Change in pulmonary arterial compliance and pulmonary pulsatile stress after balloon pulmonary angioplasty

ABSTRACT

Objective: Although the underlying pathology of chronic thromboembolic pulmonary hypertension (CTEPH) is mechanical obliteration of the major pulmonary vessels, high pulsatile stress penetrating into the normal distal pulmonary microvasculature resulting from reduced pulmonary arterial compliance ($C_{pa}$) may cause progressive deterioration in pulmonary hemodynamics. Hypothetically, balloon pulmonary angioplasty (BPA) may be beneficial in reducing $C_{pa}$ and pulsatile stress in patients with CTEPH.

Methods: In total, 26 patients with available pre- and post-BPA right heart catheterization results were included in the study. BPA was performed in a series of staged procedures by 2 experienced interventional cardiologists.

Results: The median $C_{pa}$ showed a 59.2% increase (1.03 to 1.64 mL/mm Hg, $p=0.005$). The median pre-BPA pulsatile stress product decreased by 20.7% (4,266 to 3,380 mm Hg/min, $p=0.003$). A linear regression model established that the percent change in $C_{pa}$ after BPA accounted for 21.8% of the explained variability in the change in 6-minute walk test ($p=0.009$).

Conclusion: Our results indicate that BPA decreases $C_{pa}$ and pulmonary pulsatile stress. These changes may be partly responsible for the improvement in functional capacity after BPA.

Keywords: balloon angioplasty, compliance, pulmonary embolism, pulmonary hypertension, pulsatile flow

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the potentially treatable causes of pulmonary hypertension (PH) in which high pulmonary arterial pressure results from a decrease in effective pulmonary vascular cross-sectional area (1). Although the underlying pathology of CTEPH is thromboembolic obliteration of the major vessels and elevated proximal pulmonary vascular resistance (PVR), high pulsatile stress penetrating into normal distal pulmonary microvasculature resulting from reduced pulmonary arterial compliance ($C_{pa}$) may negatively affect the remaining microvasculature. This may cause progressive deterioration in pulmonary hemodynamics (2).

Balloon pulmonary angioplasty (BPA) is a recently established method used in patients with inoperable or residual CTEPH (3). It has been shown to decrease mean pulmonary artery pressure (mPAP) and PVR and improve functional capacity, quality of life, and response to PH-specific therapy (4–9). Although the main mechanism of BPA is to eliminate proximal occlusive lesions and to reduce proximal PVR, it may also be beneficial in reducing $C_{pa}$ and pulsatile stress by decompressing the pressure-loaded pulmonary arteries. Hypothetically, this may translate into a reduced pulsatile stress in the normal distal microvasculature and prevent progressive vascular remodeling. However, the data on the effects of BPA on $C_{pa}$ and pulsatile stress are limited. In this study, we sought to explore the effects of BPA on $C_{pa}$ and pulsatile stress in patients with inoperable or residual CTEPH.

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METHODS

Statement of ethics
A Local Ethical Committee approval was obtained, all the participants gave informed consent, and the study was undertaken in accordance with the Declaration of Helsinki.

Study protocol
The study was undertaken at a tertiary center for PH. We retrospectively screened our hospital database for the patients with inoperable or postoperative residual CTEPH who underwent BPA in our hospital between October 2017 and January 2020. Patients with available pre- and post-BPA right heart catheterization (RHC) results were included in the study.

A multidisciplinary PH team including a cardiologist, a cardiovascular surgeon, a pulmonologist, a rheumatologist, and a radiologist evaluated all patients. All patients underwent a comprehensive examination, including medical assessment, transthoracic echocardiography, multi-slice computed tomography, ventilation/perfusion scintigraphy, RHC, and selective pulmonary angiography as required. CTEPH was diagnosed and managed according to the European Society of Cardiology Guidelines for the diagnosis and management of PH (10). Patients with severe medical comorbidities or surgically inaccessible lesions were regarded as inoperable. Patients with World Health Organization functional class II despite medical therapy were considered inoperable. The eligibility for BPA was determined on the basis of a consensus among the multidisciplinary PH team. The periprocedural test results were obtained via chart review and included complete blood count, kidney function tests, serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, 6-minute walk test (6MWT), and RHC measurements. RHC was performed via the right jugular vein using a Swan-Ganz catheter (Edwards Lifesciences Corporation, Irvine, CA, USA), and cardiac output was measured using the Fick method. After the last BPA session, all patients were re-evaluated with RHC at 3-month follow-up. CTEPH was diagnosed and managed according to the European Society of Cardiology Guidelines for the diagnosis and management of PH (10). The eligibility for BPA was determined on the basis of a consensus among the multidisciplinary PH team. The periprocedural test results were obtained via chart review and included complete blood count, kidney function tests, serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, 6-minute walk test (6MWT), and RHC measurements. RHC was performed via the right jugular vein using a Swan-Ganz catheter (Edwards Lifesciences Corporation, Irvine, CA, USA), and cardiac output was measured using the Fick method. After the last BPA session, all patients were re-evaluated with RHC at 3-month follow-up. C_{PA} was defined as stroke volume divided by pulmonary pressure (11). Pulsatile stress product (PSP) was defined as pulse pressure times heart rate (12).

HIGHLIGHTS
• Balloon pulmonary angioplasty has been shown to decrease mean pulmonary artery pressure and pulmonary vascular resistance (PVR) and improve functional capacity, quality of life, and response to pulmonary hypertension (PH)-specific therapy.
• Although the underlying pathology of chronic thromboembolic pulmonary hypertension is thromboembolic obliteration of the major vessels and elevated proximal PVR, high pulsatile stress penetrating into normal distal pulmonary microvasculature resulting from reduced pulmonary arterial compliance (C_{PA}) may negatively affect the remaining microvasculature.
• Decreased C_{PA} may contribute to the progression of PH.

BPA protocol
Two experienced interventional cardiologists performed BPA in a series of staged procedures using the right femoral access. A 6 French long destination sheath (Terumo Corporation, Tokyo, Japan) was used to provide the guiding catheter stability. A 6 French guiding catheter (Medtronic, Dublin, Ireland) was inserted to the respective segmental pulmonary arteries, and selective pulmonary angiography was performed. Targeted lesions were crossed with a 0.014-inch guidewire (Soft J, Asahi Intecc, Aichi, Japan), and the lesions were dilated using 1.25 to 4.0 mm×20 mm semi-compliant balloon catheters (BrosMed, Japan, for 1.25 mm balloon catheters; Simeks Tibbi Urunler, İstanbul, Turkey for 2.0 to 4.0 mm balloon catheters). In the initial sessions, undersized balloon catheters were preferred to avoid reperfusion lung injury, especially in patients who had high mPAP and PVR. Further dilatations were performed using appropriate-diameter balloon catheters (2 to 7 mm; Simeks Tibbi Urunler, İstanbul, Turkey). The lower lobe lesions were targeted first, as pulmonary blood flow at this site was high compared with the others. During one hospital admission, 2 BPA sessions were performed with an interval of 2–4 days. RHC was repeated at an interval of 4–6 weeks, and additional BPA sessions were performed until an mPAP below 30 mm Hg was achieved or when it was assumed that all the accessible lesions were treated.

Statistical analysis
Continuous variables were expressed as median [interquartile range (IQR)] and categorical variables as counts (percentages). The change in 6MWT, NT-proBNP, C_{PA}, and PSP were assessed using the paired-sample t-test. The normality of the difference in these variables was checked using the Shapiro-Wilk test. The paired-sample t-test, Wilcoxon signed-rank test, and McNemar test were used for the comparison of pre- and post-BPA hemodynamic variables. The correlations between absolute change in 6MWT and NT-proBNP with the change in C_{PA}, PSP, and PVR were assessed by Pearson’s correlation test. A simple linear regression analysis was performed to explore whether the change in C_{PA} explains any variability observed in the improvement in 6MWT. The SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) software was used for statistical analysis. For all statistical analyses, a p<0.05 was considered significant.

RESULTS
During the predetermined period, we identified 31 patients with inoperable or postoperative residual CTEPH who underwent BPA. One patient was excluded because he underwent surgical pulmonary endarterectomy after the post-BPA re-evaluation. Four patients were also excluded from the analyses because their BPA interventions were still ongoing at the time of writing of this manuscript. Therefore, the final study population consisted of 26 patients. The interval from the first diagnosis to enrollment was 42 months (IQR=39). The baseline characteristics are presented in Table 1.

The patients underwent a total of 3 BPA sessions (IQR=3, range=1–10). The number of targeted vessels per intervention was 4 (IQR=3, range=2–10). Major hemoptysis was observed only in 1 patient who was managed conservatively. No
Table 1. Baseline characteristics*

| Parameter                              | Value |
|----------------------------------------|-------|
| Age, years                             | 48.5 (28) |
| Sex, female                            | 18 (69.2) |
| Body mass index, kg/m²                 | 26.4 (10.3) |
| History of VTE, n (%)                  | 7 (26.9) |
| Inoperable disease, n (%)              | 15 (57.7) |
| Distal predominant disease, n (%)      | 10 (38.5) |
| Severe medical comorbidities, n (%)    | 5 (19.2) |
| Previous PEA (residual/recurrent), n (%) | 11 (42.3) |
| Underlying disease or hypercoagulable state, n (%) | 11 (43.3) |
| Splenectomy, n (%)                     | 1 (3.8) |
| Lupus, n (%)                           | 2 (7.7) |
| Isolated pulmonary vasculitis, n (%)   | 2 (7.7) |
| Factor V Leiden homozygosity, n (%)    | 2 (7.7) |
| Behçet’s disease, n (%)                | 1 (3.2) |
| History of cancer, n (%)               | 3 (11.5) |
| WHO functional class, n (%)            |       |
| I                                      | 0     |
| II                                     | 7 (26.9) |
| III                                    | 16 (61.5) |
| IV                                     | 3 (11.5) |
| Medications                            |       |
| PAH-specific therapy                   | 21 (80.8) |
| Riociguat, n (%)                       | 15 (57.7) |
| Endothelin receptor antagonists        | 6 (23.1) |
| Phosphodiesterase S inhibitors         | 4 (15.4) |
| Prostacyclin analog                    | 5 (19.2) |
| Medications (none/single/double/triple), n | 5/16/1/4 |
| Anticoagulant drugs                    |       |
| Warfarin, n (%)                        | 10 (38.5) |
| Newer oral anticoagulants, n (%)       | 16 (61.5) |

*Data are presented as median (interquartile range) and n (%).

Table 2. Baseline transthoracic echocardiography findings*

| Parameter                              | Value |
|----------------------------------------|-------|
| Left ventricular ejection fraction, %  | 65 (12.5) |
| Right ventricular basal diameter, mm   | 46 (11.5) |
| Right ventricular fractional area change, % | 40 (13) |
| TAPSE, mm                              | 13 (7.25) |
| Right ventricular S', cm/sec            | 9.5 (3.35) |
| The maximal tricuspid regurgitation velocity, m/sec | 4.65 (1.03) |
| Right atrial area, cm²                 | 23.5 (9.9) |

*Data are presented as median (interquartile range) and n (%).

DISCUSSION

To the best of our knowledge, this is the first study exploring whether an increase in C_Pa and a decrease in pulsatile stress with BPA are linked to a functional improvement in patients with CTEPH. Our results suggest that favorable effects of BPA on functional capacity may be at least partly related with the change in C_Pa. Although our study is predominantly a mechanistic one, it may have important implications for providing new insights into the management of the patients with CTEPH.

In accordance with our results, it has been shown that C_Pa is decreased in patients with PH, and this decrease is associated with a poor prognosis (13, 14). The temporal relationship between PH and decreased C_Pa is also a constantly evolving area of research. Some evidence indicate that C_Pa changes start early in PH process, even before pulmonary artery pressures exceed abnormality limits. A reduced C_Pa was shown in patients with exercise-induced PH despite a normal resting pulmonary artery pressure (15). Evidence also suggests that decreased C_Pa may contribute to the progression of PH (16).

As the elastic arteries, such as major pulmonary arteries, cushion the cyclical changes in pressure and provide a continuous flow to the distal microvasculature, a substantial decrease in C_Pa may cause penetration of the pressure oscillations further down into distal pulmonary microvasculature (17). Increased pulsatile stress in normal pulmonary vasculature is sensed by the endothelial cells, which transduce it into a signaling cascade leading to a proinflammatory response and maladaptive growth process (18). The decrease in C_Pa increases pulsatile component of right ventricular afterload and may induce right-sided heart failure (19).
BPA is a recently established method in patients with inoperable CTEPH (4). It is associated with moderate improvements in pulmonary vascular hemodynamics with an average 20%–30% decrease in mPAP and PVR and a similar amount of increase in cardiac index (4–9). Successful BPA can increase exercise capacity and quality of life and also decrease the requirement for supplemental oxygen therapy and the need for costly PAH-specific drug therapies (6, 9). Several recent publications have also shown an increase in C\textsubscript{PA} with BPA (20-22). Wiedenroth et al. (20) assessed C\textsubscript{PA} in 10 patients undergoing BPA and reported an increase from 3.2±2.1 to 4.1±1.7 mL/mm Hg (p=0.027). However, it is hard to interpret these data, as the patients showed unusually high C\textsubscript{PA} values both at baseline and after treatment. Magoń et al. (21) showed that C\textsubscript{PA} increased from 1.02 (0.70 to 1.39) to 2.08 (1.49 to 2.39) mL/mm Hg (p<0.001) after successful BPA in 17 patients. Go-
dinas et al. (22) evaluated 18 patients with CTEPH and reported an increase in \( C_{PA} \) from 1.30±0.51 to 2.24±0.96 mL/mm Hg (p<0.001). None of these studies attempted to elucidate the potential contribution of \( C_{PA} \) on improvement in functional outcomes. Our study is the first one to explore such a relationship. Furthermore, the presence of a significant correlation between \( C_{PA} \) and 6MWT but absence of such an association with NT-proBNP may also hint that the favorable effects on functional capacity act through the effects on pulmonary vasculature and not through lowered right ventricular afterload. This hypothesis needs to be further clarified in future studies.

**Study limitations**

Our study had several limitations. First, our study had a limited size, although the reported studies on BPA had always been relatively limited in enrollment numbers given the rare nature of CTEPH and the limited applicability of BPA. Second, \( C_{PA} \) may be overestimated by dividing stroke volume with pulmonary artery pulse pressure (17). Third, the change in \( C_{PA} \) is not independent of other hemodynamic changes, but we were unable to control for the possible cofounders owing to the limited size of our dataset.

**CONCLUSION**

Our results indicate that BPA decreases \( C_{PA} \) and pulmonary pulsatile stress. These changes may be partly responsible for the improvement in functional capacity after BPA. Further studies are needed to clarify the role of \( C_{PA} \) and pulsatile stress in the pathogenesis of CTEPH and the possible contribution of BPA in the management of these pathologic processes.

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