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Short communication

Balloon pulmonary angioplasty for symptomatic chronic thromboembolic disease without pulmonary hypertension at rest☆

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ABSTRACT

Background: Patients with chronic thromboembolic disease (CTED) have chronic thromboembolic obstructions of the pulmonary arteries with exercise intolerance, but without signs of pulmonary hypertension at rest. We investigated the efficacy of balloon pulmonary angioplasty (BPA) for CTED patients.
Methods: Fifteen CTED patients (4 males, 11 females) who underwent BPA were enrolled. The inclusion criteria were 1) chronic thromboembolic obstructions of the pulmonary artery identified on ventilation–perfusion scans and pulmonary angiography, 2) WHO functional class II or greater, and 3) mean PAP of <25 mmHg as measured by right heart catheterization. This study excluded patients with CTEPH at diagnosis.
Results: At the 6-month follow-up after the final BPA session, hemodynamics and 6-min walk distance were significantly improved. Although more than half of the patients were prescribed home oxygen therapy before BPA due to O_2 desaturation with exercise, the use ratio of home oxygen therapy was reduced at the time of follow-up (from 53% to 7%; $P = 0.01$). Furthermore, cardiopulmonary exercise tests during right heart catheterization demonstrated that BPA could ameliorate an abnormal pulmonary vascular response to exercise.
Conclusions: BPA can produce favorable outcomes in patients with CTED. Prospective, larger randomized clinical trials are needed to further investigate this treatment strategy.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as organized thrombosis in pulmonary arteries and pulmonary hypertension with a mean pulmonary arterial pressure (PAP) > 25 mmHg, as measured by resting right heart catheterization, even after a certain period of thrombolytic or anticoagulant therapy. Importantly, there is a subgroup of patients with chronic thromboembolic disease (CTED) who have chronic thromboembolic obstructions of the pulmonary arteries with exercise intolerance, but without signs of pulmonary hypertension at rest [1]. Patients with CTED also have dyspnea on exertion and sometimes demonstrate substantial hypoxemia. Thus, the therapeutic strategy for these patients needs to be carefully considered.

Balloon pulmonary angioplasty (BPA) has been developed as a promising therapeutic strategy for CTEPH, and an important treatment goal of BPA is the relief of pulmonary hypertension. However, the current treatment goals for BPA in specialized Japanese centers are freedom from symptoms and home oxygen therapy, as well as the relief of pulmonary hypertension. This retrospective study therefore investigated the efficacy of BPA for CTED.

2. Methods

Fifteen CTED patients (4 males, 11 females) underwent BPA from March 2012 to August 2017. The criteria for performance of BPA in these patients were 1) chronic thromboembolic obstructions of the pulmonary artery identified on ventilation–perfusion scans and pulmonary angiography, 2) symptoms of WHO functional class II or greater, and 3) mean PAP of <25 mmHg as measured by right heart catheterization. This study excluded patients with CTEPH at diagnosis.

This study was performed with approval of the institutional Ethics Committee (No. H30-138_1229). Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

The procedures for BPA are described in our previous report [2]. In brief, the target fluoroscopy time and amount of contrast agent in a single session were <60 min and 300 ml, respectively, and we treated as many vessels as possible in a single session. The selection of vessels to be treated and determination of procedural success were made based on functional assessment using a pressure wire or pressure catheter (i.e., targeted pressure ratio > 0.8). Balloon dilation was performed for all organized thrombotic lesions in repeated sessions while paying attention to safety, and we judged that all sessions were complete when all the dilatable lesions were treated.

Cardiopulmonary exercise tests during right heart catheterization were performed using Cpex-1 (Inter-Reha Co., Ltd., Tokyo, Japan). An incremental symptom-limited

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exercise test was performed, with an electromagnetically braked cycle ergometer (Nuclear Imaging Table with Angio Ergometer; Lode; Groningen, Netherlands) according to the Ramp protocol. Hemodynamics was measured during exertion through a catheter whose tip was placed in the pulmonary artery trunk.

Wilcoxon signed ranks test was used to compare baseline and follow-up values.

3. Results

During the study period, 141 patients with CTEPH and 18 with CTED were referred to our hospital. Among these 18 CTED patients, 3 had symptoms of WHO functional class I. Therefore, the remaining 15 CTED patients were enrolled in this study. The median patient age was 58 (interquartile range [IQR] 44–68) years old. Body mass index was 21.9 (IQR 20.6–26.7). Regarding to smoking history, 12 (80%) patients were never-smokers, 3 (20%) ex-smokers, and 0 (0%) daily or occasionally smokers. Regarding to cardiopulmonary comorbidities, 7 (47%) patients had past histories of acute pulmonary embolisms, 2 (13%) deep venous thrombosis, 1 (7%) hypertrophic obstructive cardiomyopathy, and 1 (7%) patent foramen ovale. In respiratory function tests (n = 10), percent vital capacity was 98.2% (IQR 78.2–114.4%) and percent predicted forced expiratory volume in 1 s was 79.9% (IQR 72.9–87.5%).

The median time period between diagnosis and first session of BPA was 739 (IQR 326–1332) days. All patients were prescribed ongoing therapeutic anticoagulation for at least 3 months, and 12 of the 15 enrolled patients were continued on that treatment for 6 months. During the earlier days of BPA experiences in our institution, CTEPH patients were prioritized. Later, as the experiences of BPA increased, CTED patients were also targeted. That is the reason for the long median time from diagnosis to first session of BPA in CTED patients.

The median number of sessions was 2 (IQR 1–3), and the median number of vessels treated per patient was 9 (IQR 5–15) vessels, suggesting the numbers of sessions and treated vessels in BPA for CTED seem generally less than those for CTEPH. There were no occurrences of reperfusion pulmonary edema or pulmonary injuries across the sessions.

Data before BPA and at the 6-month follow-up after the final BPA session are shown in Table 1 (follow-up catheterization was performed in the period between 2012 and 2018). The median time period between the first BPA session and follow-up was 301 (IQR 232–484) days. No patients died during the follow-up period, and overall the mean PAP, pulmonary vascular resistance (PVR), and 6-min walk distance were significantly improved at follow-up. More than half of the patients in this study were prescribed home oxygen therapy before BPA due to O_2 desaturation with exercise, although no patients had co-existing comorbidities that can cause dyspnea, such as parenchymal lung issue or intracardiac shunt. Importantly, the use ratio of home oxygen therapy was reduced at the time of follow-up (from 53% to 7%; $P = 0.01$).

Furthermore, cardiopulmonary exercise tests accompanied by hemodynamic measurements during right heart catheterization were performed immediately prior to the BPA and at the six-month follow-up after BPA in six of the study patients (Fig. 1). Hemodynamics in exercise right heart catheterization demonstrated that mean PAP and PVR at peak exercise significantly improved at the six-month follow-up after BPA, respectively. Furthermore, there was a significant reduction in mean PAP–cardiac output (CO) slope at follow-up. Cardiopulmonary exercise tests demonstrated that minute ventilation (VE) vs. carbon dioxide output (VCO_2) slope was also significantly reduced at follow-up.

Table 1
Data before BPA and at the 6-month follow-up in patients with chronic thromboembolic disease.

	Before BPA	Follow-up	*P*-value
WHO functional class			<0.001
I	0 (0%)	14 (93%)	
II	15 (100%)	1 (7%)	
III	0 (0%)	0 (0%)	
IV	0 (0%)	0 (0%)	
Mean RAP (mmHg)	4.0 (IQR 2.0–6.0)	4.0 (IQR 3.0–5.0)	0.59
RV systolic pressure (mmHg)	35 (IQR 28–39)	25 (IQR 24–31)	0.01
Mean PAP (mmHg)	20 (IQR 16–22)	16 (IQR 13–17)	0.001
PVR (Wood units)	1.8 (IQR 1.4–3.9)	1.6 (IQR 1.4–2.0)	0.04
CO (L/min)	5.2 (IQR 4.1–6.2)	4.4 (IQR 4.0–5.2)	0.35
Cardiac index (L/min/m^2)	3.3 (IQR 2.4–4.2)	2.6 (IQR 2.5–3.1)	0.23
PAWP (mmHg)	9 (IQR 7–11)	8 (IQR 5–10)	0.23
PaO_2 (mmHg)	70.6 (IQR 65.0–81.4)	76.2 (IQR 71.7–103.0)	0.06
SaO_2 (%)	94.7 (IQR 93.3–96.7)	96.7 (IQR 94.0–98.3)	0.046
SvO_2 (%)	72.1 (IQR 68.6–75.0)	71.9 (IQR 68.1–75.5)	0.85
Hemoglobin concentration (g/dL)	12.9 (IQR 10.8–14.2)	12.5 (IQR 10.9–14.1)	0.37
6-min walk distance (m)	408 (IQR 358–468)	444 (IQR 380–566)	0.03
BNP (pg/mL)	29.1 (IQR 15.3–44.5)	28.8 (IQR 7.5–37.8)	0.43

Data are given as the number (%) or the median (IQR).
BPA, balloon pulmonary angioplasty; RAP, right atrial pressure; RV, right ventricular; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; PAWP, pulmonary arterial wedge pressure; CO, cardiac output; PaO_2, partial pressure of arterial oxygen; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation; BNP, B-type natriuretic peptide; IQR, interquartile range.

4. Discussion

According to the 2016 guidelines for the diagnosis and treatment of pulmonary hypertension published by the European Society of Cardiology and the European Respiratory Society [3], BPA has been accepted as a therapeutic strategy for CTEPH (IIb recommendation for patients with technically inoperable disease or with unfavorable risk-to-benefit ratio for surgery). However, the indication of BPA for CTED has not been established.

One important treatment goal of BPA should be the relief of pulmonary hypertension. However, the indications for BPA in specialized Japanese centers currently go beyond the relief of pulmonary hypertension, with the aim of achieving freedom from symptoms and chronic therapies. In these cases, BPA treatment is considered completely accomplished when patients are free of symptoms, pulmonary hypertension-specific drugs, and home oxygen therapy, or when patients feel that they no longer require additional BPA sessions [4].

The present findings indicate that BPA can produce favorable outcomes even in patients with CTED and could ameliorate an abnormal pulmonary vascular response to exercise. Importantly, 10 of the 15 enrolled patients had borderline range (19–24 mmHg) pulmonary hypertension before BPA, suggesting that these patients could have contributed more significantly to the overall successful outcomes and that such patients with borderline hypertension could be a target group for BPA.

In cardiopulmonary tests, VE vs. VCO_2 slope reflects exercise ventilatory efficiency. The data in the present study suggest that BPA could ameliorate exercise ventilatory efficiency in CTED. Furthermore, values >3.0 for the mean PAP–CO slope, which is defined as a linear correlation based on serial measurements of mean PAP and CO during incremental exercise, reflect an abnormal pulmonary vascular response to exercise and may be indicative of pulmonary vasculopathy without pulmonary hypertension at rest [5]. In the present study, mean PAP–CO slope at the six-month follow-up after BPA reduced <3.0 in all six patients enrolled, suggesting that BPA could ameliorate an abnormal pulmonary vascular response to exercise.

In fact, it has been reported that BPA can improve exercise capacity in some patients without pulmonary hypertension at rest [6]. Furthermore, Wiedenroth et al. recently demonstrated the safety and efficacy of BPA in 10 patients with CTED at two German institutions [7]. Some specialist centers for pulmonary endarterectomy have reported improved symptoms and exercise capacity in CTED [8]. With respect to

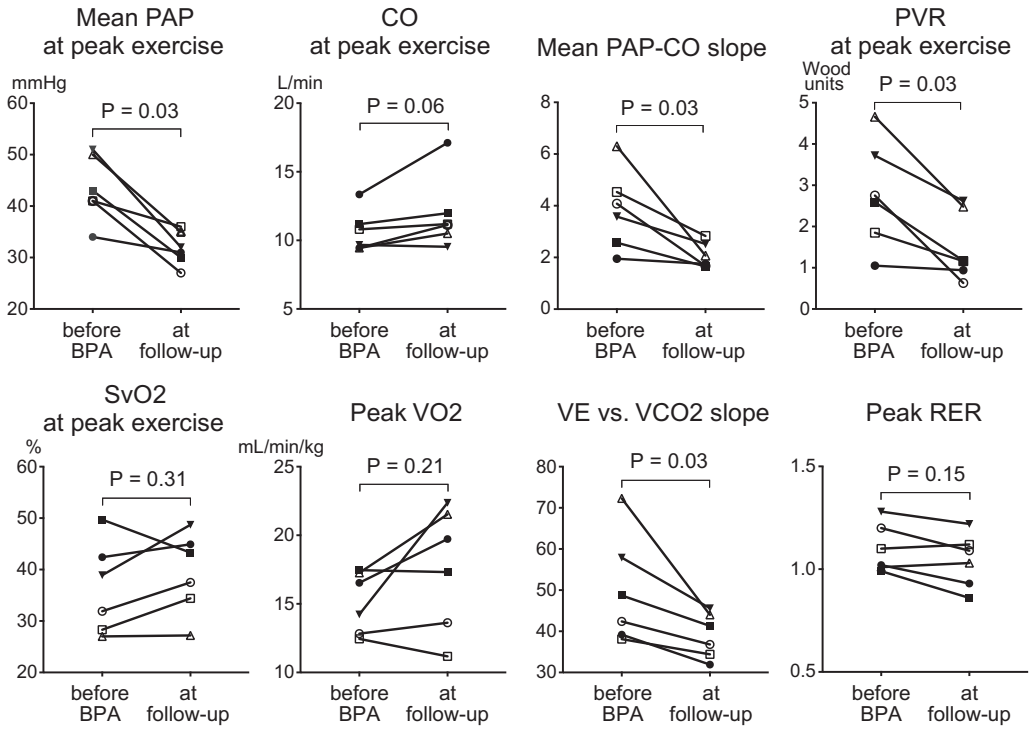

Fig. 1. Parameters in exercise right heart catheterization before balloon pulmonary angioplasty (BPA) and at follow-up. Hemodynamics and the data of cardiopulmonary test are described with individual lines for each patient. PAP, pulmonary arterial pressure; CO, cardiac output; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen saturation; VO_2, oxygen consumption; VE, minute ventilation; VCO_2, carbon dioxide output; RER, respiratory exchange ratio.

the risk-to-benefit ratio of pulmonary endarterectomy, BPA could therefore be a promising alternative therapeutic strategy for CTED patients, when these patients are treated in referral centers with experience in BPA technic.

In conclusion, BPA seems to be safe and effective in the patient population studied herein, and now prospective, larger randomized clinical trials are needed to further investigate this treatment strategy.

Declarations of interest

None.

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