 13	61 ± 13	46 ± 12	0.106	0.029
LVESVI (ml/m^2)	28 ± 9	26 ± 7	0.092	32 ± 10	29 ± 7	25 ± 7	24 ± 7	0.007	0.012
LVEF (%)	56 ± 7	59 ± 6	0.009	53 ± 8	56 ± 6	58 ± 5	61 ± 5	0.006	0.002

Values are expressed as mean ± SD. 6MWD, 6 minute walk distance; BNP, brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CMR, cardiovascular magnetic resonance; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; ND, normalized dysfunction; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterisation; RD, residual dysfunction; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index; SaO_2, aortic oxygen saturation; SvO_2, mixed venous oxygen saturation; WHO-FC, World Health Organization functional class.

Two patients died after the follow-up. One of the patients in RD group suddenly died, and the other in ND group died of gastrointestinal bleeding. The RD group had significantly worse WHO-FC at follow-up (Supplementary material S4). There were no significant differences in the hemodynamic findings between the two groups at either baseline or follow-up as shown in Table 2. However, the RD group had higher RVEDVI, RVESVI, and LVESVI, and lower RVEF and LVEF, at both baseline and follow-up. Moreover, the RD group had significantly lower RVEF improvement than the ND group (the change in RVEF, 6.9 ± 9.7% vs. 12.0 ± 8.7%, p = 0.033).

3.4. Predictors of residual RV dysfunction following BPA

To identify the clinical predictors of residual RV dysfunction after BPA, we performed univariable logistic regression analysis using the following 13 variables: age at BPA, sex, BNP level, duration from symptom onset to BPA, total number of BPA sessions, mean right atrial pressure, mean PAP, diastolic PAP, PVR, PR duration, QRS duration, R/S ration > 1 in V1 and S wave amplitude in V5 (Table 3). Variables with a p value < 0.25 in the univariable analysis were then evaluated using multivariable logistic regression models with the forward stepwise selection method. Multivariable analysis indicated that male sex and QRS duration at baseline were independently associated with residual RV dysfunction after BPA (male sex, odds ratio [OR] 12.5, 95% confidence interval [CI] 2.25–60.3, p = 0.004; QRS duration, OR 1.08, 95% CI 1.01–1.15, p = 0.029). The ROC curve analysis for QRS duration at baseline for residual RV dysfunction is shown in Supplementary material S5. Baseline QRS duration demonstrated good predictive accuracy (area under the curve 0.785, 95% CI 0.669–0.901, p < 0.001, cut-off value 102 ms). Male patients had lower RVEF (39 ± 7 vs. 48 ± 7%, p < 0.001) and comparable RVEDVI (79 ± 15 vs. 73 ± 18 ml/m^2, p = 0.179) despite having lower PVR than their female counterparts (Supplementary material S6). Patients with prolonged QRS duration (>102 ms) at baseline had larger RV volumes (RVEDVI, 82 ± 18 vs. 69 ± 14 ml/m^2, p = 0.002; RVESVI, 49 ± 14 vs. 35 ± 9 ml/m^2, p < 0.001) and lower RVEF (41 ± 8 vs. 50 ± 5%, p < 0.001) at follow-up than patients with narrow QRS duration despite comparable hemodynamic status (Supplementary material S6). Baseline QRS duration was correlated with follow-up RVEDVI and RVEF (Supplementary material S7). Additionally, the cut-off values of RVEF and RVEDVI at baseline for residual RV dysfunction were calculated as 41% and 104 ml/m^2, respectively, using the ROC curve analysis.

Table 3
Predictors for residual RV dysfunction.

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age at BPA	0.97 (0.93–1.02)	0.371		
Male	20.0 (3.97–100.8)	0.001	12.5 (2.25–60.3)	0.004
BNP level	1.01 (1.00–1.01)	0.014		
Duration from onset to BPA	1.01 (1.00–1.02)	0.103		
Total BPA sessions	1.26 (0.93–1.69)	0.131		
Mean RAP	0.95 (0.74–1.21)	0.682		
Mean PAP	0.993 (0.99–1.05)	0.816		
Diastolic PAP	1.04 (0.94–1.15)	0.481		
PVR	0.98 (0.88–1.11)	0.784		
PR duration	1.02 (0.99–1.05)	0.086		
QRS duration	1.11 (1.04–1.19)	0.002	1.08 (1.01–1.15)	0.029
R/S ratio > 1 in V1	3.47 (1.18–10.2)	0.023		
S wave amplitude in V5	2.30 (0.66–8.07)	0.191		

BNP, Brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CI, confidence interval; OR, odds ratio; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

3.5. Histopathological analysis from CTEPH autopsy cases

To clarify the underlying mechanisms of prolonged QRS duration in residual RV dysfunction, we evaluated the correlation between QRS duration and the extent of RV fibrosis in a series of 11 CTEPH autopsy cases collected from 1989 to 2014 at our center. Clinical characteristics and hemodynamic data of 11 deceased patients with CTEPH who were autopsied are shown in Supplementary material S4. Compared with the CMR cohort of the present study, CTEPH autopsy cases included a higher proportion of female patients (82% vs. 69%) and had higher mean PAP (47 ± 4 vs. 40 ± 10 mm Hg), higher PVR (14.5 ± 5.1 vs. 10.5 ± 4.9 Wood Units), and lower cardiac index (1.9 ± 0.6 vs. 2.3 ± 0.6 L/min/m^2). RV histopathological evaluation in autopsy cases revealed interstitial fibrosis (mean RV CFA, 15.7 ± 5.5%), which was significantly correlated with QRS duration (R = 0.664, p = 0.026) (Fig. 1).

4. Discussion

The major findings of the present study are that in patients with CTEPH, 1) RV dysfunction remained in 44% of the patients despite hemodynamic improvement at 12 months after the final BPA, 2) male sex and prolonged QRS complex were independent risk factors for residual RV dysfunction after BPA, and 3) additional histopathological analysis revealed that QRS duration was correlated with RV fibrosis area.

4.1. Residual RV dysfunction

Residual RV dysfunction after a treatment of CTEPH has not been evaluated in detail but may affect clinical outcomes. In evaluating the changes in RV function before and after PEA, tricuspid annular plane systolic excursion (TAPSE) was found to be improved, although the assessment of RV function using TAPSE is limited by pericardial adhesions and the change in overall heart motion (rocking motion) after surgery [21]. CMR imaging, the gold standard for the assessment of RV volume and function, has revealed that RV function is improved but not normalized after PEA, although the frequency of residual RV dysfunction has not been reported [6,7]. RV function after PEA might be multifactorial, resulting from myocardial damage due to deep hypothermic circulatory arrest during PEA as well as other factors such as cytokines during the open surgery. Residual RV dysfunction can be more thoroughly assessed after BPA because it is a less invasive procedure. In the present study, we revealed BPA improved RV volume and function overall in average, consistent to our previous report [12]. However, we also found a high incidence (44%) of unrecognized residual RV dysfunction at 12-month follow-up even after hemodynamic improvement after a series of BPA, that is because this study had larger and longer follow-up cohort. Additionally, we considered that the RD group may have had advanced and irreversible RV remodeling and dysfunction before the BPA treatment since they had significantly lower RVEF improvement than the ND group. To our knowledge, this report is the first to identify the exact frequency of residual and progressive RV dysfunction following hemodynamic improvement in CTEPH patients treated with BPA.

As shown in Table 2 and Supplementary material S4, WHO functional status was significantly worse in the RD group than in the ND group. RV function is a major determinant of symptoms, functional capacity, and prognosis in pulmonary arterial hypertension (PAH) and CTEPH [1,2]. Poor functional status might result from the reduced RV performance and stroke volume response during exercise [22,23]. Additionally, RD group had unexpected sudden death, and residual RV dysfunction would be associated with long-term poor outcome. In a serial CMR assessment of patients with PAH, the deterioration of RV function was observed in 25% of patients with PVR reduction after PAH medical therapies and was associated with poor survival [24]. Long-term follow-up in a prospective manner is necessary to clarify the impact of residual RV dysfunction on the prognosis of CTEPH following BPA.

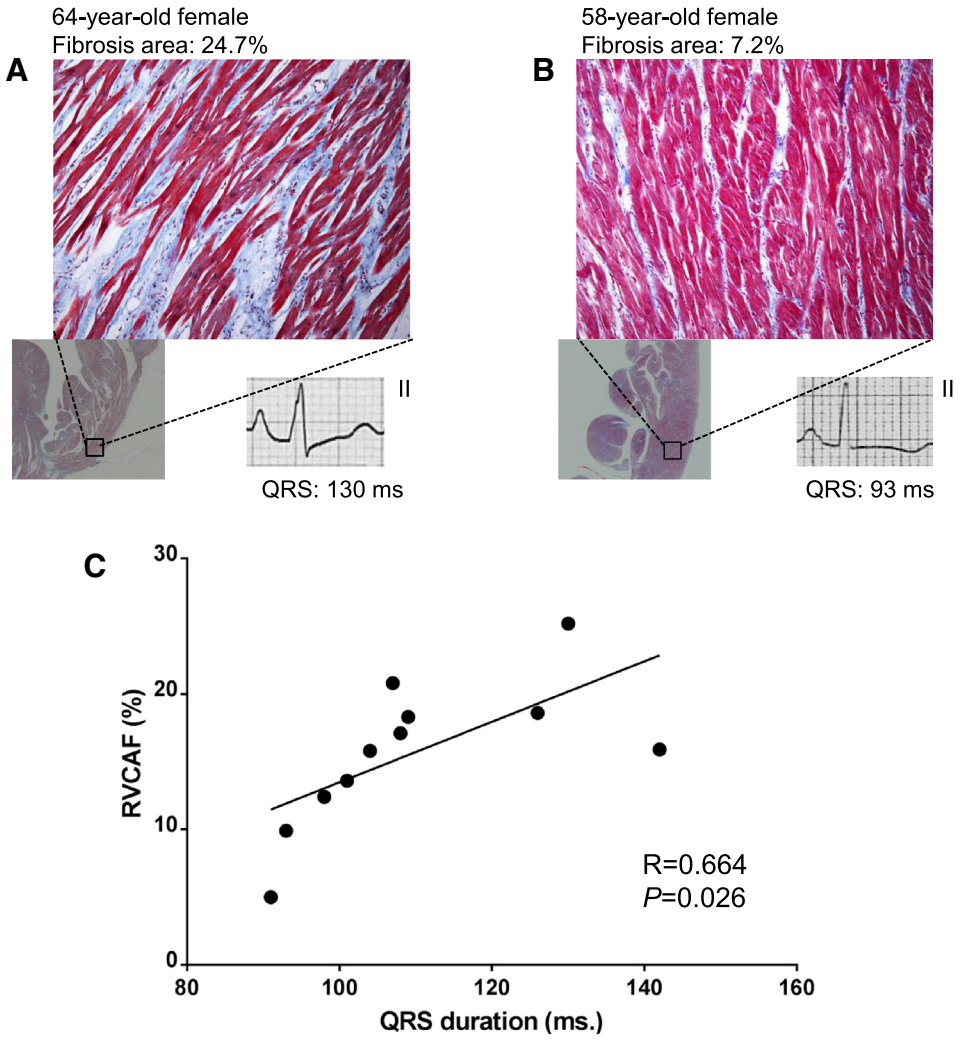

Fig. 1. The correlation of QRS duration with right ventricular collagen area fraction (RV CAF) in autopsy series of chronic thromboembolic pulmonary hypertension (CTEPH). Two representative autopsy cases of CTEPH are shown. A 64-year-old female patient (A) with prolonged QRS complex exhibited severe RV fibrosis (24.7%). In contrast, a 58-year-old female patient (B) with narrow QRS complex exhibited mild RV fibrosis (7.2%). C) Baseline QRS duration was correlated with RV CAF in 11 autopsy cases of CTEPH ($R = 0.664$, $p = 0.026$).

4.2. Prolonged QRS duration

One of the most notable findings in this study was that prolonged QRS complex at baseline was independently associated with residual RV dysfunction after BPA. Furthermore, histopathological analysis of CTEPH autopsy cases revealed that the QRS duration was significantly correlated with the extent of RV fibrosis, a hallmark of maladaptive remodeling [25].

In the present study, baseline CMR volumetric data might predict RV reversibility after BPA, but CMR could not be routinely performed. Prolonged QRS duration, simple ECG parameter, might be helpful in predicting myocardial damage of the RV. We examined multivariable analysis for residual RV remodeling after BPA including ECG signs that associated with PH, and identified QRS duration was the only independent predictor. R/S ratio in V1 and S wave amplitude in V5 were known as the evidence of RV hypertrophy. QRS duration would be different from the other ECG parameters. In idiopathic PAH, prolongation of the QRS duration was positively correlated with RV diameter and independently associated with cardiopulmonary mortality [26]. Prolonged QRS duration would reflect the intra-ventricular conduction delay due to progressive remodeling (RV dilatation and fibrosis), which resulted in limited reversibility of RV following hemodynamic improvement. ECG, a non-invasive and convenient examination, may provide valuable information to predict the response to treatment and stratify the clinical risk in patients with CTEPH. To clarify the mechanism underlying the association of QRS duration with the degree of improvement in RV function and volume following BPA, further histological CMR imaging, such as delayed contrast enhancement and T1 mapping, should be performed prospectively [27,28].

4.3. Sex

In the present study, male sex was also independently associated with residual RV dysfunction following BPA. Moreover, male patients had lower RVEF and comparable RVEDVI despite having lower PVR than female patients at baseline (Supplemental material S6). Sex difference in PH has garnered great attention because female patients demonstrate better survival and better RV function than their male counterparts [29]. The superior survival of female patients was associated in part with better RV function [30]. Recent studies in healthy subjects have shown that estrogen metabolites are associated with better RV systolic function, whereas testosterone is associated with higher RV mass, volume, and lower RVEF [31]. However, the association of sex differences with RV adaptation to chronic pressure overload and

response to treatment has not been investigated in detail [32]. The detailed mechanisms of sex differences and potential implications of our findings require further investigation in the future.

4.4. Study limitations

Several limitations of the present study should be noted. First, it was a retrospective cohort study, and the possibility of selection bias could not be avoided. Moreover, the number of patients in this study was relatively small. Therefore, these findings should be confirmed in a larger prospective study. Second, this study included short-term follow-up data. The long-term outcome of residual RV dysfunction after BPA was not addressed in this study. Finally, we examined the histopathological findings of RV fibrosis in 11 CTEPH autopsy cases. These subjects were an entirely different cohort with relatively more severe clinical characteristics.

5. Conclusions

The present findings indicate that RV dysfunction remained with worse symptoms in nearly half of CTEPH patients following BPA and was associated with male sex and prolonged QRS duration at baseline. QRS duration was correlated with the extent of RV fibrosis in histopathological analysis and could be a useful marker to predict poor RV function recovery after BPA.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.026.

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