Heart, Lung and Circulation (2021) ■, ■–■
1443-9506/21/$36.00
https://doi.org/10.1016/j.hlc.2021.10.009

ORIGINAL ARTICLE

Balloon Pulmonary Angioplasty in Patients With Inoperable or Recurrent/Residual Chronic Thromboembolic Pulmonary Hypertension: A Single-Centre Initial Experience

Halil Atas, MD [a,*], Bulent Mutlu, MD [a], Dursun Akaslan, MD [a], Derya Kocakaya, MD [b], Batur Kanar, MD [a], Nevsun Inanc, MD [c], Sait Karakurt, MD [b], Cagatay Cimsit, MD [d], Bedrettin Yildizeli, MD [e]

[a]Marmara University, School of Medicine, Department of Cardiology
[b]Marmara University, School of Medicine, Department of Pulmonology
[c]Marmara University, School of Medicine, Department of Internal Medicine, Division of Rheumatology
[d]Marmara University, School of Medicine, Department of Radiology
[e]Marmara University, School of Medicine, Department of Thoracic Surgery

Received 26 August 2020; received in revised form 31 May 2021; accepted 16 October 2021; online published-ahead-of-print xxx

Background Patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) are often treated with pulmonary arterial hypertension-specific drugs. However, most of these patients remain symptomatic, despite medical treatment. Balloon pulmonary angioplasty (BPA) is an emerging therapeutic intervention for patients with inoperable CTEPH. This study aimed to report the initial experience of BPA in a tertiary referral centre for CTEPH.

Methods A total of 26 consecutive patients, who underwent 91 BPA sessions, were included in the study. All patients underwent a detailed examination, including 6-minute walking distance (6MWD), and right heart catheterisation at baseline and 3 months after the last BPA session.

Results The mean age of the patients was 51±17 years. Fifteen (15) patients had inoperable CTEPH and 11 patients had residual or recurrent CTEPH post pulmonary endarterectomy (PEA). Functional class improved in 17 of 26 (65%) patients. The 6MWD increased from a mean 315±129 to 411±140 m ($p<0.001$), and NT pro-BNP reduced from a median 456 to 189 pg/mL ($p=0.001$). The number of patients who required supplemental oxygen decreased from 11 (42.3%) to five (19%) ($p=0.031$) after BPA treatment. The mean pulmonary artery pressure decreased from a mean 47.5±13.4 to 38±10.9 mmHg ($p<0.001$), the pulmonary vascular resistance decreased from a mean 9.3±4.7 to 5.8±2.8 Wood units ($p<0.001$), and the cardiac index increased from a mean 2.4±0.7 to 2.9±0.6 L/min/m^2 ($p=0.008$).

Conclusions Balloon pulmonary angioplasty improved haemodynamics, 6MWD, and functional class, and reduced the requirement for supplemental oxygen, with an acceptable risk-benefit ratio in patients with inoperable CTEPH and with residual/recurrent CTEPH.

Keywords Balloon pulmonary angioplasty • Inoperable CTEPH

*Corresponding author at: Göztepe mh, Fahrettin Kerim Gökay Cd, No: 184/7, Kadıköy, İstanbul, Turkey; Email: dratashalil@gmail.com

Please cite this article in press as: Atas H, et al. Balloon Pulmonary Angioplasty in Patients With Inoperable or Recurrent/Residual Chronic Thromboembolic Pulmonary Hypertension: A Single-Centre Initial Experience. Heart, Lung and Circulation (2021), https://doi.org/10.1016/j.hlc.2021.10.009

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease caused by persistent obstruction of the pulmonary arteries by organised fibrotic clots, leading to flow redistribution and secondary remodelling of pulmonary microvascular vessels. CTEPH is a significant cause of pulmonary hypertension (PH), leading to right heart failure and death if left without treatment [1]. Pulmonary endarterectomy (PEA) is the established therapeutic intervention with the most published evidence and is the guideline-recommended treatment for patients with CTEPH. However, approximately one-third of patients are ineligible for PEA because of diffuse distal lesions that are technically inaccessible during surgery or the presence of severe comorbidities that prohibit surgery. On the other hand, about half of all patients undergoing PEA have persistent PH, which is commonly mild, but sometimes moderate or severe and requiring additional treatment [2–4]. In addition, patients with CTEPH may develop pulmonary embolism due to ineffective anticoagulation or thrombophilia, resulting in recurrent PH, even in those who have previously undergone curative surgery. Patients with both inoperable CTEPH and residual or recurrent PH after PEA are treated with pulmonary arterial hypertension (PAH)-specific drugs. However, despite treatment with PAH-specific drugs, the vast majority of these patients remain significantly symptomatic.

Balloon pulmonary angioplasty (BPA) is an emerging therapeutic intervention that was first described by Feinstein et al. in patients with CTEPH [5]. However, despite the improvement in haemodynamics, it was abandoned due to the high frequency of significant complications such as reperfusion lung injury and pulmonary bleeding. Japanese investigators then refined BPA by repeated staged procedures to reduce reperfusion lung injury and pulmonary bleeding [6,7]. An increasing number of studies have recently shown improvement in haemodynamics, symptoms and functional capacity, with significantly lower rates of major complications with a refined BPA technique [8–11]. Therefore, a BPA program was started at the current centre in October 2017 for patients who were deemed inoperable or with residual or recurrent PH. This study aimed to report the initial experience of BPA in the current centre, which is a tertiary referral CTEPH centre.

Materials and Methods

Study Patients

The study conformed to the principles outlined in the Declaration of Helsinki. The local ethics committee approved the study and all patients gave written informed consent. A total of 31 patients with inoperable CTEPH underwent BPA interventions at the centre between October 2017 and January 2020. One patient was re-evaluated at the multidisciplinary PH meeting after the first session, and it was decided that PEA would be more appropriate and he was referred for PEA; this patient was excluded from the study. The data of four patients were not included in the analyses because their BPA interventions were still ongoing. As a result, 26 patients who completed the BPA treatment course were included in the study. A multidisciplinary PH team, consisting of cardiologists, pulmonologists, an expert surgeon for PEA, a rheumatologist, and a radiologist expert in pulmonary vascular imaging, evaluates all patients who are referred to the centre with a suspicion of CTEPH. All patients undergo a comprehensive examination, including medical history, echocardiography, multislice computed tomography (CT), ventilation/perfusion scintigraphy, right heart catheterisation (RHC), and selective pulmonary angiography, if required. Given the new haemodynamic definition of PH in the sixth world symposium on PH, patients with mean pulmonary artery pressure (mPAP) >20 mmHg and pulmonary vascular resistance (PVR) >3 Wood units were accepted as CTEPH. CTEPH is diagnosed and treatment processes are determined according to the guideline of the European Society of Cardiology for the diagnosis and management of PH [1].

Therefore, PEA is considered as the first choice of treatment in the current centre. Patients are regarded as inoperable if they have severe medical comorbidities and surgically inaccessible lesions. PAH-specific drugs are initiated in all patients with PH but who are ineligible for PEA. Patients with functional class III or IV despite medical therapy are considered for BPA. The eligibility for BPA is determined based on a consensus among the multidisciplinary PH team. All patients are informed about the potential risks and benefits of the procedure and they provide written informed consent.

Clinical Evaluation

All patients underwent a comprehensive clinical assessment before the first BPA intervention. After a detailed physical examination, the medical history of the patients and their demographic data were recorded on the prepared patient follow-up form. World Health Organization (WHO) functional class, CTEPH diagnosis date, history of venous thromboembolism, hypercoagulable status, and all pharmacologic treatments were recorded. The periprocedural tests included complete blood count, kidney function tests, serum N terminal prohormone-brain natriuretic (NT pro-BNP) levels, 6-minute walk test (6MWT), and RHC to measure mPAP, right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), PVR, pulmonary artery oxygen saturation, and cardiac output (CO). RHC was performed via the right jugular vein using a Swan-Ganz catheter, and CO was measured using the indirect Fick method. After the last BPA session, all patients were re-evaluated at 3 months' follow-up to determine the efficacy of BPA guided by repeating the above tests.

BPA Procedure

Warfarin therapy was switched with enoxaparin, and the procedure was performed when the INR level was <2. Direct

Please cite this article in press as: Atas H, et al. Balloon Pulmonary Angioplasty in Patients With Inoperable or Recurrent/Residual Chronic Thromboembolic Pulmonary Hypertension: A Single-Centre Initial Experience. Heart, Lung and Circulation (2021), https://doi.org/10.1016/j.hlc.2021.10.009

oral anticoagulation drugs were omitted one day before the intervention without switching with enoxaparin. During the procedure, 5,000 IU of unfractionated heparin was given intravenously, and 1,000 IU additional heparin was administered after one hour if the intervention was prolonged. RHC (Swan-Ganz catheter, Edwards Lifesciences, Irvine, CA, USA) was performed at the beginning of each procedure as standard.

Two (2) interventional cardiologists performed BPA in a series of staged procedures using right femoral access. A 6-F long destination sheath (65 cm; Terumo, Tokyo, Japan) guided by a pigtail catheter was used in the pulmonary artery to provide guiding catheter stability. A 6-F–guiding catheter (Medtronic multi-purpose, Judkins right 4, Left Amplatz 1, Medtronic, Dublin, Ireland) was inserted in the segmental pulmonary artery and selective pulmonary angiography was performed. The target lesion was crossed using a 0.014-inch guidewire (Soft J, Asahi Intecc, Japan) and then the lesion was dilated using 1.25–4.0 mm x 20 mm semi-compliant balloon catheters (1.25 mm Brossmed, Japan; 2.0 to 4.0 Simeks, Turkey). Under-sized balloon catheters were often used in the initial sessions to avoid reperfusion lung injury, especially in patients who had high mean pulmonary artery pressure and PVR; after the mPAP and PVR decreased, all vessels were dilated using appropriate-diameter balloon catheters (2–7 mm Simeks, Turkey). The lower lobe lesions were first targeted because the pulmonary blood flow at this site was high compared with others. Thus, more reduction in mPAP and PVR was able to be achieved in the initial sessions. During the first few cases, mainly ring-like, subtotal, and web lesions on unilateral lungs were treated per session; however, as experience increased, all types of lesions (webs, tortuous, and occlusions) were treated. When the haemodynamics were favourable, multiple lesions within a unilateral lung were treated in a single session. Balloon support and guidewires with medium tip weights (Miracle 3 and 6 g, Asahi Intecc, Japan) were used for crossing total occlusions, and patients were instructed to hold their breath while crossing tortuous lesions. During one hospital admission, two 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 mPAP <30 mmHg was reached or when it was assumed that all accessible lesions had been treated [9].

Assessment of Complications

Vessel injury was described as contrast extravasation of the outside of lumen, retention of the contrast within the arterial wall, or prolonged persistence of contrast in the interstitial area vascularised by the injured artery. Haemoptysis was classified as mild with a total haemoptysis volume <50 mL, and as severe with a total amount ≥50 mL or lasting more than one day [12]. Reperfusion lung injury was staged based on the Inami classification [13].

Table 1 Baseline characteristics of the study population.

Age, yr	51±17
Sex, female	18 (69.2%)
Body mass index, m/kg^2	27.7±6.8
History of VTE, n (%)	7 (26.9%)
Inoperable disease, n (%)	15 (57.7%)
Predominant distal disease, n (%)	10 (38.5%)
Severe medical comorbidities, n (%)	5 (19.2%)
Previous PEA (residual or recurrent), n (%)	11 (42.3%)
Underlying disease or hypercoagulable state, n (%)	11 (42.3%)
Splenectomy, n (%)	1 (3.8%)
Lupus, n (%)	2 (7.7%)
Isolated pulmonary vasculitis, n (%)	2 (7.7%)
Factor V Leiden homozygote, n (%)	2 (7.7%)
Behçet disease, n (%)	1 (3.8%)
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 analogue	5 (19.2%)
Medications (none/single/double/triple), n	5/17/1/3
Anticoagulant drugs	
Warfarin, n (%)	10 (38.5%)
Direct oral anticoagulant, n (%)	16 (61.5%)

Abbreviations: VTE, venous thromboembolism; PEA, pulmonary endarterectomy; WHO, World Health Organization.
Data are presented as mean± standard deviation and n (%).

Statistical Analysis

SPSS (version 22.0; IBM Corp., SPSS Inc., Armonk, NY, USA) statistics software was used for statistical analysis. Categorical variables were expressed as numbers and percentages, and compared using the Chi-square test. Continuous variables were expressed as mean±standard deviation. Continuous variables with parametric distribution were compared using the independent samples *t*-test, and those without normal distribution were compared using the Mann-Whitney U test. The Kolmogorov-Smirnov test was used to determine whether continuous variables were normally distributed. The paired sample *t*-test and McNemar test were used for comparison of parameters before and after the BPA procedure, where appropriate. For all statistical analyses, a p-value <0.05 was considered significant.

Please cite this article in press as: Atas H, et al. Balloon Pulmonary Angioplasty in Patients With Inoperable or Recurrent/Residual Chronic Thromboembolic Pulmonary Hypertension: A Single-Centre Initial Experience. Heart, Lung and Circulation (2021), https://doi.org/10.1016/j.hlc.2021.10.009

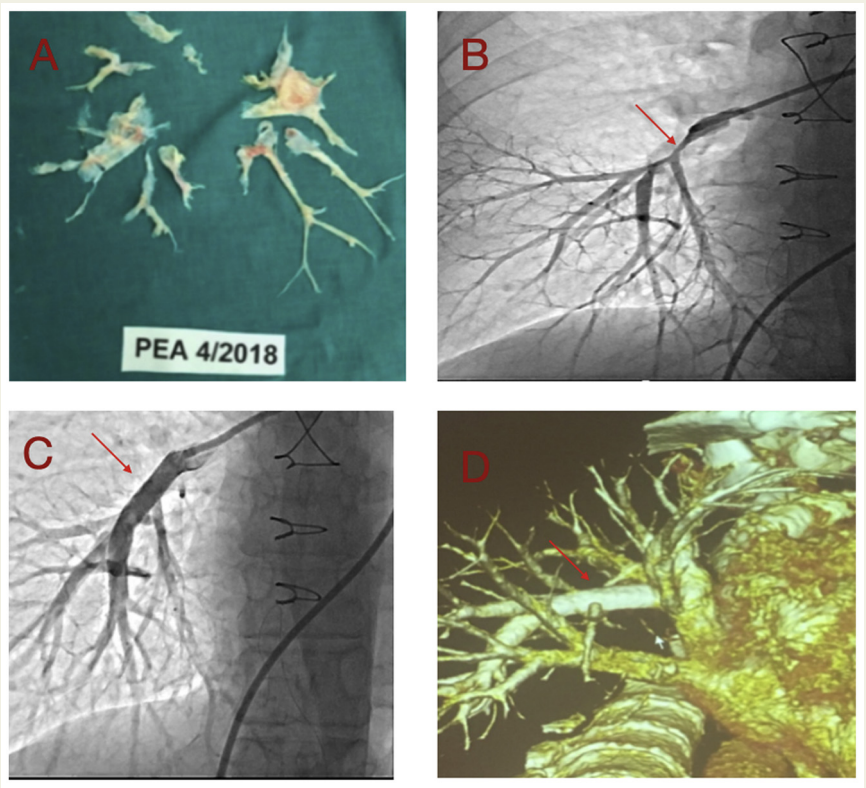

Figure 1 **A.** Endarterectomy specimen of a patient with isolated pulmonary vasculitis and recurrent pulmonary hypertension. **B.** Selective pulmonary angiography showing a severe tubular lesion (arrow) at the orifice of right lower lobar artery. **C.** Due to recoil observed despite repeated balloon pulmonary angioplasty, a balloon-expanding stent (red arrow) was deployed. **D.** Computed tomography pulmonary angiography showing patency of the stent (arrow) at 6 months after the procedure.

Results

Baseline Characteristics of the Study Population

Twenty-six (26) consecutive patients were enrolled in the study. The mean age of the patients was 51±17 years and 18 (69.2%) were female. Fifteen (15) patients were deemed to have inoperable CTEPH, and 11 patients had residual or recurrent CTEPH post PEA. The median duration for diagnosis of CTEPH was 42 (range, 12–120) months. The demographic and clinical characteristics of the patients are listed in Table 1. All patients were on anticoagulant therapy and 21 (80%) were receiving PAH-specific drugs. Despite receiving targeted therapy, 19 (73.0%) patients were in functional class III or IV. Riociguat was the most commonly used PAH-specific drug. One (1) patient was receiving a combination of PAH-specific drugs targeting two pathogenic pathways and three were receiving a combination of PAH-specific drugs targeting three pathogenic pathways. PAH-specific drugs were reduced in five of 21 patients taking these drugs and the total number of drugs decreased by 18% after completing the BPA course.

Efficacy of BPA

A total of 91 sessions were performed and the median number of sessions per patient was three (range, 2–7). The median numbers of vessel targeted per intervention was four (range, 2–10). One (1) patient, who had isolated pulmonary vasculitis and recurrent PH after successful PEA, required stent implantation. A balloon-expanding stent (7.0/37 mm, Boston Scientific, Marlborough, MA, USA) was deployed to maintain the patency at the orifice of the right lower lobar artery because recoil was observed, despite repeated BPA (Figure 1). The other segmental lesions of this patient were treated with appropriately sized balloon dilations. The efficacy of BPA on haemodynamics, functional capacity, supplemental oxygen requirement, and NT-pro BNP levels is presented in Table 2. There was significant improvement in functional class after BPA treatment. WHO functional class improved in 17 of 26 (65%) patients, but remained unchanged in nine (35%). Deterioration of functional class was not observed (Figure 2). The 6-minute walking distance (6MWD) increased from a mean 315 to 411 m ($p<0.001$), and NT pro-BNP levels reduced from a median 456 to 189 pg/mL ($p=0.001$). There was also an improvement in the

Please cite this article in press as: Atas H, et al. Balloon Pulmonary Angioplasty in Patients With Inoperable or Recurrent/Residual Chronic Thromboembolic Pulmonary Hypertension: A Single-Centre Initial Experience. Heart, Lung and Circulation (2021), https://doi.org/10.1016/j.hlc.2021.10.009

Table 2 Changes in the haemodynamics and clinical data before and after BPA treatment.

Variable	Baseline (n=26)	Final (n=26)	P-value
Haemodynamics			
Systolic PAP, mmHg	77.6±19.2	65±17.8	**<0.001**
Mean PAP, mmHg	47.5±13.4	38±10.9	**<0.001**
Diastolic PAP, mmHg	25.8±8.3	22.6±7.2	**0.013**
PCWP, mmHg	11.1±2.1	10.9±3.3	0.860
Right atrial pressure, mmHg	9.8±4.2	9.2±4.6	0.465
PVR, Wood units	9.3±4.7	5.8±2.8	**<0.001**
Pulmonary artery O_2 saturation (%)	60.1±12.9	65.6±7.7	**0.029**
CO, L/min	4.4±1.6	5.1±1	**0.039**
CI, L/min/m^2	2.4±0.7	2.9±0.6	**0.008**
Clinical and laboratory			
WHO ≥3, n (%)	19 (73.1%)	5 (19.2%)	**<0.001**
6MWD, m	315±129	411±140	**<0.001**
NT pro-BNP, pg/mL	456 (2,517)	189 (374)	**0.001**
Supplemental oxygen, n (%)	11 (42.3%)	5 (19.2%)	**0.031**

Abbreviations: BPA, balloon pulmonary angioplasty; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; CO, cardiac output; CI, cardiac index; WHO, World Health Organization; 6MWD, 6-minute walking distance.
Data are presented as mean±standard deviation and median (interquartile range).
Significant p-values were marked with bold text.

supplemental oxygen requirement of the patients; the number of patients who required supplemental oxygen therapy decreased from 11 (42.3%) to 5 (19%) (p=0.031) after BPA treatment.

In terms of haemodynamics, there was a statistically significant improvement in PAP, PVR, cardiac index (CI), and pulmonary arterial oxygen saturation, but not in RA pressure. The mean PAP decreased from a mean 47.5±13.4 to 38±10.9 mmHg (p<0.001) and the PVR decreased from a mean 9.3±4.7 to 5.8±2.8 Wood units (p<0.001) (Figure 3). Although CI significantly increased from a mean 2.4±0.7 to 2.9±0.6 L/min/m^2 (p=0.008), the change in the RA pressure did not reach statistical significance.

Complications

Neither death nor invasive mechanical ventilation occurred due to procedure-related causes. However, a patient required noninvasive mechanical ventilation because of pulmonary vascular injury with haemoptysis due to wire

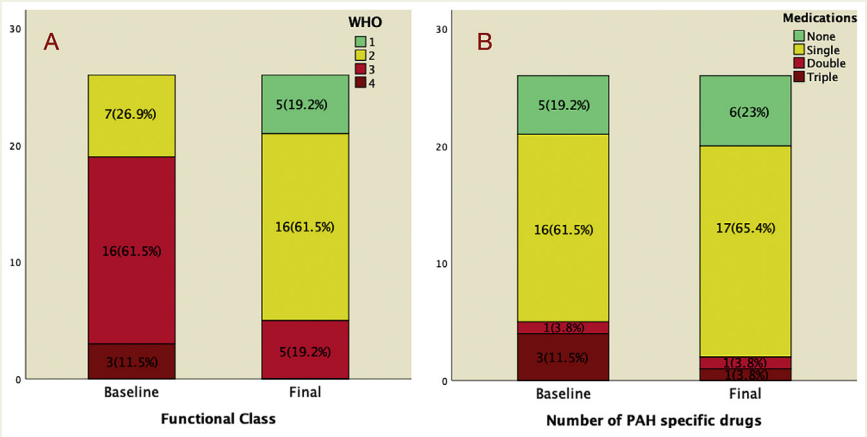

Figure 2 A. Improvements in WHO functional classes of the patients at baseline and after balloon pulmonary angioplasty. **B.** Reduction in number of targeted drugs at baseline and after BPA.
Abbreviations: WHO, World Health Organization; BPA, balloon pulmonary angioplasty; PAH, pulmonary artery hypertension.

Please cite this article in press as: Atas H, et al. Balloon Pulmonary Angioplasty in Patients With Inoperable or Recurrent/Residual Chronic Thromboembolic Pulmonary Hypertension: A Single-Centre Initial Experience. Heart, Lung and Circulation (2021), https://doi.org/10.1016/j.hlc.2021.10.009

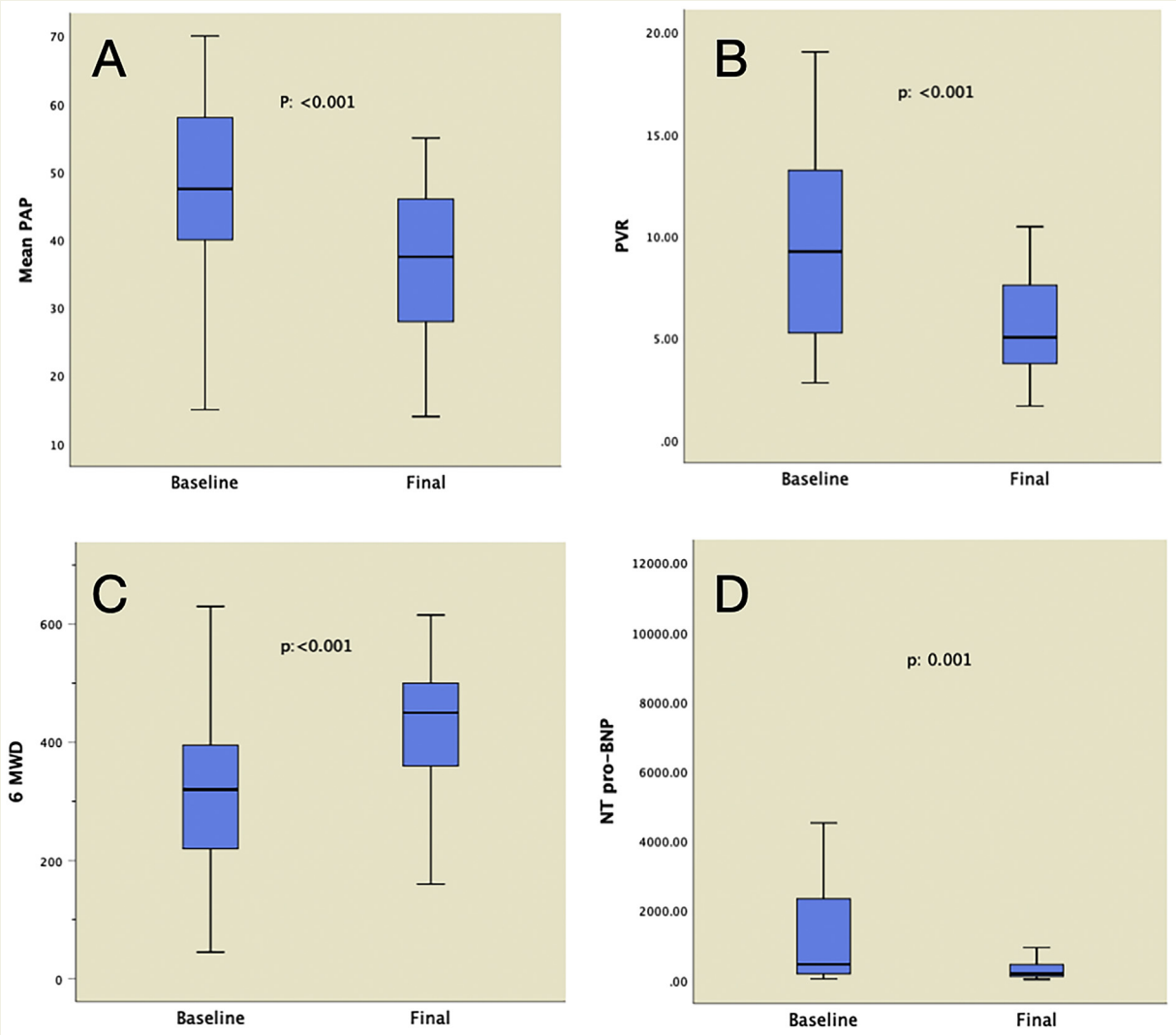

Figure 3 Box plots showing changes in **A.** mPAP; **B.** PVR; **C.** 6MWD; and **D.** NT pro-BNP with BPA treatment. Abbreviations: mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; 6MWD, 6-minute walking distance; BPA, balloon pulmonary angioplasty.

perforation. A total of 20 intervention-related complications occurred in 10 patients during 91 sessions (22% of all interventions, 38% of the entire study population). The most common complication was haemoptysis due to pulmonary vascular injury through wire perforation. The majority of these events were mild and did not require any intervention. A total of five pulmonary artery dissections developed in the segmental and subsegmental branches, which did not limit the blood flow and did not cause symptoms. All complications are listed in Table 3.

Discussion

This study confirms that BPA is an effective treatment for patients with inoperable CTEPH or patients who have residual or recurrent PH. It demonstrates that BPA treatment improved the exercise capacity, oxygenation, NT pro-BNP levels, and haemodynamics of patients with inoperable or residual or recurrent CTEPH.

Patients with inoperable or residual CTEPH are often treated with riociguat, which is approved for CTEPH therapy, or other PAH-specific drugs [14]. Riociguat improves haemodynamics, with a 10% decrease in mPAP, a 33% decrease in PVR, and a 10% increase in 6MWD [15]. Many patients who receive PAH-specific therapy for CTEPH have significant symptoms, despite medication, and they may be candidates for BPA. The recent "Riociguat Versus Balloon Pulmonary Angioplasty in Non-operable Chronic Thromboembolic Pulmonary Hypertension" (RACE) trial [16], which compared BPA with riociguat therapy, found that BPA was more effective than riociguat in reducing PVR and improving functional class. However, there was a safety cost for the greater efficacy of BPA, and no significant difference

Please cite this article in press as: Atas H, et al. Balloon Pulmonary Angioplasty in Patients With Inoperable or Recurrent/Residual Chronic Thromboembolic Pulmonary Hypertension: A Single-Centre Initial Experience. Heart, Lung and Circulation (2021), https://doi.org/10.1016/j.hlc.2021.10.009

Table 3 Periprocedural characteristics and complications related to BPA.

Total sessions	91 (100%)
Intervention per patient	3 (2–7)
Targeted vessel per intervention	4 (2–10)
Contrast agent, mL	254±72
Fluoroscopy time, min	48.7±15.9
Haemoptysis due to vascular injury	9 (9.8%)
Mild	8 (8.8%)
Severe	1 (1.1%)
Reperfusion lung injury	3 (3.3%)
Mild	2 (2.2%)
Moderate	1 (1.1%)
Dissection	5 (5.5%)
Access site complication	2 (2.2%)
Non-invasive mechanical ventilation	1 (1.1%)
Renal dysfunction	1 (1.1%)
Overall complications	20 (22%)
Mild	16 (17.6%)
Moderate to severe	4 (4.4%)

Abbreviation: BPA, balloon pulmonary angioplasty.
Data are presented as n (%) and median (minimum-maximum).

could be shown in 6MWD. Indeed, PAH-specific therapy and BPA may not be competitive, but complement each other, treating different aspects of the disease: PAH-specific drugs target distal pulmonary vasculopathy and remodelling, and BPA addresses the mechanical component of the disease by restoring distal pulmonary flow in the segmental and subsegmental levels [17] (Figure 4). The majority of patients in this study received PAH-specific drugs and the benefits of BPA were additive to medical therapy.

Balloon pulmonary angiography was associated with moderate improvements in haemodynamics, with a 20% decrease in mPAP, 37% decrease in PVR, and 20% increase in CI in this study. The reductions in mPAP and PVR are similar to previous European series [8,12] (between 18–30% and 26–43%, respectively) and less than compared with Japanese reports [18] (31–49% and 45–69%, respectively). Similarly, the RACE trial reported an approximately 60% decrease in PVR. This difference between the current results and those of previous investigators may be associated with greater experience with BPA in those centres and patient selection criteria. The first treatment option for patients with CTEPH in the current centre is PEA, and patients who have an unfavourable risk-benefit ratio or who have residual or recurrent CTEPH are candidates for the BPA procedure. This situation leads to limited BPA experience and more patients with residual or recurrent CTEPH who need BPA in the current centre. Indeed, a high ratio of residual or recurrent PH (11 of 26 patients, 45.3%) was found compared with previous studies. BPA procedures in patients with residual or recurrent CTEPH are more complicated than those of inoperable patients. Patients with residual or recurrent CTEPH after PEA usually have more severe and prolonged disease. These patients generally have very hard, tortuous, calcific, and multiple pouch-type lesions, which are difficult to cross with a standard guidewire and dilate with a balloon catheter. Dilation is also often associated with high rates of re-occlusion due to elastic recoil. Weakening of vessels with the coexistence of high pressure may result in pulmonary artery aneurysms, making the manipulation of catheters inside the artery very difficult in patients who have previously undergone PEA [3]. These vessels require guidewires that have a heavy tip weight and large balloon diameter, which may lead to dissection or perforation of the vessel. Thus, a previous PEA history independent of residual or recurrent disease is associated with a decrease in efficacy of BPA and an increase in adverse events related with the procedure.

The benefit of BPA treatment is not limited to exercise capacity and haemodynamic parameters, it also decreases the requirement for supplemental oxygen therapy and PAH-specific therapy needs. Previous studies have shown the beneficial effect of BPA on oxygen saturation and, consequently, on the ability of patients to withdraw from supplemental oxygen [19,20]. The percentage of patients who were receiving supplemental oxygen significantly decreased from 11 (42%) to five (19%) in the current study. It was observed that the benefit of BPA on oxygenation became apparent earlier than its haemodynamic benefits. PAH-specific drugs are expensive and require life-long therapy; therefore, it is associated with a high economic burden, especially in developing countries. Furthermore, parenteral drugs have many serious adverse effects and decrease quality of life. The current study was able to reduce the use of PAH-specific drugs in three patients and remove intravenous epoprostenol in one patient. Although it did not quantitatively measure quality of life, it is believed that BPA may improve quality of life due to the reduced need for PAH-specific drugs and supplemental oxygen therapy. The new clinical decision flow chart has started to be implemented in clinical practice, given increasing BPA experience and new data (Figure 5).

Balloon pulmonary angioplasty is an interventional treatment and accordingly prone to potentially life-threatening complications; however, some of these may be avoided by using the refined BPA methodology. Overall, adverse events are observed in approximately 10% of interventions in contemporary practice. A recent meta-analysis reported that the periprocedural mortality rate is 2.9% in patients undergoing BPA [3]. In a Japanese multi-centre registry, severe complications requiring mechanical ventilation were observed in 5.5% of treated patients, and the periprocedural mortality rate was 2.6% [17]. In terms of mortality, the current results favourably compare with those from these previous reports. Although there was no periprocedural mortality, procedure-related complications were observed in 22% of interventions, and 38% of patients had at least one procedure-related complication. The most common complication was haemoptysis due to vascular injury, which was

Please cite this article in press as: Atas H, et al. Balloon Pulmonary Angioplasty in Patients With Inoperable or Recurrent/Residual Chronic Thromboembolic Pulmonary Hypertension: A Single-Centre Initial Experience. Heart, Lung and Circulation (2021), https://doi.org/10.1016/j.hlc.2021.10.009

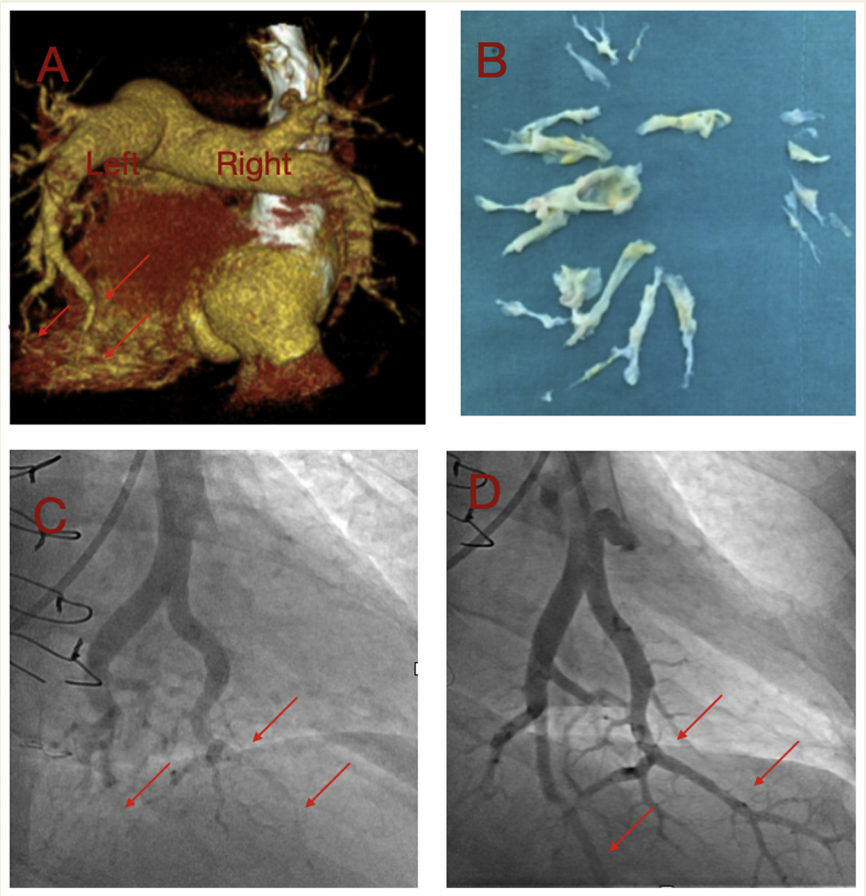

Figure 4 Computed tomography pulmonary angiography (preoperative) showing: **A.** subsegmental lesions (arrow) in a patient with residual pulmonary hypertension after pulmonary endarterectomy. **B.** Demonstration of an endarterectomy specimen. **C.** Selective pulmonary angiography showing residual subsegmental lesions (arrows) after pulmonary endarterectomy. **D.** Distal pulmonary artery flow restoring with balloon pulmonary angioplasty (arrows).

mild and required no intervention in the majority of cases. However, one patient was transferred to the intensive care unit and required non-invasive mechanical ventilation after the procedure. Reperfusion lung injury, which was the main complication of BPA in previous reports, was rare and occurred in three patients (3.3%). However, subclinical pulmonary injury could not be identified because all patients were not screened with CT imaging for detecting subclinical reperfusion lung injury and pulmonary bleeding after the procedure. The frequency of adverse events is highly dependent on the experience of the operator and case selection. This centre is still on a learning curve and will achieve even better results with increased experience. Indeed, most of the complications mentioned above occurred during the first few cases.

Although there were clinically and haemodynamically significant improvements with BPA in this study, the goal of cure (reduction of mPAP <20 mmHg with relief of all symptoms attributed to PH) was not achieved in most of the patients. Several factors may explain this finding. First, because these were the first few cases, some patients who would not have benefitted from BPA may have been selected. Second, to avoid potentially life-threatening complications, undersized balloon catheters were used, especially in the first few cases, and not all targeted lesions were able to be treated, especially in patients with residual or recurrent CTEPH. The vast majority of patients had a long-standing diagnosis of CTEPH, and some may have developed distal pulmonary vasculopathy, which would have reduced the benefits of the procedure.

Finally, it should be kept in mind that patients with CTEPH are at risk of recurrent pulmonary embolism. This underlines the need for life-long anticoagulation therapy. This study used direct oral anticoagulants (DOACs) in most patients, although this is not recommended by the current guidelines. However, a recent report [14] indicated that DOACs could be a safe and effective alternative to warfarin treatment in CTEPH patients. This may be especially important for patients with limited access to health care facilities and noncompliance issues.

This study had several limitations. First, it was a single-centre study with a small sample size and short follow-up

Please cite this article in press as: Atas H, et al. Balloon Pulmonary Angioplasty in Patients With Inoperable or Recurrent/Residual Chronic Thromboembolic Pulmonary Hypertension: A Single-Centre Initial Experience. Heart, Lung and Circulation (2021), https://doi.org/10.1016/j.hlc.2021.10.009

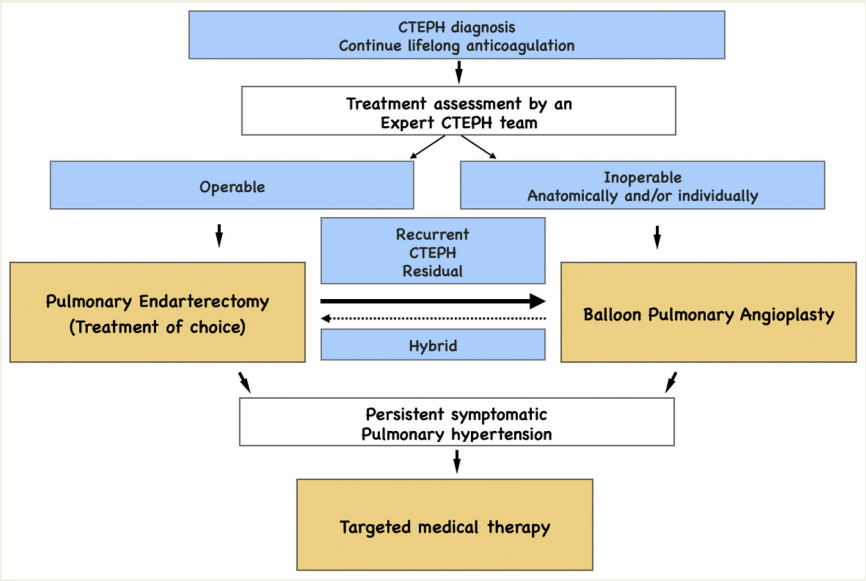

Figure 5 The new clinical decision flow chart has started to be implemented in clinical practice, given increasing balloon pulmonary angioplasty experience and new data.
Abbreviation: CTEPH, chronic thromboembolic pulmonary hypertension.

period; there were no long-term results. Thus, there may have been some patients who experienced worse PH after this period. Second, the majority of patients were on PAH-specific drugs and there was no control group who received only medical therapy. Therefore, the impact of medication on post-procedural outcomes cannot be eliminated. Finally, all measures – including WHO functional class, 6MWD, and haemodynamics – were obtained by study personnel, and neither the investigators nor the patients were blinded to the treatment.

Conclusion

This study presents initial experience of BPA in a tertiary referral centre for CTEPH. It found that BPA was associated with improvement in haemodynamics, functional capacity, oxygenation, and serum NT-pro BNP levels in patients with inoperable and residual or recurrent CTEPH. Although it is not free from intervention-related complications such as pulmonary bleeding, a refined BPA strategy has an acceptable risk-benefit ratio in an experienced centre with a multidisciplinary approach. However, the potential benefit of mortality and long-term effects of BPA still need to be investigated in a prospective multicentre study.

Conflicts of Interest

We report no relevant funding sources associated with this manuscript. There are no conflicts of interest to disclose.

References

[1] Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Resp J. 2015;46(4):903–75.
[2] Yildizeli B, Tas S, Yanartas M, Kaymaz C, Mutlu B, Karakurt S, et al. Pulmonary endarterectomy for chronic thrombo-embolic pulmonary hypertension: an institutional experience. Eur J Cardiothorac Surg. 2013;44(3):e219–27. discussion e27.
[3] Karyofyllis P, Demerouti E, Papadopoulou V, Voudris V, Matsubara H. Balloon pulmonary angioplasty as a treatment in chronic thromboembolic pulmonary hypertension: past, present, and future. Curr Treatment Options Cardiovasc Med. 2020;22(3):7.
[4] Olgun Yildizeli S, Kepez A, Tas S, Yanartas M, Durusoy AF, Erkilinc A, et al. Pulmonary endarterectomy for patients with chronic thromboembolic disease. Anatol J Cardiol. 2018;19(4):273–8.
[5] Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation. 2001;103(1):10–3.
[6] 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(6):748–55.
[7] Sugimura K, Fukumoto Y, Satoh K, Nochioka K, Miura Y, Aoki T, et al. Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension. Circ J. 2012;76(2):485–8.
[8] Olsson KM, Wiedenroth CB, Kamp JC, Breithecker A, Fuge J, Krombach GA, et al. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience. Eur Resp J. 2017;49(6).
[9] Brenot P, Jais X, Taniguchi Y, Garcia Alonso C, Gerardin B, Mussot S, et al. French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Eur Resp J. 2019;53(5).

Please cite this article in press as: Atas H, et al. Balloon Pulmonary Angioplasty in Patients With Inoperable or Recurrent/Residual Chronic Thromboembolic Pulmonary Hypertension: A Single-Centre Initial Experience. Heart, Lung and Circulation (2021), https://doi.org/10.1016/j.hlc.2021.10.009

[10] Velazquez M, Albarran A, Hernandez I, Lopez-Gude MJ, Sarnago F, Martin R, et al. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. Observational study in a referral unit. Revista Espanola de Cardiologia. 2019;72(3):224–32.

[11] Kanar BG, Mutlu B, Atas H, Akaslan D, Yildizeli B. Improvements of right ventricular function and hemodynamics after balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension. Echocardiography. 2019;36(11):2050–6.

[12] Kurzyna M, Darocha S, Pietura R, Pietrasik A, Norwa J, Manczak R, et al. Changing the strategy of balloon pulmonary angioplasty resulted in a reduced complication rate in patients with chronic thromboembolic pulmonary hypertension. A single-centre European experience. Kardiol Pol. 2017;75(7):645–54.

[13] Inami T, Kataoka M, Shimura N, Ishiguro H, Yanagisawa R, Taguchi H, et al. Pulmonary edema predictive scoring index (PEPSI), a new index to predict risk of reperfusion pulmonary edema and improvement of hemodynamics in percutaneous transluminal pulmonary angioplasty. JACC Cardiovasc Interven. 2013;6(7):725–36.

[14] Sena S, Bulent M, Derya K, Deniz K, Halil A, Okan E, et al. Real-life data of direct anticoagulant use, bleeding risk and venous thromboembolism recurrence in chronic thromboembolic pulmonary hypertension patients: an observational retrospective study. Pulmon Circ. 2020;10(1):2045894019873545.

[15] Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. New Engl J Med. 2013;369(4):319–29.

[16] Jais X, Brenot P, Bouvaist H, Canuet M, Chabanne C, Chaouat A, et al. Late Breaking Abstract - Balloon pulmonary angioplasty versus riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension: results from the randomised controlled RACE study. Eur Resp J. 2019;54(suppl 63):RCT1885.

[17] Hoole SP, Coghlan JG, Cannon JE, Taboada D, Toshner M, Sheares K, et al. Balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: the UK experience. Open Heart. 2020;7(1):e001144.

[18] Ogawa A, Satoh T, Fukuda T, Sugimura K, Fukumoto Y, Emoto N, et al. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: results of a multicenter registry. Circ Cardiovasc Qual Outcomes. 2017;10(11).

[19] Zoppellaro G, Badawy MR, Squizzato A, Denas G, Tarantini G, Pengo V. Balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension- a systematic review and meta-analysis. Circ J. 2019;83(8):1660–7.

[20] Anand V, Frantz RP, DuBrock H, Kane GC, Krowka M, Yanagisawa R, et al. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: initial single-center experience. MCP: IQ&O. 2019;3(3):311–8.

Please cite this article in press as: Atas H, et al. Balloon Pulmonary Angioplasty in Patients With Inoperable or Recurrent/Residual Chronic Thromboembolic Pulmonary Hypertension: A Single-Centre Initial Experience. Heart, Lung and Circulation (2021), https://doi.org/10.1016/j.hlc.2021.10.009