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BRIEF REPORT
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Preprocedural frailty is strongly associated with symptoms after balloon pulmonary angioplasty

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Abstract: Balloon pulmonary angioplasty (BPA) has improved the survival rate of patients with chronic thromboembolic pulmonary hypertension (CTEPH). The resolution of symptoms is one of the remaining goals of BPA. Frailty affects the outcome of cardiovascular diseases or treatments. The aim of this study is to assess the association between frailty and outcome of BPA. The resolution of symptoms is evaluated by the post-BPA World Health Organization functional class (WHO-FC). A total of 54 patients with CTEPH were divided into 2 groups by post-BPA WHO-FC (WHO-FC I group; $n = 34$ *vs.* WHO-FC ≥ II group; $n = 20$). Frailty was assessed by physicians using the clinical frailty scale (CFS) at the point of patient admission for their first BPA sessions. Compared to the WHO-FC ≥ II group, the WHO-FC I group was younger (65.6 ± 13.9 years *vs.* 74.3 ± 8.0 years) and had a lower CFS (3 [3, 4] *vs.* 4 [4, 6]) (median [25th, 75th percentiles]). The WHO-FC I achievement rates for each CFS score were CFS 3: 82.8%; 4: 53.8%; 5: 25.0%; 6: 33.3%; and 7: 20.0%. Logistic regression analysis showed that CFS was an independent predictor of WHO-FC I achievement (odds ratio 0.50, $p = 0.012$), but pre-BPA hemodynamic parameters and age were not independent predictors. Whether WHO-FC I can be achieved is predicted by pre-BPA patient frailty but not by pre-BPA hemodynamic parameters and age.

Keywords: chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, frailty, WHO functional class

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a Group 4 pulmonary hypertension (PH) caused by organized thrombi, and prognosis is very poor if these patients are not treated properly (*1,2*). Balloon pulmonary angioplasty (BPA) is emerging as a promising complement to pulmonary endarterectomy (PEA), especially in patients with distal type or inoperable CTEPH (*3-7*). In 2017, multicenter registry results from Japan showed that the improvements in hemodynamic status and survival rates after BPA were excellent (*8*). However, many patients still had symptoms of World Health Organization functional class (WHO-FC) II or more at the follow-up periods, even though they underwent BPA (*8,9*). Currently, the resolution of symptoms is one of the biggest remaining goals of BPA. Even in the last few years, with innovations in techniques and technologies of BPA, certain patients still fail to reach WHO-FC I (*3,7,10-14*).

Compared to those with Group 1 PH, patients with CTEPH are older and have many comorbidities (*5,6*). Patients who are elderly and patients with comorbidities have reduced physiological reserve and increased vulnerability to stress. Recently, the concept of frailty has become increasingly used when evaluating the general condition of patients, especially in patients who are elderly. High frailty is associated with an increased risk of dependency and poor life prognosis, and frailty affects the outcome of cardiovascular diseases or treatments (*15-19*).

The purpose of this study is to assess the association between frailty, hemodynamic status, and outcome of BPA.

Materials and Methods

Study patients

The study subjects were 54 consecutive patients with CTEPH who underwent BPA from April 2016 to March 2020 at Toho University Ohashi Medical Center and were evaluated pre- and post-BPA to determine their WHO-FC using questionnaires. CTEPH was diagnosed based on the presentation of organized thrombi in pulmonary arteries by pulmonary angiography or contrast computed tomography, perfusion lung scintigraphy, pulmonary function tests, blood tests,

echocardiography and right heart catheterization (mean pulmonary artery pressure 25 mmHg or more and pulmonary artery wedge pressure 15 mmHg or less). Other causes of PH were ruled out. Patient characteristics, frailty, pre and post-BPA hemodynamic parameters, 6-minute walk distance (6MWD), and BPA results were retrospectively collected from their medical records. Exclusion criteria were lack of data before and after BPA, and patients who refused use of their data refused to use the data. Study patients were divided into two groups (WHO-FC I group *vs.* WHO-FC ≥ II group). The definition of WHO-FC is shown in supplemental Table 1.

Evaluation of frailty

Frailty was assessed by physicians using the clinical frailty scale (CFS) at the point of patient admission for their first BPA sessions (Figure 1). The CFS level (1: Very Fit to 9: Terminally Ill) was determined by a validation study and revised in 2008 (*20*).

BPA procedures

The BPA procedure was as follows. An 8.2-Fr sheath was inserted into the femoral or right internal jugular vein. From the sheath, a 70-cm-long 6-Fr guiding sheath (ParentPlus60®, Medikit Co. Ltd, Tokyo) was advanced to the right or left main pulmonary arteries. Through the guiding sheath, a 6-Fr guiding catheter was advanced to the segmental or subsegmental pulmonary arteries. Contrast media was injected to visualize the angiographic features of the target lesions. Under fluoroscopic guidance, a 0.014-inch wire was advanced distal to the target lesions, and the lesions were dilated using adequate size balloons (from 1.2 mm to 8.0 mm). The sizes of balloons were selected mainly by angiography. The goal of BPA at our institution is to properly treat all lesions accessible by catheters, and repeated BPA sessions are performed to achieve this goal.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the normality of variable distributions. Continuous variables are presented as the means ± SDs or medians and the interquartile ranges [25th, 75th percentiles]. Categorical variables are presented as counts or proportions (percentages). To evaluate the predictive values of patient characteristics and pre-BPA status for achievement of WHO-FC I, logistic regression analysis was used, and odds ratios and 95% confidence intervals (95% CIs) are presented. Variables with a p-value < 0.1 were included in the multivariable analysis. All of the tests were two-sided, and p-values < 0.05 were considered significant. SPSS (IBM Japan, Tokyo) software package (ver. 23) was used for the analyses.

Ethical considerations

This study was performed in accordance with the Code of Federal Regulations and the Declaration of Helsinki. The present study was approved by the Ethics Committee of Toho University Ohashi Medical Center (approval number: H20001). Written informed consent for comprehensive agreement was obtained from all patients, and an opt-out form on the website of Toho University Ohashi Medical Center provided the target

Table 1. Patient characteristics and the effect of BPA on haemodynamic parameters and 6-minute walk distance

Variables	Pre-BPA	Post-BPA	p value
Total number of patients	54		
Age (y)	68.8 ± 12.7		
Male sex	17 (31.5%)		
Body weight (kg)	57.5 ± 14.3		
Duration from onset (y)	2.9 ± 0.4		
Pulmonary vasodilator	22 (40.7%)		
Endothelin receptor antagonist	3 (5.6%)		
Phosphodiesterase type 5	2 (3.7%)		
Prostacyclin	9 (16.7%)		
Soluble guanylate cyclase	17 (31.5%)		
Deep vein thrombosis and/or Pulmonary embolism	29 (53.7%)		
Coronary artery disease	2 (3.7%)		
Chronic obstructive pulmonary disease	6 (11.1%)		
Clinical frailty scale	3 [3, 4]	–	–
6MWD (m)	296 ± 132	424 ± 150	< 0.0001
sPAP (mmHg)	60.1 ± 18.5	37.1 ± 11.5	< 0.0001
dPAP (mmHg)	20.4 ± 5.9	13.4 ± 4.6	< 0.0001
mPAP (mmHg)	35.4 ± 9.0	22.2 ± 6.0	< 0.0001
CI (L/min/m^2)	2.7 ± 0.7	3.0 ± 0.8	0.028
PVR (dyne·s/cm^5)	497 ± 236	225 ± 107	< 0.0001

mean ± SD, median [25th, 75th percentiles]; 6MWD: six-minute walk distance; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance.

Figure 1. Clinical frailty scale (*Data source*: permission received from Dalhousie University).

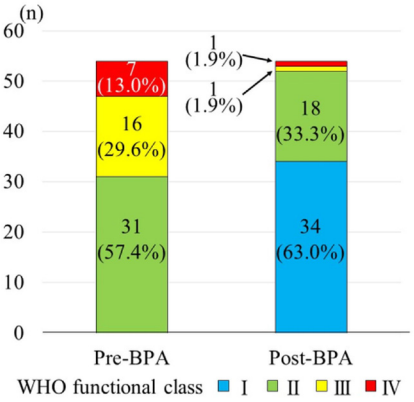

Figure 2. Change of WHO-functional class. WHO-functional class pre- and post- balloon pulmonary angioplasty (BPA).

patients with the opportunity to refuse participation in the present study.

Results and Discussion

Effects of BPA

In 54 patients who underwent BPA, 34 (63%) achieved post-BPA WHO-FC I, and 20 (37%) achieved post-BPA WHO-FC ≥ II (Figure 2). BPA significantly improved hemodynamic parameters and the 6MWD (Table 1).

WHO-FC I achievement and pre-BPA status

Regarding pre-BPA status, compared to the WHO-FC ≥ II group, the WHO-FC I group was significantly younger (65.6 ± 13.9 years *vs.* 74.3 ± 8.0 years) and had lower CFS scores (3 [3, 4] *vs.* 4 [4, 6]) (Table 2). Figure 3 shows the WHO-FC I achievement rate for each CFS score (CFS 3: 82.8%; 4: 53.8%; 5: 25.0%; 6: 33.3%; and 7: 20.0%).

WHO-FC I achievement and post-BPA status

Regarding post-BPA status, the WHO-FC I group showed significantly lower post-BPA systolic and mean pulmonary artery pressure (sPAP: 34.1 ± 8.6 mmHg *vs.* 42.6 ± 14.2 mmHg; mPAP: 20.8 ± 5.0 mmHg *vs.* 24.7 ± 6.9 mmHg), lower pulmonary vascular resistance (PVR: 197 ± 76 dyne·s/cm^5 *vs.* 272 ± 134 dyne·s/cm^5) and longer post-BPA 6MWD (475 ± 140 m *vs.* 331 ± 123 m) (Table 2). However, WHO-FC I achievement rate stratified by quartiles of post-BPA mPAP reached a plateau (post-BPA mPAP 1st quartile 11-18 mmHg: 76.9% [10/13]; 2nd quartile 19-20 mmHg: 75% [9/12]; 3rd quartile 21-23 mmHg: 60% [9/15]; and 4th quartile 24-42 mmHg: 42.9% [6/14]) (Figure 4).

Predictors of WHO-FC I achievement

Multivariable logistic regression analysis showed that CFS was an independent predictor of WHO-FC I achievement, but pre-BPA hemodynamic parameters and age were not independent predictors (Table 3).

Main findings

In daily clinical practice, we tend to have the impression that both the improvement of patient hemodynamic parameters and pre-BPA status affect patient symptoms after BPA. The principle finding of our study is that frailty, not age, is a limitation for the improvement of symptoms after BPA. Although post-BPA hemodynamic status was associated with the WHO-FC I achievement rate, not all hemodynamically well-improved patients reached WHO-FC I. Figure 4 shows an upward trend and plateau of the WHO-FC I ratio with decreasing post-BPA mPAP. Pre-BPA patient conditions also strongly affected post-BPA patient symptoms.

Table 2. Patient characteristics, 6-minute walk distance and haemodynamic parameters of pre/post balloon pulmonary angioplasty

Variables	WHO-FC I	WHO-FC II or more	*p* value
Total number of patients	34	20	–
Age (y)	65.6 ± 13.9	74.3 ± 8.0	0.006
Male sex	11 (32.4%)	6 (30.0%)	1.00
Body weight (kg)	59.6 ± 13.8	54.0 ± 14.7	0.16
Duration from onset (y)	2.6 ± 3.2	3.6 ± 3.2	0.15
Pulmonary vasodilator	13 (38.2%)	9 (45.0%)	0.78
Clinical frailty scale	3 [3, 4]	4 [4, 6]	< 0.0001
Total number of BPA sessions	4.8 ± 2.1	4.5 ± 2.6	0.60
Total amount of contrast medium (mL)	836 ± 378	880 ± 544	0.76
eGFR, Pre-BPA/Post-BPA (mL/min/1.73m^2)	59.6 ± 12.9/62.6 ± 13.5	51.9 ± 15.3/55.7 ± 13.2	0.12/0.15
Mixed venous blood oxygen saturation, Pre-BPA/Post-BPA (%)	67.4 ± 5.9/72.4 ± 4.6	57.8 ± 9.0/64.6 ± 10.6	0.003/0.11
Pre-BPA			
6MWD (m)	312 ± 145	239 ± 131	0.096
sPAP (mmHg)	58.6 ± 19.3	63.5 ± 16.3	0.34
dPAP (mmHg)	20.6 ± 6.0	19.8 ± 5.6	0.65
mPAP (mmHg)	35.1 ± 10.0	35.9 ± 7.2	0.75
CI (L/min/m^2)	2.8 ± 0.6	2.7 ± 0.8	0.56
PVR (dyne·s/cm^5)	456 ± 219	566 ± 254	0.10
Post-BPA			
6MWD (m)	475 ± 140	331 ± 123	0.002
sPAP (mmHg)	34.1 ± 8.6	42.6 ± 14.2	0.016
dPAP (mmHg)	12.7 ± 4.4	14.7 ± 4.7	0.14
mPAP (mmHg)	20.8 ± 5.0	24.7 ± 6.9	0.030
CI (L/min/m^2)	3.0 ± 0.9	2.8 ± 0.8	0.49
PVR (dyne·s/cm^5)	197 ± 76	272 ± 134	0.030

BPA: balloon pulmonary angioplasty; mean ± SD, median [25th, 75th percentiles]; BPA: balloon pulmonary angioplasty; eGFR: estimated glemerular filtration rate; 6MWD: six-minute walk distance; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance.

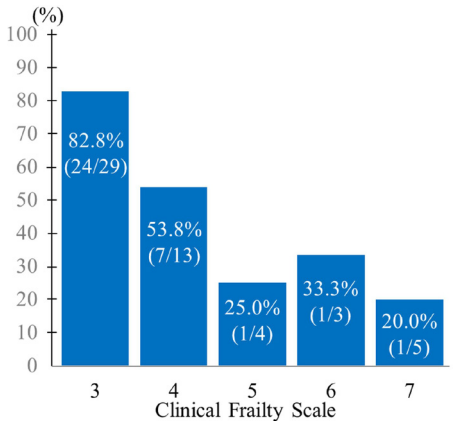

Figure 3. WHO-functional class I achievement and frailty. Achievement rate of WHO-functional class I at each level of the clinical frailty scale (CFS).

Development of BPA

The results of the multicenter registry of Japan reported by Oagawa in 2017 indicated acceptable hemodynamic improvement and survival rates (*8*). However, the accumulation of previous expert center findings, plus the participation of catheter interventionalists, has led to the application of percutaneous coronary intervention (PCI) and peripheral arterial endovascular therapy (EVT) techniques and technologies to improve the outcomes of contemporary BPA. Today, the expected clinical goals of BPA are even higher, as new technologies have improved the results and safety of BPA (*3,4,7,10-14,21-24*). The BPA performed in Japan, which is based on catheter intervention techniques, has improved hemodynamics compared to other countries (*3,4,7,21,22*). Retrograde approach or intravascular ultrasound-guided BPA for completely occluded lesions and gadolinium BPA for patients allergic to contrast media are particularly noteworthy (*10,11,13*).

In terms of a target mPAP, "the lower, the better" has been considered (*7*). In addition, Inami *et al.* reported excellent results with BPA in chronic thromboembolic pulmonary disease without PH (*23,24*). These refined BPAs have markedly improved the hemodynamics and quality of life of patients. Ikeda *et al.* reported a case in which a patient with severe CTEPH was able to carry a child with planned BPA and anticoagulation (*12*). At our institution, more than 60% of the patients who underwent contemporary BPA achieved WHO-FC I, but a certain proportion still had symptoms, even when all accessible lesions were treated. Pre-BPA patient status is one of the limitations to relieving symptoms.

Frailty and results of BPA

Frailty is a phenotype of a multidimensional state of vulnerability that includes a complex of biological, cognitive and social factors (*15,16,20,25-27*). Therefore, highly frail patients potentially have many internal medical or orthopedic disorders, and the improvement

Table 3. The odds ratios for achievement of WHO-functional class I

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age	0.93 (0.88-0.99)	0.024	0.95 (0.89-1.02)	0.14
Male sex	1.12 (0.34-3.69)	0.86	-	-
Body weight	1.03 (0.99-1.08)	0.16	-	-
Duration from onset	0.91 (0.77-1.08)	0.91	-	-
Pulmonary vasodilator	0.76 (0.25-2.32)	0.63	-	-
Clinical frailty scale	0.44 (0.25-0.76)	0.003	0.50 (0.29-0.86)	0.012
eGFR	1.04 (0.99-1.10)	0.12		
Pre-BPA				
6MWD (each 10 m)	1.04 (0.99-1.09)	0.10	-	-
sPAP	0.99 (0.96-1.02)	0.34	-	-
dPAP	1.02 (0.93-1.13)	0.64	-	-
mPAP	0.99 (0.93-1.05)	0.75	-	-
CI	1.29 (0.56-2.99)	0.56	-	-
PVR (each10 dyne·s/cm^5)	0.98 (0.96-1.00)	0.11	-	-

BPA: balloon pulmonary angioplasty; 6MWD: six-minute walk distance; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance.

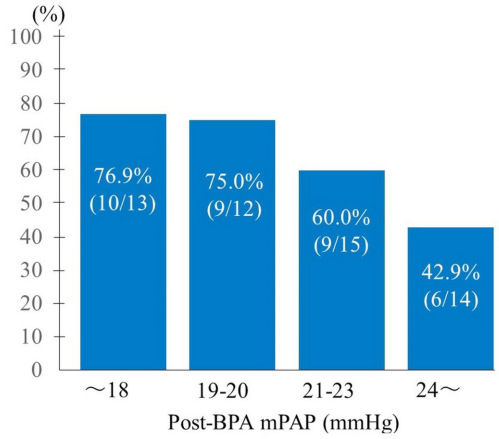

Figure 4. WHO-functional class I achievement and mean pulmonary artery pressure (mPAP). Achievement rate of WHO-functional class I, stratified by post-BPA mean pulmonary artery pressure (mPAP).

of cardiopulmonary function by BPA in such patients may not directly lead to improvement of symptoms. Frail patients show a high rate of comorbidities such as ischemic heart disease, chronic obstructive pulmonary disease and other diseases that are not CTEPH but cause cardiopulmonary dysfunction, cerebrovascular disorders, muscle weakness, *etc.* Such patients remain symptomatic, even if their pulmonary circulation is improved by BPA.

In our study, 8 of the 54 patients failed to complete all planned BPA procedures due to the patient's decision (n = 3) or due to the discovery or worsening of malignancy or problems of general conditions (n = 4). Five of the 8 patients who failed to complete all planned BPA procedures had frailty with a CFS score of 5 or more. Frail patients are less active, and may wish to discontinue BPA if relieved from their dyspnea at rest, especially in cases with malignancy, in whom a long survival period is not expected. We included all patients who underwent BPA, even for one session, in the study because dropout by various reasons is also one of the limitations of BPA. Further discussion is needed on how aggressively BPA should be performed for highly frail patients. Furthermore, multifactorial interventions for frailty, such as nutrition guidance and rehabilitation, need to be considered.

Age and hemodynamic status

Age did not independently prevent the achievement of WHO-FC I. For elderly patients with CTEPH, BPA is a less invasive and attractive treatment option. It is clear that "the lower the mPAP the better," as the first quartile (mPAP 11-18 mmHg) showed the highest WHO-FC I rate (Figure 4). However, the upward trend of achievement rate of WHO-FC I looks as if it reached a plateau. Frailty, not age, should be considered in selecting BPA candidates and deciding how much to treat.

Limitations

Our study has some important limitations. First, the number of patients in this study was relatively small. Second, the results of this study were based on an analysis of BPA outcomes at a single institution (Toho University Ohashi Medical Center, Tokyo, Japan). In our institution, the strategy of BPA using PCI/EVT techniques was aggressive, and all lesions accessible by catheters were treatment targets. These strategies should be considered in the interpretation of our results. Third, the pre-BPA hemodynamic parameters were relatively mild. The patients with severely high pulmonary artery pressures were intensively treated with a combination of oral pulmonary vasodilators before BPA. Intensive combination therapy affected

baseline hemodynamic parameters. Fourth, WHO-FC was tabulated based on patient self-reports using questionnaires. Patients accustomed to dyspnea from effort might have underestimated their symptoms after BPA. Fifth, the results of respiratory function tests could not be presented because of the large number of missing post BPA tests. Sixth, patients receiving oxygen prior to BPA were included in the study. Mixed venous blood oxygen saturation was not included in the logistic regression analysis, because it was strongly influenced by oxygen administration.

Conclusions

Whether WHO-FC I can be achieved is predicted by pre-BPA patient frailty, not pre-BPA hemodynamic parameters and age. The selection of BPA candidates should be carried out according to frailty rather than age.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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