



Clinical Research

Pulmonary Artery Elastic Properties After Balloon Pulmonary Angioplasty in Patients With Inoperable Chronic Thromboembolic Pulmonary Hypertension

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ABSTRACT

Background: A significant proportion of the right ventricular afterload is determined by the elastic properties of the pulmonary artery (PA). We aimed to assess the effect of balloon pulmonary angioplasty (BPA) on PA elastic properties in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

Methods: We enrolled adult patients with CTEPH treated with BPA and controls without PH. Total PA compliance (CPa) was calculated as stroke volume/PA pulse pressure. PA distensibility (DC) and compliance (CC) coefficients were assessed by intravascular ultrasound to denote local elastic properties of the treated PA segments.

Results: We performed 103 BPA sessions in 17 patients with CTEPH (5 men [29%], aged 66 [64 to 73] years) who were followed for 6 (5 to 7) months after the last BPA. The median time between BPA sessions was 39 (28 to 52) days. The CPa, CC, and DC were lower in patients

RÉSUMÉ

Contexte : Une proportion importante de la postcharge du ventricule droit est déterminée par les propriétés élastiques de l'artère pulmonaire (AP). Nous avons pour objectif d'évaluer l'effet de l'angioplastie pulmonaire par ballonnet (APB) sur les propriétés élastiques de l'AP chez des patients qui présentaient une hypertension pulmonaire thromboembolique chronique (HPTC) inopérable.

Méthodologie : Nous avons recruté des patients adultes atteints d'HPTC inopérable et traités au moyen d'une APB ainsi que des témoins non atteints d'hypertension pulmonaire (HP). La compliance totale de l'AP (CAP) a été calculée en divisant le débit systolique par la pression différentielle de l'AP. Les coefficients de distensibilité (CD) et de compliance (CC) de l'AP ont été évalués par échographie intravasculaire pour que les propriétés élastiques locales des segments de l'AP traités puissent être déterminées.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare and progressive disease caused by obstruction of pulmonary arteries (PAs) by organized thrombi accompanied with microvascular remodelling.¹ It leads to a chronic increase in the right ventricular (RV) afterload, which is composed of a steady and a pulsatile component.² Traditionally, only the steady component, referred to as pulmonary vascular resistance (PVR), has been used to assess the effectiveness of targeted therapies. The reduction of PVR after pulmonary endarterectomy (PEA) was shown to be the main determinant of survival in patients with CTEPH.³ However, a significant proportion of the RV energy is spent generating pulsations, which is imposed by the elastic properties of the PA.⁴

PEA remains a treatment of choice for most patients with CTEPH. It was shown to reduce PVR and also to increase total PA compliance (CPa),^{5,6} which results in the reversal of RV remodelling and an improvement in RV function. Recently, a refined balloon pulmonary angioplasty (BPA) has been proposed as a treatment option for patients with CTEPH who are not eligible for PEA.⁷⁻¹² To achieve a significant hemodynamic effect, it is usually required to perform a series of BPA sessions each, including BPAs of a few diseased PA segments.

CPa is considered as a storage capacity of the entire PA tree and is defined as an increase in blood volume in the arterial system that produces a unit increase in arterial transmural pressure. CPa depends on the volume of the reservoir and on the elastic properties of the PAs determined by their walls' content and mean PA pressure (mPAP).¹³

The mechanisms of CPa reduction after PEA and BPA are not fully understood. Both methods reduce mPAP and increase the capacity of the pulmonary circulation, but their effect on local elastic properties may be different. In the PEA, organized thrombi are removed together with an internal and partly medial layer of the PA wall,¹⁴ whereas in the BPA,

Received for publication November 20, 2018. Accepted January 27, 2019.

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with CTEPH than in controls without PH ($n = 10$). Complete BPA treatment led to increase of CPa from 1.02 (0.70 to 1.39) to 2.08 (1.49 to 2.39) mL/mm Hg ($P < 0.001$) at the 6-month follow up, and this increase was in proportion to a decrease in pulmonary vascular resistance (PVR) ($R^2 = 0.74$; $P = 0.001$). CPa increased immediately after BPA session by 0.13 (−0.05; 0.33) mL/mm Hg ($P = 0.001$) and remained unchanged until the next BPA session. CC and DC exhibited no immediate change after catheter balloon inflation ($\Delta = 0$ [−0.03; 0.02] mm²/mm Hg, $P = 0.52$, and $\Delta = 0$ [−0.13; 0.13] %/mm Hg, $P = 0.91$, respectively) and remained unchanged at the 6-month follow-up.

Conclusions: BPA improved total CPa in proportion to a decrease in PVR despite no improvement in local elastic properties of the treated PA segments.

thromboembolic lesions are compressed against the vessel walls with the use of catheter balloons and are not removed.^{15,16}

In the current study, we aimed to assess the effect of BPA on CPa and local elastic properties of the treated arterial segments in a group of patients with inoperable CTEPH.

Methods

Study population

The study group consisted of adult patients with inoperable CTEPH who underwent complete BPA treatment between 2015 and 2017 in a single pulmonary hypertension (PH) reference centre. We started to enroll consecutive patients in the study after performing 10 BPA sessions in our centre. The flowchart, presenting enrollment of study patients, is shown in [Supplemental Fig. S1](#).

We recruited 2 control groups. The first was composed of age- and sex-matched healthy patients with normal pulmonary hemodynamics, who underwent right heart catheterization (RHC) in our institution. Patients were eligible for the control group if they did not have significant diseases affecting pulmonary function. The second control group included age-, sex-, and mPAP-matched treatment-naïve patients with idiopathic pulmonary PH (IPAH).

The Jagiellonian University Ethics Committee approved the study protocol No. 122.6120.237.2015, and written informed consent was obtained from each patient of the study group and of the controls before entering the study. All clinical investigations have been conducted according to the principles of the Declaration of Helsinki.

Baseline evaluation of the study group

Diagnosis of CTEPH was established according to the guidelines, and the operability and eligibility for BPA were assessed for each patient by the local CTEPH team, consisting of a cardiac surgeon, interventional cardiologist experienced in

Résultats : Nous avons réalisé 103 séances d'APB chez 17 patients atteints d'HPTC inopérable (5 hommes [29 %], âgés de 66 [64 à 73] ans) qui ont fait l'objet d'un suivi de 6 (5 à 7) mois après la dernière APB. Le temps médian écoulé entre les séances d'APB était de 39 (28 à 52) jours. La CAP, le CC et le CD étaient plus faibles chez les patients atteints d'HPTC inopérable que chez les témoins non atteints d'HP ($n = 10$). Le traitement complet au moyen d'une APB a entraîné une augmentation de la CAP de 1,02 (0,70 à 1,39) à 2,08 (1,49 à 2,39) ml/mm Hg ($p < 0,001$) à l'évaluation de suivi de 6 mois, et cette augmentation était proportionnelle à une diminution de la résistance vasculaire pulmonaire (RVP) ($R^2 = 0,74$; $p = 0,001$). La CAP a augmenté immédiatement après la séance d'APB de 0,13 (−0,05; 0,33) ml/mmHg ($p = 0,001$) et elle est demeurée inchangée jusqu'à la séance d'APB suivante. Le CC et le CD n'ont pas changé immédiatement après le gonflement du ballonnet ($\Delta = 0$ [−0,03; 0,02] mm²/mm Hg, $p = 0,52$, et $\Delta = 0$ [−0,13; 0,13] %/mm Hg, $p = 0,91$, respectivement) et ils sont demeurés inchangés au suivi du 6^e mois. **Conclusions :** L'APB a amélioré la CAP totale en proportion à une diminution de la RVP malgré l'absence d'amélioration des propriétés élastiques locales des segments de l'AP traités.

BPA, and PH specialist.¹⁷ In patients with CTEPH, we evaluated World Health Organization functional class (WHO-FC), serum level of the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and 6-minute walking distance (6MWD).

Assessment of total CPa

RHC with calculation of total CPa was performed in accordance with contemporary standards.¹⁸ The effects of complete BPA treatment for each patient was a difference between the values obtained at the 6-month follow-up (FU) and before the first BPA session ([Fig. 1A](#)). To assess the effect of each BPA session ([Fig. 1B](#)) we analyzed CPa at 3 time points: before the analyzed BPA session, immediately after the analyzed BPA session (immediate change), and before the next consecutive BPA session (early FU).

In the control groups, the RHC was performed once, during the diagnostic evaluation.

We used the following formula to calculate CPa

$$\text{Pulmonary artery compliance (CPa)} = \frac{\text{stroke volume}}{\text{pulmonary artery pulse pressure}}$$

where PA pulse pressure (PP) is the difference between systolic (sPAP) and diastolic (dPAP) PA pressure.

Cardiac output was assessed with the use of the Fick method with direct measurement of oxygen consumption. Stroke volume was calculated as cardiac output divided by heart rate.

To evaluate the relationship between CPa and PVR, we calculated the RC-time from the following equation:

$$RC - \text{time} = PVR \times CPa$$

BPA

The BPA procedures were performed according to recent reports.⁸ Our protocol of BPA treatment is presented in [Supplemental Methods S1](#) and [S2](#).

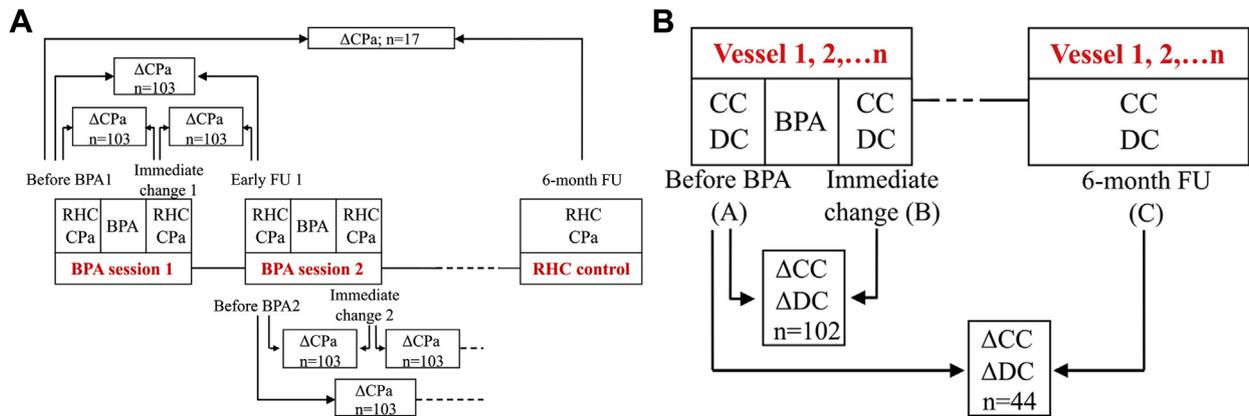


Figure 1. Time points of measurements of (A) pulmonary artery compliance (CPa) and (B) compliance coefficient (CC) and distensibility coefficient (DC) in a study group. CPa was measured before each balloon pulmonary angioplasty (BPA) (before BPA), immediately after each BPA (immediate change), and before the next BPA session (early follow-up [FU]). Comparisons of CPa at these 3 time points are available for 103 individual BPA sessions. Comparison of CPa before the first BPA and at the 6-month FU is available for 17 patients enrolled in the study. CC and DC were measured before BPA (before BPA), immediately after BPA (immediate change) and at the 6-month follow-up (6-month FU). Comparisons of DC and CC before BPA and immediately after BPA are available for 102 PA segments. Comparisons of DC and CC before BPA and at the 6-month FU are available for 44 PA segments. n, number of stenotic segments of the pulmonary artery treated with BPA; RHC, right heart catheterization.

Calculation of local elastic parameters: distensibility coefficient (DC) and compliance coefficient (CC)

Evaluation of the local elastic properties was performed by means of intravascular ultrasound (IVUS) both in the CTEPH (Supplemental Fig. S2) and the control groups (Supplemental Fig. S3) as described in the Supplemental Methods S3. Calculation of DC and CC (Supplemental Fig. S4) was performed in the IVUS recordings acquired before BPA, immediately after BPA, and at the 6-month FU in the CTEPH group (Fig. 1B) and only once during diagnostic RHC in the control groups. The measurements were calculated as the average value of the 3 consecutive cardiac cycles. For the purposes of this study, only ring and web lesions were analyzed, provided that we achieved adequate stabilization of the IVUS probe.

The following formulas were used for calculation of DC and CC:

$$DC = \frac{IVUS \text{ max. vessel area} - IVUS \text{ min. vessel area}}{PP \times IVUS \text{ min. area}} \times 100\%$$

$$CC = \frac{IVUS \text{ max. vessel area} - IVUS \text{ min. vessel area}}{PP}$$

To ensure evaluation of the same arterial segments of PA at different time points, we used selective angiography and IVUS. The use of selective pulmonary angiography to determine the anatomical position of the analyzed PA segment was previously shown feasible by Lau et al., who used IVUS technology to assess local elastic properties of the PA in patients with PAH before and after treatment with bosentan.¹⁹

Statistics

The categorical variables are presented as counts and percentages and the continuous variables as medians and interquartile ranges. To compare patients with CTEPH and controls, we used the Mann–Whitney U test. Parameters of

the PA elastic properties at different time points were compared with use of the Friedman test with *post hoc* analysis with the Wilcoxon matched-pairs signed-rank test.

As evaluation of the local elastic properties requires additional contrast and radiation usage we adapted power calculation to limit the number of arterial segments to be assessed (Supplemental Methods S4).

Spearman correlation was used to estimate the relationship between CPa and CC, DC and markers of disease severity, and between CC or DC and mPAP and vessel diameter. To adjust for multiple comparisons, we used Bonferroni correction. Interobserver and intraobserver variability of CC and DC measurements were assessed using the method of Bland and Altman.²⁰ The significance level was set at $P < 0.05$. The statistical analysis was performed with Stata/SE 12.1 StatCorp LP and RStudio version 0.99.467 (StataCorp LLC, College Station, Texas).

Results

Study group

Between January 2015 and June 2017, we treated 541 PA segments including 81 (15%) ring and 351 (65%) web lesions in 159 (29%) segmental and 382 (71%) subsegmental arteries during 103 BPA sessions in 17 patients with CTEPH, aged 66 (64 to 73) years (men, $n = 5$ [29%]). One (6%) patient had persistent CTEPH after PEA. Nine (53%) patients were treated with specific medications, including subcutaneous treprostinil (4 [29%]), riociguat (2 [12%]), and a combination of subcutaneous treprostinil with riociguat (2 [12%]) or sildenafil (1 [6%]), according to local availability. The doses of the drugs were stable for at least 3 months before starting BPA. We did not modify these therapies during the study period. Baseline characteristics of the study group compared with controls are presented in Supplemental Table S1.

Table 1. Clinical and hemodynamic characteristics of 17 patients with chronic thromboembolic pulmonary hypertension before the first session of balloon pulmonary angioplasty and 6 months after completing interventional treatment

Variable	Before BPA	After BPA	<i>P</i> value
WHO class: I/II/III/IV [n]	0/1/16/0	6/11/0/0	0.001
6MWD [m]	360 [290-390]	393 [350-450]	0.003
NT-proBNP [pg/mL]	1807 [477-2634]	228 [144-722]	0.001
mPAP [mm Hg]	39 [36-49]	29 [22-31]	0.001
RAP [mm Hg]	4 [3-6]	4 [3-6]	0.10
CI [L/min/m ²]	2.21 [1.85-2.46]	2.45 [2.21-2.80]	0.13
SV [mL]	57 [46-61]	69 [57-80]	0.04
PVR [WU]	9.0 [6.1-11.3]	3.9 [3.5-5.5]	0.001
mvSatO ₂ [%]	59 [57-64]	66 [61-70]	0.01
AoSatO ₂ [%]	90 [88-92]	95 [92-96]	0.002
HR [1/min]	74 [62-80]	67 [56-75]	0.16
CPa [mL/mm Hg]	1.02 [0.70-1.39]	2.08 [1.49-2.38]	0.005
PP [mm Hg]	50 [45-68]	35 [29-44]	0.005

Continuous variables are presented as median and interquartile ranges. AoSatO₂, arterial oxygen saturation; CI, cardiac index; CPa, total pulmonary artery compliance; HR, heart rate; mPAP, mean pulmonary artery pressure; mvSatO₂, mixed venous oxygen saturation; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PP, pulse pressure; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; SV, stroke volume; 6MWD, 6-minute walking distance.

Hemodynamic and clinical effects of BPA at 6-month follow-up

The median number of BPA sessions per patient was 6 (5 to 8), and the median number of treated segments was 32 (22 to 41). Hemodynamic and clinical data before the first BPA and at the 6-month follow-up are presented in the Table 1.

BPA safety

Ninety-one (88%) BPA sessions were performed without clinically significant complications. In 12 (12%) we observed mild complications,²¹ as presented in detail in Supplemental Results S1.

CPa and local elastic properties in patients with CTEPH and controls

In patients with CTEPH, the evaluation of the local elastic properties was feasible in 102 diseased PA segments (28%) for which we gained IVUS recordings of a sufficient quality. The measurements of CC and DC were reproducible as shown in the Bland and Altman plot in the Supplemental Fig. S5A and B. The DC and CC were lower in patients with CTEPH than in controls with normal hemodynamics (DC [%/mm Hg]: 0.33 [0.20 to 0.47] vs 1.13 [0.82 to 1.30]; *P* < 0.001, CC [mm²/mm Hg]: 0.06 [0.03 to 0.11] vs 0.13 [0.06 to 0.20]; *P* < 0.001) and similar to IPAH patients (DC [%/mm Hg]: 0.33 [0.20 to 0.47] vs 0.27 [0.13 to 0.47], *P* = 0.25, CC [mm²/mm Hg]: 0.06 [0.03 to 0.11] vs 0.03 [0.01 to 0.08], *P* = 0.42).

In patients with CTEPH, the median diameter of the evaluated PA segments was 4.1 (3.5 to 5.1) mm with the median vessel and lumen area of 13.5 (9.4 to 20.2) and 4.4 (3.2 to 5.9) mm², respectively. Both CC and DC correlated with mPAP (*r* = -0.26; *P* = 0.01 for CC and *r* = -0.38; *P* = 0.0001 for DC), whereas only CC, but not DC, correlated with vessel area (*r* = 0.73; *P* = 0.0001 for CC and *r* = 0.10; *P* = 0.32 for DC).

CPa was assessed in all study participants. It was lower in patients with CTEPH than in controls with normal hemodynamics (1.0 [0.7 to 1.4] vs 5.1 [4.8 to 7.2] mL/mm Hg; *P* < 0.001) and similar to IPAH patients (1.0 [0.7 to 1.4] vs 0.9 [0.5 to 1.2]; *P* = 0.32).

In the CTEPH group, we observed correlation between CPa and NT-proBNP (*r* = -0.73; *P* = 0.0022) and 6MWD

(*r* = 0.61; *P* = 0.01) and also a weak correlation with CC (*r* = 0.24; *P* = 0.02) and DC (*r* = 0.33; *P* = 0.001).

In Supplemental Table S2 we compared the indices of local and total PA compliance among patients with CTEPH, patients with IPAH, and controls without PH.

Changes of CPa and local elastic properties induced by BPA

Analysis of CPa in 17 patients showed that CPa increased from 1.02 (0.70 to 1.39) before the first BPA session to 2.08 (1.49 to 2.39) mL/mm Hg (*P* < 0.001) at the 6-month FU.

Analysis of each of the 103 BPA sessions (Fig. 2A) showed that CPa increased immediately after the BPA session and remained unchanged at the early FU (before the next BPA session). A similar observation was made for PVR. In contrast, there was no change in mPAP immediately after BPA, but it was significantly lower at the early FU. In Supplemental Fig. S6 we show changes (Δ values) of CPa, mPAP, and PVR among the analyzed time points.

After BPA, we observed an increase in the median diameter (4.1 [3.5 to 5.1] vs 4.3 [3.6 to 5.3] mm; *P* = 0.001), the median vessel area (13.5 [9.4 to 20.2] vs 14.3 [10.0 to 22.4] mm²; *P* = 0.001) and the median lumen area (4.4 [3.2 to 5.9] vs 5.8 [4.2 to 8.1] mm²; *P* = 0.001) of the treated PA segments. Local elastic properties of the 102 treated PA segments exhibited no immediate change after BPA, as shown in Fig. 2B. In 44 (43%) lesions, for which we were able to perform IVUS examination at the 6-month FU, we found no change in either DC or CC (Fig. 2B). The median time between each BPA session (the time to early FU) was 39 (28 to 52) days.

RC-time

Analysis of 103 BPA sessions showed that the RC-time did not change immediately after the BPA session (Δ = 0.00 [-0.08; 0.09] s; *P* = 0.61) or at the early FU examination (Δ = 0.00 [-0.07; 0.07] s; *P* = 0.91), as shown in Supplemental Fig. S7. The RC-time also remained unchanged when assessed before first BPA session and at 6-month FU (0.53 [0.47 to 0.64] vs 0.51 [0.49 to 0.62] s; *P* = 0.31; Supplemental Fig. S7).

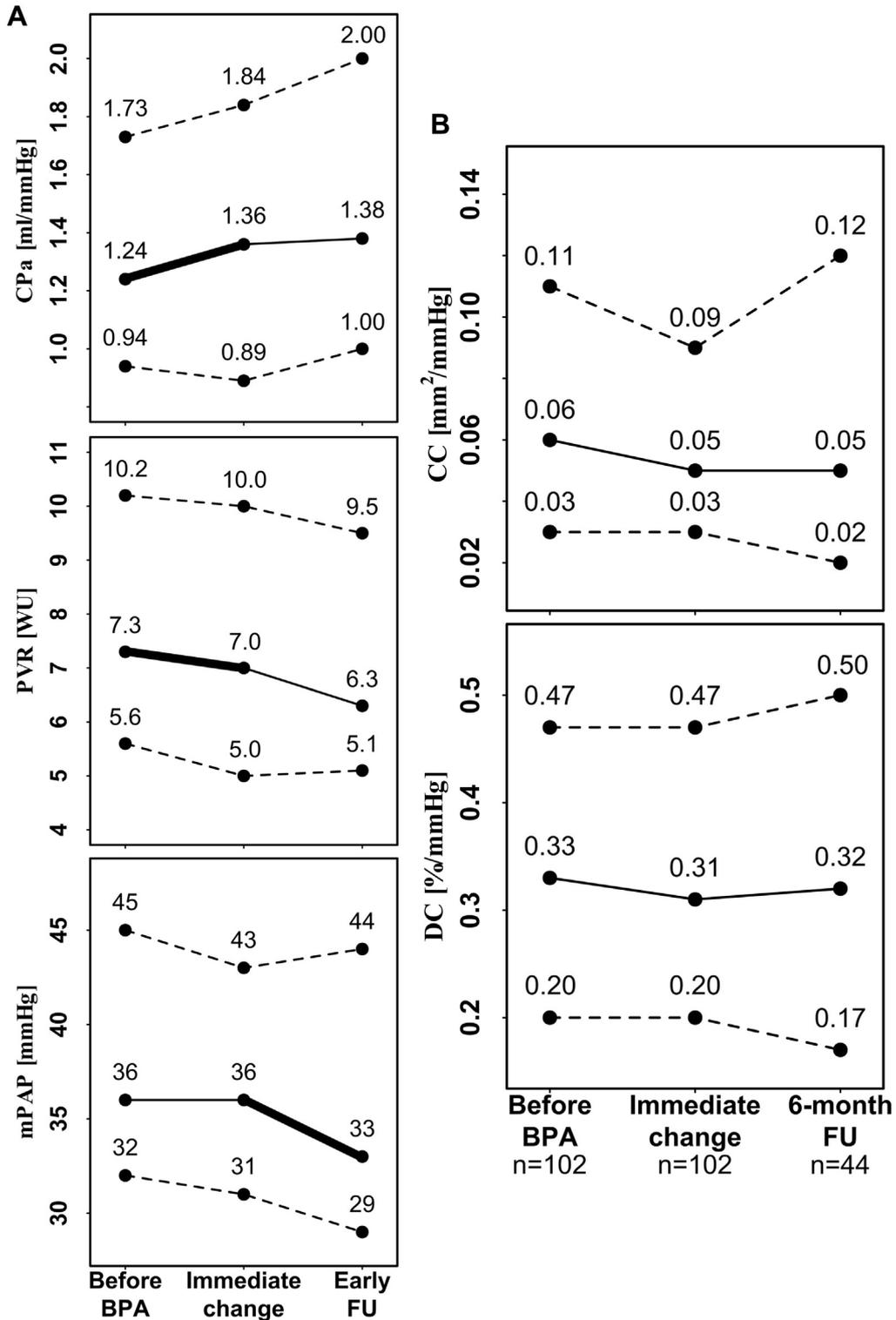


Figure 2. (A) The effect of each BPA sessions on pulmonary artery compliance (CPa), pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (mPAP). (B) The effect of BPA on compliance coefficient (CC) and distensibility coefficient (DC) of diseased PA segments. The median number of BPA sessions per patient was 6 (5 to 8). The **solid and dashed lines** represent median values and interquartile ranges, respectively. **Thick solid lines** represent significant ($P < 0.05$) changes between 2 adjacent time points.

Discussion

In the current study, we showed that both local and total compliance of the PA are decreased in patients with

inoperable CTEPH compared with patients without PH. We further showed that treatment with BPA improved CPa in proportion to a reduction of PVR despite the lack of

improvement of local compliance of the treated PA segments.

Previous studies showed an improvement in CPa after PEA in patients with operable CTEPH^{6,22} and after BPA in patients with CTEPH²³ and chronic thromboembolic disease.²⁴ However, to the best of our knowledge, we are the first to describe the local PA elastic properties at the segmental and subsegmental level in patients with CTEPH (the validity and repeatability of IVUS measurements in PA are discussed in [Supplemental Discussion 1](#)). Previous reports on local PA compliance were focused only on PAH population^{19,25} and showed that both CC and DC were decreased compared with controls without PH. In our study, CC and DC were also decreased in patients with CTEPH compared with age- and sex- matched patients without PH. The values of CC and, to a lesser extent of DC, differ among studies and are difficult to compare because of differences in mPAP and, especially in the case of CC,²⁶ owing to a different calibre of the measured PA segments. However, our study shows that decreased local compliance of PA is not specific for CTEPH but is a feature of PH in general. We observed that CC, DC, and CPa were similar in age-, sex-, and mPAP-matched patients with CTEPH and IPAH.

Local elastic properties as measured by IVUS are subjective to improvement in patients with PAH treated with epoprostenol as shown by Rodes-Sabau et al.²⁷ but not to bosentan, as shown in a more recent paper by Lau et al.¹⁹ In our study, based on the pressure dependence of the arterial wall stiffness, we expected both CC and DC to improve after BPA due to lowering of mPAP, especially at the 6-month FU, as the mPAP decrease was significant at that point. In fact, both CC and DC remained unchanged after BPA, which could suggest a negative effect of BPA on the local elasticity of treated PA segments. The potential mechanisms of the failure to improve local elastic properties by BPA include stretching of the vessel wall and an injury to the elastic lamina by balloon inflation with high pressure. We propose 2 mechanisms of this effect ([Supplemental Discussion S2](#)).^{15,26,28}

Although CC and DC are indices of local arterial compliance, CPa is a measure of the total compliance of the lung vasculature. CPa is determined by the prevailing mPAP and by the elasticity of the PA wall, which is mainly determined by its content.¹³ Consequently, CPa can be changed with or without changes in the intrinsic arterial wall features. Although worsening of the local elastic properties of a few segments submitted to BPA would probably not have a significant impact on the total CPa, it should be noticed that BPA treatment requires dilation of several PA segments to achieve good hemodynamic results. In our study, the median number of treated segments in a patient was 32 (22 to 41).

Nevertheless, despite a failure to improve local elastic properties in our study, we observed an increase in CPa after BPA. We speculate that this improvement was due to the reduction in mPAP as well as an increased volume of pulmonary vessels, which were stretched by BPA. It might have also been attributed to the improvement in endothelial function of the pulmonary vessels. Studies on systemic circulation showed that the endothelium may influence arterial stiffness by both short-term and long-term alterations in the content, organization, and function of arterial wall components.²⁹

Skoro-Sayer et al. showed that the increase in CPa occurred immediately after the PEA and remained constant during long-term FU.⁶ This is in line with our findings demonstrating that the CPa and the PVR improved directly after BPA and remained constant in the FU. This immediate effect of BPA on CPa and PVR, however, did not translate into an immediate decrease in the mPAP. The other authors³⁰ found that the mPAP decreases no earlier than 5 to 14 days after BPA.

The RC-time constant is calculated as the product of PVR and CPa and represents the pressure decay in the PA during diastole.¹³ Several studies showed that RC-time is constant over a wide range of severities, etiologies, and treatments of PH.³¹ However, recent studies suggest that the RC-time is decreased in patients with heart failure and increased PA wedge pressure and in patients with CTEPH and proximal localization of the organized thrombi.^{22,32} This means that in these patients at any given level of PVR the CPa is lower and, consequently, the RV afterload greater than expected.

Ross et al.²² found that, after PEA, a decrease in PVR was not matched by an equivalent increase in the CPa, leading to a decrease in RC-time. The authors speculated that the removal of tunica intima together with a part of the tunica media of the PAs with subsequent healing after PEA may not leave the arterial wall with the same compliance properties as the normal PA.

In our study, the RC-time was not changed after the series of BPAs, which means that CPa increased in proportion to a decrease of PVR. The differences between our findings and those of Ross et al. may result from the fact that BPA acts locally and may affect the elastic properties only of the small arterial segments.

We also found in our study that a higher CPa at baseline was associated with lower NT-proBNP, and longer 6MWD. This corresponds with previous observations, in which higher CPa was related to better RV function.³³ It has been shown that exercise tolerance after PEA is strongly related to CPa improvement.³⁴

Strengths

Our study has several strengths. First our results are novel. We are the first to describe the local elastic properties of PA in patients with CTEPH using a direct visualization of the PA wall. We also presented, for the first time, the changes of the local PA elastic properties after BPA. Second, we measured CC and DC, recommended indices of the local elastic properties,³⁵ using *in vivo* imaging with the use of IVUS, a validated tool to assess arterial morphology reliably. Third, our study has an important clinical meaning. Considering the lack of favourable effect of current BPA treatment on the elastic properties of the treated segments, it evokes further improvement of interventional techniques in CTEPH.

Limitations

Our study has some limitations. First, our group was relatively small. However, we aimed to understand the mechanisms of BPA but not to prove its efficacy or safety, which was done by other authors.^{8,9} Despite a relatively small group of patients, we analyzed a large number of arterial segments. Second, we have chosen for analysis only a fraction

of all diseased PA segments, in which we obtained a steady position of the IVUS probe. To immobilize the IVUS probe, the patient needed to hold breath for a few seconds, and the operator needed to manipulate the guiding catheter and the guidewire under fluoroscopy guidance. We consider that the selection of the segments could have been biased, but it resulted more from a random effect of anatomic and technical difficulties rather than from some consistent effect, and it did not influence our main aim, which was to assess the changes in the same lesions both before and after BPA. Third, the total compliance was approximated with the CPa based on the simplified approach; however, this is a widely used and a clinically relevant estimate.^{13,36}

Conclusions

The elastic properties of PAs were decreased in patients with CTEPH compared with controls, who had normal hemodynamics. BPA improved total CPa in proportion to a decrease in pulmonary vascular resistance despite no improvement in local elastic properties of the treated PA segments.

Funding Sources

Research grant of the Polish Cardiac Society: "Servier Research Grant 2015". Research grant of the Jagiellonian University Medical College No K/ZDS/006136.

Disclosures

The authors have no conflicts of interest to report.

References

1. Simonneau G, Torbicki A, Dorfmüller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev* 2017;26:1-14.
2. Champion HC, Michelakis ED, Hassoun PM. Comprehensive invasive and noninvasive approach to the right ventricle-pulmonary circulation unit state of the art and clinical and research implications. *Circulation* 2009;120:992-1007.
3. Cannon JE, Su L, Kiely DG, et al. Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: results from the United Kingdom National Cohort. *Circulation* 2016;133:1761-71.
4. Saouti N, Westerhof N, Helderma F, et al. Right ventricular oscillatory power is a constant fraction of total power irrespective of pulmonary artery pressure. *Am J Respir Crit Care Med* 2010;182:1315-20.
5. Madani MM, Auger WR, Pretorius V, et al. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. *Ann Thorac Surg* 2012;94:97-103.
6. Skoro-Sajer N, Marta G, Gerges C, et al. Surgical specimens, haemodynamics and long-term outcomes after pulmonary endarterectomy. *Thorax* 2014;69:116-22.
7. Lang I, Meyer BC, Ogo T, et al. Balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension. *Eur Respir Rev* 2017;26:160119.
8. Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv* 2012;5:748-55.
9. Kimura M, Kohno T, Kawakami T, et al. Midterm effect of balloon pulmonary angioplasty on hemodynamics and subclinical myocardial damage in chronic thromboembolic pulmonary hypertension. *Can J Cardiol* 2017;33:463-70.
10. Kopeć G, Stępniewski J, Waligóra M, Kurzyna M, Biederman A, Podolec P. Staged treatment of central and peripheral lesions in chronic thromboembolic pulmonary hypertension. *Pol Arch Med Wewn* 2016;126:97-9.
11. Roik M, Wretowski D, Łabyk A, et al. Refined balloon pulmonary angioplasty driven by combined assessment of intra-arterial anatomy and physiology: multimodal approach to treated lesions in patients with non-operable distal chronic thromboembolic pulmonary hypertension: technique, safety and efficacy of 50 consecutive angioplasties. *Int J Cardiol* 2016;203:228-35.
12. D'Arsigny CL. Treatment for patients with chronic thromboembolic pulmonary hypertension: where does balloon pulmonary angioplasty sit in the treatment algorithm? *Can J Cardiol* 2017;33:430-2.
13. Chemla D, Lau EMT, Papelier Y, Attal P, Hervé P. Pulmonary vascular resistance and compliance relationship in pulmonary hypertension. *Eur Respir J* 2015;46:1178-89.
14. Mercier O, Fadel É, Mussot S, et al. Surgical treatment of chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2014;43:994-1007.
15. Kitani M, Ogawa A, Sarashina T, Yamadori I, Matsubara H. Histological changes of pulmonary arteries treated by balloon pulmonary angioplasty in a patient with chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv* 2014;7:857-9.
16. Kopeć G, Waligóra M, Stępniewski J, Zmudka K, Podolec P, Matsubara H. In vivo characterization of changes in composition of organized thrombus in patient with chronic thromboembolic pulmonary hypertension treated with balloon pulmonary angioplasty. *Int J Cardiol* 2015;186:279-81.
17. Galìè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2016;37:67-119.
18. Kurzyna M, Araszkiwicz A, Błaszczak P, et al. Summary of recommendations for the haemodynamic and angiographic assessment of the pulmonary circulation. Joint Statement of the Polish Cardiac Society's Working Group on Pulmonary Circulation and Association of Cardiovascular Interventions. *Kardiologia Pol* 2015;73:63-8.
19. Lau EMT, Iyer N, Ihsar R, Bailey BP, Adams MR, Celermajer DS. Abnormal pulmonary artery stiffness in pulmonary arterial hypertension: in vivo study with intravascular ultrasound. *PLoS ONE* 2012;7:e33331.
20. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-10.
21. Kopeć G, Stępniewski J, Magoń W, Waligóra M, Podolec P. Prolonged catheter balloon inflation for the treatment of hemoptysis complicating balloon pulmonary angioplasty. *Polish Arch Intern Med* 2017;127:129-30.
22. MacKenzie Ross RV, Toshner MR, Soon E, Naeije R, Pepke-Zaba J. Decreased time constant of the pulmonary circulation in chronic thromboembolic pulmonary hypertension. *AJP Heart Circ Physiol* 2013;305:259-64.
23. Wiedenroth CB, Ghofrani HA, Adameit MSD, et al. Sequential treatment with riociguat and balloon pulmonary angioplasty for patients with

- inoperable chronic thromboembolic pulmonary hypertension. *Pulm Circ* 2018;8: 204589401878399.
24. Wiedenroth CB, Olsson KM, Guth S, et al. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic disease. *Pulm Circ* 2018;8:204589321775312.
 25. Shen J, Cai Z, Sun L, Yang C, He B. The application of intravascular ultrasound to evaluate pulmonary vascular properties and mortality in patients with pulmonary arterial hypertension. *J Am Soc Echocardiogr* 2016;29:103-11.
 26. Hunter KS, Lammers SR, Shandas R. Pulmonary vascular stiffness: measurement, modeling, and implications in normal and hypertensive pulmonary circulations. *Compr Physiol* 2011;1:1413-35.
 27. Rodés-Cabau J, Domingo E, Román a, et al. Intravascular ultrasound of the elastic pulmonary arteries: a new approach for the evaluation of primary pulmonary hypertension. *Heart* 2003;89:311-5.
 28. Shimokawahara H, Ogawa A, Mizoguchi H, Yagi H, Ikemiyagi H, Matsubara H. Vessel stretching is a cause of lumen enlargement immediately after balloon pulmonary angioplasty: intravascular ultrasound analysis in patients with chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv* 2018;11:e006010.
 29. Kopeć G, Podolec P, Podolec J, Rubiś P, Zmudka K, Tracz W. Atherosclerosis progression affects the relationship between endothelial function and aortic stiffness. *Atherosclerosis* 2009;204:250-4.
 30. Hosokawa K, Abe K, Oi K, Mukai Y, Hirooka Y, Sunagawa K. Negative acute hemodynamic response to balloon pulmonary angioplasty does not predicate the long-term outcome in patients with chronic thromboembolic pulmonary hypertension. *Int J Cardiol* 2015;188:81-3.
 31. Vonk Noordegraaf A, Chin KM, Haddad F, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. *Eur Respir J* 2018:1801900.
 32. Tedford RJ, Hassoun PM, Mathai SC, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. *Circulation* 2012;125:289-97.
 33. Stevens GR, Garcia-Alvarez A, Sahni S, Garcia MJ, Fuster V, Sanz J. RV dysfunction in pulmonary hypertension is independently related to pulmonary artery stiffness. *JACC Cardiovasc Imaging* 2012;5:378-87.
 34. Ghio S, Morsolini M, Corsico A, et al. Pulmonary arterial compliance and exercise capacity after pulmonary endarterectomy. *Eur Respir J* 2014;43:1403-9.
 35. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27:2588-605.
 36. Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. *J Am Coll Cardiol* 2006;47:799-803.

Supplementary Material

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