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

ORIGINAL INVESTIGATION

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 over class II despite medical therapy were considered for BPA. 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 pulse 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 Intec, 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 were 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	
Age, years	48.5 (28)
Sex, female	18 (69.2)
Body mass index, kg/m^2	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 (3.2)
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 5 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 (%). PAH - pulmonary arterial hypertension; PEA - pulmonary endarterectomy; VTE - venous thromboembolism; WHO - World Health Organization

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 (3.55)
The maximal tricuspid regurgitation velocity, m/sec	4.65 (1.03)
Right atrial area, cm^2	23.5 (9.9)

*Data are presented as median (interquartile range) and n (%). TAPSE - tricuspid annular plane systolic excursion

other major complications occurred during the study period. The interval from baseline to the final RHC was 129.5 days (IQR=111). Most of the hemodynamic parameters showed a favorable change after BPA procedures compared with the pre-BPA values as summarized in Table 2.

The differences in C_{PA}, PSP, and 6MWT were normally distributed as assessed by the Shapiro-Wilk test (p=0.904, p=0.538, and p=0.864, respectively). The median baseline C_{PA} was 1.03 mL/mm Hg (IQR=1.11 mL/mm Hg). It showed a significant increase of 59.2% to a level of 1.64 mL/mm Hg (IQR=1.12 mL/mm Hg) after serial BPA procedures [95% confidence interval (CI)=0.14 to 0.74, t=3.084, p=0.005] (Fig. 1a). The median pre-BPA PSP was 4,266 mm Hg/min (IQR=2,375 mm Hg/min), which showed a 20.7% significant decrease to a level of 3,380 mm Hg/min (IQR=1,739.5 mm Hg/min, 95% CI= −1,422 to −339, t=3.348, p=0.003) (Fig. 1b). The 6MWT duration increased from 320 m (IQR=179) to 450 m (IQR=143). The median absolute increase in 6MWT was 112.5±178.5 m (95% CI=50 to 141, t=4.322, p<0.001). This was positively correlated with the percent increase in C_{PA} (r=0.500, p=0.009) (Fig. 2), whereas the change in PSP (r= −0.250, p=0.219) and PVR (r=0.366, p=0.066) did not show such a relationship. The NT-proBNP levels decreased from 456 ng/mL (IQR=2,517) to 189 ng/mL (IQR=374) (Z= −3.419, p=0.001). The absolute median decrease in NT-proBNP was 219 ng/mL (IQR=1,959). This decrease did not show any correlation with C_{PA} (r=0.303, p=0.133) or PSP (r= −0.171, p=0.404). The linear regression model established that the percent change in C_{PA} after BPA accounted for 21.8% of the explained variability (R=0.500, R^2=0.250, coefficient ß=61.479) in the change in 6MWT after BPA (p=0.009).

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).

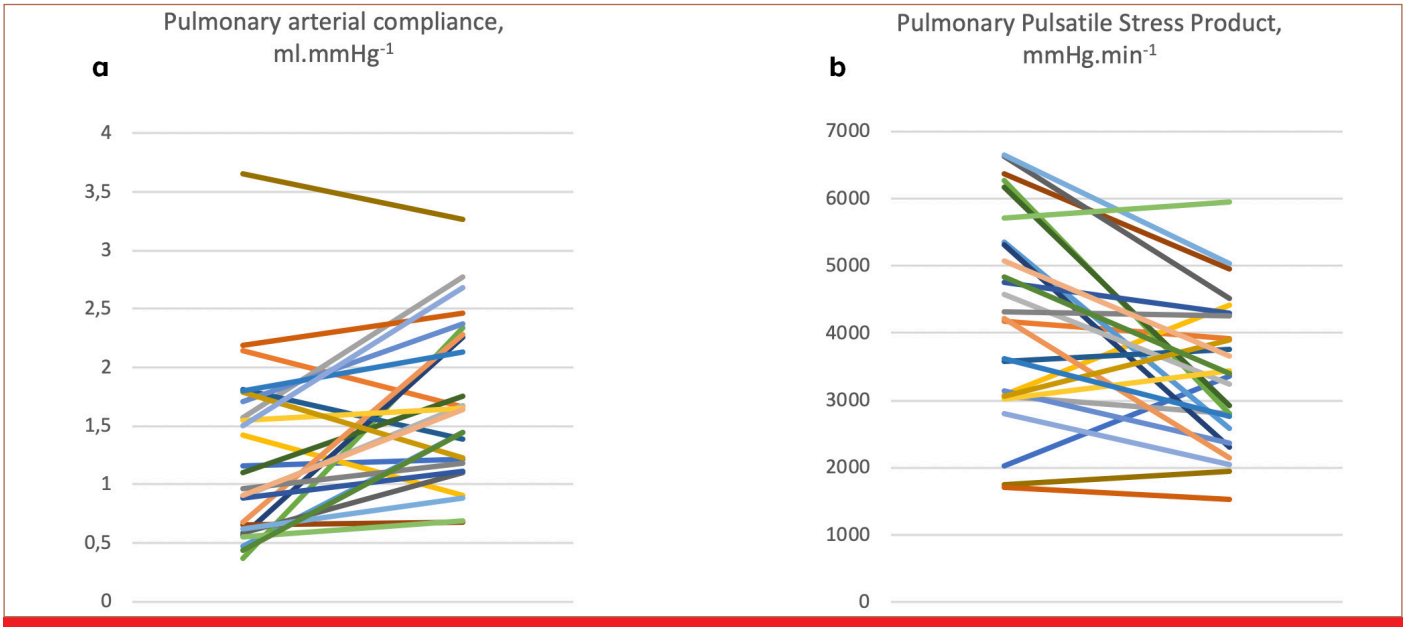

Figure 1. (a) Change in pulmonary arterial compliance and (b) pulmonary pulsatile stress product before and after balloon pulmonary angioplasty

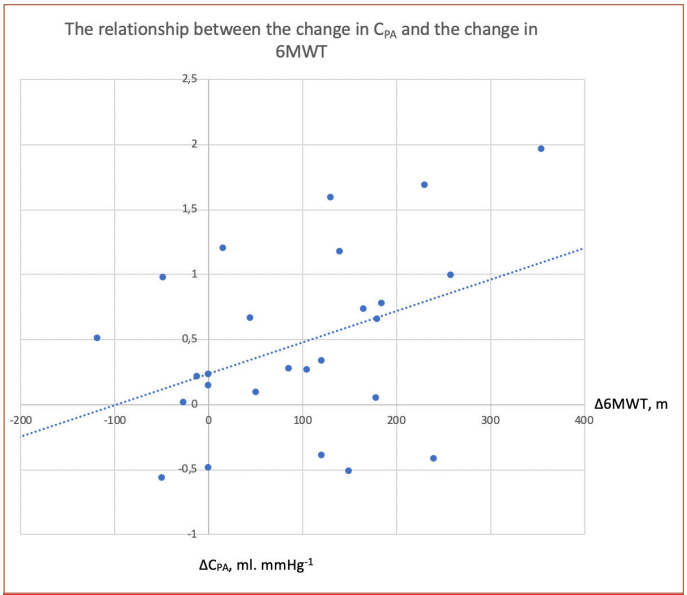

Figure 2. Relationship between the change in pulmonary arterial compliance (ΔC_{PA}) and the change in 6-minute walk test (Δ6MWT)

Table 3. Changes in the hemodynamics and clinical data before and after BPA treatment*

Variables	Baseline (n=26)	Final (n=26)	*P*-value
Hemodynamics			
Systolic PAP, mm Hg	77.5 (20)	65 (28)	<0.001
Mean PAP, mm Hg	47.5 (18)	37.5 (19)	<0.001
Diastolic PAP, mm Hg	26.5 (8.5)	23 (10.25)	0.013
PCWP, mm Hg	10.5 (4)	10 (3)	0.860
Right atrial pressure, mm Hg	9 (4.25)	8 (5.25)	0.465
PVR, Woods unit	9.24 (8.13)	5.11 (3.96)	<0.001
Pulmonary artery O_2 saturation (%)	60.1 (12.9)	65.6 (7.7)	0.029
CO, L/min	4.19 (2.3)	5.07 (1.34)	0.039
CI, L.m^2/min	2.43 (0.93)	2.88 (0.8)	0.008
SV, mL	47.4 (31.6)	65.8 (62.8)	0.137
HR, beats/min	85 (16.25)	80 (12.5)	0.537
Clinical and laboratory			
WHO class III, n (%)	19 (73.7)	7 (26.3)	<0.001
6MWT distance, meters	320 (179)	450 (143)	<0.001
NT-proBNP, ng/mL	456 (2,517)	189 (374)	0.003
Supplemental oxygen, n (%)	11 (42.3)	5 (19.2)	0.031

*Data are presented as median (interquartile range) or n (%). 6MWT - six-minute walking test; BPA - balloon pulmonary angioplasty; CI - cardiac index; CO - cardiac output; HR – heart rate; NT-proBNP - N-terminal pro-brain natriuretic peptide; PAP - pulmonary artery pressure; PCWP - pulmonary capillary wedge pressure; PVR - pulmonary vascular resistance; SV – stroke volume; WHO - World Health Organization

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_{PA} with BPA (20-22). Wiedenroth et al. (20) assessed C_{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_{PA} values both at baseline and after treatment. Magoń et al. (21) showed that C_{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} form 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.

Conflict of interest: None declared.

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