



HAL
open science

Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: Evaluation of haemodynamic effects, complication rates and radiation exposure over time

Nicolas Piliero, Frédéric Thony, Alicia Guillien, Julia Rousseau, Mathieu Finas, Estelle Vautrin, Bruno Degano, H el ene Bouvaist

► To cite this version:

Nicolas Piliero, Fr ed eric Thony, Alicia Guillien, Julia Rousseau, Mathieu Finas, et al.. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: Evaluation of haemodynamic effects, complication rates and radiation exposure over time. Archives of cardiovascular diseases, 2022, 115 (5), pp.295 - 304. 10.1016/j.acvd.2022.02.010 . hal-04301008

HAL Id: hal-04301008

<https://hal.science/hal-04301008>

Submitted on 22 Nov 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destin ee au d ep ot et  a la diffusion de documents scientifiques de niveau recherche, publi es ou non,  emanant des  tablissements d'enseignement et de recherche fran ais ou  trangers, des laboratoires publics ou priv es.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License



Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en



CLINICAL RESEARCH

Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: Evaluation of haemodynamic effects, complication rates and radiation exposure over time

L'angioplastie pulmonaire pour le traitement de l'hypertension pulmonaire thromboembolique chronique : évaluation de l'efficacité, de la sécurité et des doses d'irradiations au cours du temps

Nicolas Piliero^a, Frédéric Thony^b, Alicia Guillien^{c,d},
 Julia Rousseau^b, Mathieu Finas^b, Estelle Vautrin^a,
 Bruno Degano^{e,f,*}, Hélène Bouvaist^a

^a Service de Cardiologie, Pôle Thorax et Vaisseaux, Centre Hospitalier Universitaire Grenoble Alpes, 38043 Grenoble, France

^b Pôle Imagerie, Centre Hospitalier Universitaire Grenoble Alpes, 38043 Grenoble, France

^c Université Grenoble Alpes, 38058 Grenoble, France

^d Épidémiologie environnementale appliquée à la reproduction et à la santé respiratoire, Inserm, CNRS, Université Grenoble Alpes, Institut pour l'Avancée des Biosciences (IAB), U1209, 38058 Grenoble, France

^e Service Hospitalier Universitaire Pneumologie Physiologie, Pôle Thorax et Vaisseaux, Centre Hospitalier Universitaire Grenoble Alpes, 38043 Grenoble, France

^f Laboratoire HP2, Inserm U1300, Université Grenoble Alpes, 38058 Grenoble, France

Received 10 August 2021; received in revised form 18 February 2022; accepted 21 February 2022
 Available online 21 April 2022

Abbreviations: BPA, balloon pulmonary angioplasty; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; DSA, digital subtraction angiography; IQR, interquartile range; KAP, Kerma area product; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance.

* Corresponding author at: Service Hospitalier Universitaire Pneumologie Physiologie, CHU Grenoble Alpes, 38043 Grenoble cedex, France.
 E-mail address: bdegano@chu-grenoble.fr (B. Degano).

<https://doi.org/10.1016/j.acvd.2022.02.010>

1875-2136/© 2022 Elsevier Masson SAS. All rights reserved.

KEYWORDS

Balloon pulmonary angioplasty;
Chronic thromboembolic pulmonary hypertension;
Haemodynamics;
Complications;
Radiation exposure

Summary

Background. – In patients undergoing balloon pulmonary angioplasty (BPA) for inoperable chronic thromboembolic pulmonary hypertension (CTEPH), single-centre series from expert centres have recognized a learning curve for the magnitude of haemodynamic benefits.

Objective. – To report our 7-year experience with BPA, focusing on haemodynamic effects, complication rates and radiation exposure over time.

Methods. – Patients with CTEPH who were treated with BPA between May 2013 and February 2020 were analysed during the ‘initial period’ versus the ‘recent period’ (split date: March 2017).

Results. – Among 192 patients who underwent at least one BPA procedure, 156 were included in the safety/radiation analysis and 119 were included in the efficacy analysis. During the ‘recent period’ versus the ‘initial period’, the median [interquartile range] number of procedures per patient was higher (4.5 [4.0–6.0] vs. 4.0 [3.0–4.0]; $P=0.03$), as was the number of dilated vessels per procedure (4.0 [3.5–5.0] vs. 3.5 [3.0–4.0]; $P=0.002$). Changes in haemodynamic parameters were also greater (mean pulmonary artery pressure: -22% [-31% to -14%] vs. -37% [-44% to -29%]; $P=0.001$; pulmonary vascular resistance: -38% [-51% to -8%] vs. -53% [-69% to -33%]; $P=0.002$); complication rates were similar (5.7% vs. 9.3% of procedures; $P=0.38$); and radiation exposure was lower (effective dose per patient: 43.9 [31.6–66.5] vs. 67.8 [47.9–101.9] mSv; $P<0.001$).

Conclusion. – Our analysis is consistent with a learning curve for the magnitude of haemodynamic improvements. The complication rate was low and did not change over time, but radiation exposure decreased.

© 2022 Elsevier Masson SAS. All rights reserved.

MOTS CLÉS

Angioplastie pulmonaire par ballonnet ;
Hypertension pulmonaire thromboembolique chronique ;
Hémodynamique ;
Complications ;
Exposition aux radiations

Résumé

Contexte. – Le traitement par angioplastie pulmonaire a montré son efficacité chez les patients atteints d’hypertension pulmonaire thromboembolique chronique dans plusieurs études observationnelles monocentriques, avec néanmoins un effet « courbe d’apprentissage » sur les résultats.

Objectif. – L’objectif est de rapporter notre expérience des 7 dernières années sur l’angioplastie pulmonaire, en termes d’efficacité hémodynamique et de sécurité.

Méthodes. – Les patients traités dans notre centre par angioplastie pulmonaire entre mai 2013 et février 2020 ont été inclus dans l’analyse. La cohorte a été séparée en 2 sous-groupes (« période initiale » vs « période récente »).

Résultats. – Parmi les 192 patients qui ont bénéficié d’au moins une séance d’angioplastie pulmonaire, 156 patients avaient des données disponibles concernant la sécurité et l’irradiation, et 119 patients avaient une évaluation complète et étaient ainsi inclus dans l’analyse d’efficacité. En comparaison de la « période initiale », nous avons mis en évidence sur la « période récente » les constatations suivantes : un nombre de procédure par patient et un nombre de vaisseaux dilatés par procédure plus importants ($4,6 \pm 1,9$ vs $3,8 \pm 1,3$; $p=0,02$ et $4,1 \pm 1,0$ vs $3,5 \pm 1,1$; $p=0,002$, respectivement) ; une meilleure efficacité hémodynamique (variation de résistances vasculaires pulmonaires : $4,4 \pm 3,4$ vs $2,9 \pm 3,4$ UW ; $p=0,04$) ; un taux de complications similaire (6 % vs 9 % des procédures ; $p=0,38$) ; et un taux d’irradiation plus faible (Air Kerma par patient : 2991 ± 2019 vs 3958 ± 2686 mGy ; $p=0,02$).

Conclusion. – Notre étude confirme la présence d’une courbe d’apprentissage sur l’impact hémodynamique de l’angioplastie pulmonaire. Le taux de complication n’a pas évolué au cours du temps mais le taux d’irradiation a diminué.

© 2022 Elsevier Masson SAS. Tous droits réservés.

Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive pulmonary vascular disease that results

from occlusion of large pulmonary arteries by persistent thrombi and from distal small-vessel vasculopathy leading to pulmonary hypertension (PH), right ventricular failure and, if untreated, to death [1]. Pulmonary endarterectomy

(PEA) is the gold standard treatment for operable CTEPH, but approximately 40% of patients with CTEPH are judged inoperable because of distal lesions and/or the presence of comorbidities [2]. Balloon pulmonary angioplasty (BPA), alone or in combination with PH-targeted drugs, has emerged in recent years as a novel treatment approach in patients with CTEPH [3]. After an initial experience reported in 2001 that was associated with high morbidity and mortality [4], BPA has been refined by Japanese teams [5–7] and, thereafter, by an increasing number of teams all over the world [8]. Data have now been accumulated on the effectiveness of BPA in terms of functional and haemodynamic status, cardiac biomarkers, right ventricular function, quality of life and even survival [9–14]. However, despite a large consensus regarding effectiveness, there are still questions that are worthy of being addressed. Firstly, the learning curve for BPA that has been reported even in highly experienced centres [9] warrants confirmation. Indeed, although increasing numbers of centres are performing BPA worldwide, many data suggest that the effectiveness of BPA is poorer in centres reporting their initial experience [15–18] than in more experienced centres [10,19]. As CTEPH is a rare disease, data linking experience and effectiveness may be useful in estimating the number of centres that can provide access to the technique for all eligible patients. Secondly, whether the number of complications decreases with increasing experience remains a matter of debate. Some referral centres have reported ‘a considerable number of complications’ with their initial experience [18], while others have considered the safety profile ‘acceptable’ [20]. Thirdly, a parameter that has been largely neglected in patients undergoing BPA is radiation exposure. In particular, despite a rise in the use of BPA, there is a dearth of data on radiation exposure over time from BPA procedures.

In France, our centre in Grenoble was the first to develop a BPA programme, in 2013 [21]. Here, we report our 7-year experience, focusing on the evolution of haemodynamic effects, complication rates and radiation exposure over time.

Methods

Study design

We analysed data from the ongoing, prospective, hospital-based registry of patients with CTEPH treated by BPA at Grenoble University Hospital, France (NCT02844036). All patients provided written informed consent before participation. The study protocol was approved by the Institutional Review Board (Comité de Protection des Personnes Sud-Est V, 2013-AO1036-39).

Patients

All consecutive patients with CTEPH who were treated by BPA between May 2013 and February 2020 were considered for inclusion in the current analysis. The diagnosis of CTEPH complied with current guidelines [2], based on medical history, physical examination, right-side heart catheterization, ventilation/perfusion lung scan, computed tomography (CT) pulmonary angiography, digital subtraction

angiography (DSA) and dual energy computed tomography findings. All patients had been deemed ineligible for PEA based on the consensus of a multidisciplinary team at the Paris-Sud University, as described elsewhere [9].

Balloon pulmonary angioplasty

Pulse oxygen saturation and non-invasive systemic arterial pressure were carefully monitored during the procedure and for 24 hours thereafter. Electrocardiographic monitoring was used during the procedure. Vitamin K antagonists were maintained, with an international normalized ratio of 2–3. Direct oral anticoagulation therapies were stopped and replaced by parenteral anticoagulation during hospitalization. A right heart catheterization was performed at the beginning of the procedure to measure pulmonary artery pressure (PAP) and cardiac output (by thermodilution). Mapping of the target lesions was elaborated before the procedure using data from the ventilation/perfusion scan, CT pulmonary angiography, DSA and, when available, dual energy computed tomography. Four operators (three interventional cardiologists [H. B., N. P. and E. V.] and one interventional radiologist [F. T.]) performed all BPA procedures. A 6F long sheath (Flexor, Cook Medical, Bloomington, USA) was introduced using a 0.035" guidewire (Guiderright, St Jude Medical, St Paul, USA) through the right femoral vein to the right atrium under local anaesthesia. Inhalation of a 50/50 nitrous oxide/oxygen mixture was added, if necessary. A 6F guide catheter (Judkins Right, Judkins Left or Multipurpose Launcher, Medtronic, Minneapolis, MN, USA) was introduced into the long sheath (using a hydrophilic Terumo 0.035" wire) to the chosen pulmonary artery and angiography was performed during a short apnoea. The targeted lesion was crossed with a 0.014" hydrophilic wire (Pilot 150, Abbott Vascular, Santa Clara, CA, USA or Versaturn, Abbott Vascular, Santa Clara, CA, USA). The appropriate size of the balloon was determined by angiography. Balloon angioplasty was performed with a percutaneous transluminal angioplasty balloon dilatation catheter of diameter 2–7 mm diameter and length 20 mm (Euphora, Medtronic, Minneapolis, MN, USA; RX Muso, Terumo, Tokyo, Japan). Selective angiography was performed after each inflation to (1) confirm a good result of the angioplasty, defined as an angiographic pulmonary flow grade 3 with good venous return flow and (2) exclude a potential lung injury. All patients underwent a chest X-ray after the procedure.

Two to 10 segmental or subsegmental arteries were treated during each BPA procedure, depending on patient severity, procedure time and the amount of contrast media given. As patients were from a large area in the south-east part of France, BPA procedures were performed in a stage-by-stage manner with two procedures per week separated by a minimum of 2 days with the aim of avoiding multiple hospitalizations. When procedures were uncomplicated, discharge from hospital occurred 24 hours after the last procedure. The number of procedures required was at the discretion of the operators.

BPA procedure-related complications

Complications were prospectively recorded and adjudicated by the four operators. BPA procedure-related complications

included haemoptysis, lung injury, use of non-invasive positive pressure ventilation, oral intubation with mechanical ventilation and peri-procedural death. Haemoptysis within the 24 hours after the BPA procedure was defined as a procedure-related event. Lung injury was defined as the presence of lung opacities on a chest X-ray and/or CT scan that occurred within 1 day after the procedure and induced prolongation of hospitalization. Non-invasive positive pressure ventilation or oral intubation with mechanical ventilation was performed at the discretion of the intensive care unit physicians. Peri-procedural death was defined as death that occurred within 30 days of a BPA procedure.

Radiation exposure

Data regarding radiation exposure during BPA were collected automatically with a dosimetry archiving and communication system (Radiation Dose Monitor, Medsquare, Paris, France). The metrics that were recorded were Kerma area product (KAP), fluoroscopy time and reference air kerma. The effective dose was calculated by applying an appropriate conversion factor of 0.2 mSv/Gy.cm² to KAP values [22]. Data were analysed per procedure and the cumulative dose was calculated for each patient.

Statistical analysis

Data stored in the hospital-based registry of CTEPH of the Grenoble University Hospital (NCT02844036) were analysed.

All statistical analyses were performed using R software (version 3.6).

After assessment with the Shapiro–Wilk test, most of the continuous variables were not normally distributed and results for all continuous variables were therefore presented as medians and interquartile ranges (IQRs). Categorical variables are presented as number (%). Comparisons of pre- and post-BPA parameters were performed using the Wilcoxon signed-rank test for paired data and the McNemar test for continuous and categorical variables, respectively. Comparisons between subgroups ('initial period' vs. 'recent period' and 'included' vs. 'excluded') were performed using the Wilcoxon–Mann–Whitney test. Applying the Bonferroni correction for multiple tests [23], $P < 0.0025$ was considered significant for the 'efficacy analysis' (number of tests = 20). Similarly, $P < 0.0015$ was considered significant for the 'safety/radiation analysis' (number of tests = 32). For the comparison of 'included' vs. 'excluded' (supplemental analysis), $P < 0.0025$ was considered significant (number of tests = 20).

The haemodynamic effects of BPA ('efficacy analysis') as well as the complication rates and radiation exposure ('safety/radiation analysis') were compared between the 'initial period' of the programme versus the 'recent period'. These two periods were separated by the date at which half the patients included in the 'efficacy analysis' had undergone their first BPA procedure. We also used this date to separate the 'initial period' and the 'recent period' for the 'safety/radiation analysis'. Thus, although the num-

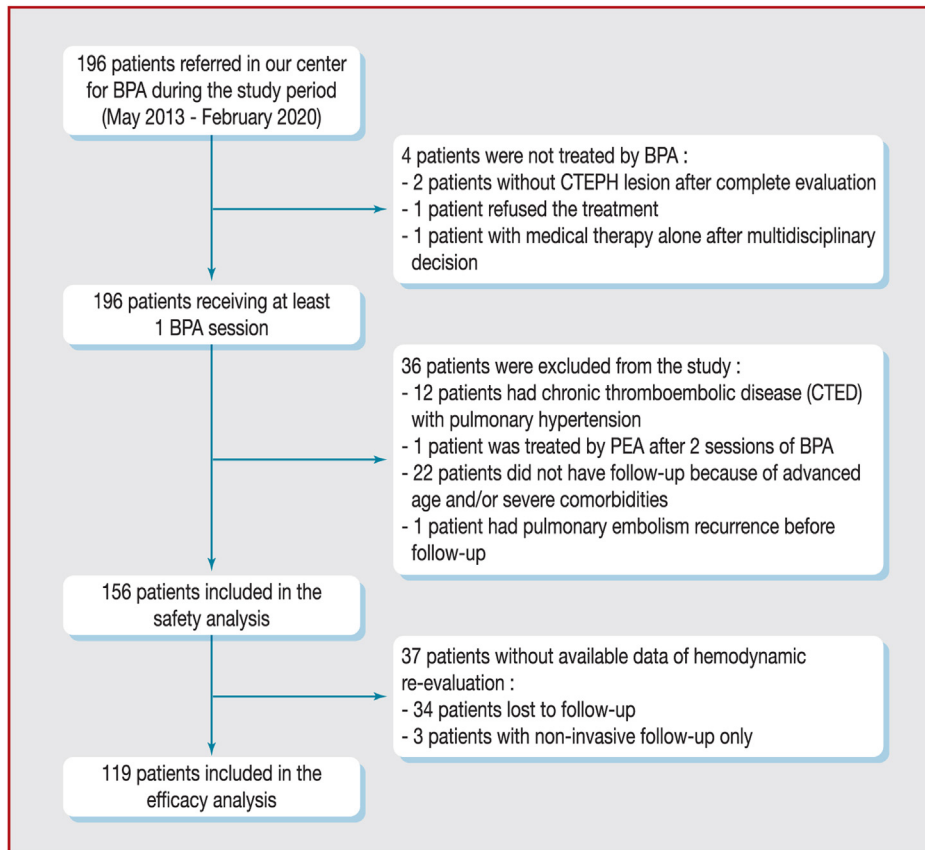


Figure 1. Flow chart of the study population. BPA: balloon pulmonary angioplasty; CTEPH: chronic thromboembolic pulmonary hypertension; CTED: chronic thromboembolic disease; PEA: pulmonary endarterectomy; PH: pulmonary hypertension.

ber of patients was, by definition, the same in the 'initial period' and the 'recent period' for the 'efficacy analysis', this was not necessarily the case for the 'safety/radiation analysis'.

Results

Patient characteristics

Between May 2013 and February 2020, 192 patients were treated by BPA in our centre. Among them, 156 were included in the safety/radiation analysis' and 119 had a complete invasive evaluation available in the database both before and after BPA and were therefore included in the 'efficacy analysis' of BPA (Fig. 1). The 73 patients who were excluded from the 'efficacy analysis' generally had similar characteristics to the 119 included patients, although mean PAP (mPAP) and pulmonary vascular resistance (PVR) were lower in the excluded patients (Table A.1). The 'initial period' (May 2013 to March 2017) included 59 patients in the 'efficacy analysis' and 61 patients in the 'safety/radiation analysis'; 60 and 95 patients were included in the 'efficacy' and 'safety/radiation' analyses, respectively, during the 'recent period' (April 2017 to February 2020). Reasons for exclusion from the 'safety/radiation' and 'efficacy' analyses are summarized in Fig. 1.

Baseline characteristics of the 156 patients included in the 'safety/radiation analysis' are shown in Table 1. The median (IQR) age of the patients was 70.0 (62.0–77.6) years and 53.8% were female. A history of acute venous thromboembolism was reported in 34 patients (21.8%). Before BPA, 85.9% of patients were in New York Heart Association (NYHA) functional class II or III and 66.0% were receiving at least one PAH-targeted therapy. The main indications for BPA were distal lesions (73.7%), unfavourable risk/benefit ratio for PEA (11.5%), refusal of PEA (7.7%) and persistent or recurrent PH after surgery (7.1%).

Select baseline characteristics of the 119 patients included in the 'efficacy analysis' are shown in Table 2.

Effects of BPA on functional and haemodynamic parameters

The median (IQR) number of procedures per patient was 4 (3–5) and the number of dilated vessels per procedure was 4 (3–5). The median (IQR) duration between the last BPA procedure and the invasive evaluation post-BPA was 189 (143–284) days. The effects of BPA on serum N-terminal pro-B-type natriuretic peptide (NT-proBNP), exercise capacity and haemodynamic parameters are presented in Table 2. NYHA functional class improved in 76 patients (63.9%), remained unchanged in 40 patients (33.6%) and deteriorated in three patients (2.5%). NT-proBNP improved, as did 6-minute walk distance, with a median (IQR) improvement of 51 (–14 to 90) m (11% increase from baseline). Haemodynamic assessment showed improvements in mPAP (median improvement of 28%), cardiac index (by 10%) and PVR (by 49%).

The main haemodynamic and functional characteristics of patients did not differ at baseline between the two

Table 1 Baseline characteristics of the patients with CTEPH in the 'safety/radiation analysis'.

	Patients (n = 156)
Clinical characteristics	
Age (years)	70.0 (62.0–77.6)
Women	84 (53.8)
Body mass index (kg/m ²)	25.1 (22.3–28.9)
Recurrent thromboembolic disease	34 (21.8)
Functional status	
NYHA functional class	
I	3 (1.9)
II	51 (32.7)
III	83 (53.2)
IV	19 (12.2)
6-minute walk distance (m)	354 (252–51)
Haemodynamic parameters	
mPAP (mmHg)	45.0 (38.0–50.0)
PAWP (mmHg)	10.0 (7.3–13.0)
RAP (mmHg)	8.0 (6.0–11.0)
Cardiac index (L/min/m ²)	2.2 (1.8–2.7)
PVR (Wood units)	8.4 (6.0–11.7)
BPA indication	
Distal lesions	115 (73.7)
Unfavourable risk/benefit ratio for PEA	18 (11.5)
Refusal of PEA	12 (7.7)
Post-PEA	11 (7.1)
Associated conditions	
Cancer or myeloproliferative disorder	20 (12.8)
Splenectomy	12 (7.7)
Chronic inflammatory disease	4 (2.6)
Permanent intravascular device	2 (1.3)
Antiphospholipid syndrome	1 (0.6)
PAH therapies	
0	53 (34.0)
1	70 (44.9)
2	33 (21.1)
Anticoagulation	
Vitamin K antagonist	95 (60.9)
Direct oral anticoagulation	60 (38.5)
Oxygen therapy	43 (27.6)

Data are expressed as median (interquartile range) or number (%). BPA: balloon pulmonary angioplasty; CTEPH: chronic thromboembolic pulmonary hypertension; mPAP: mean pulmonary artery pressure; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PAWP: pulmonary artery wedge pressure; PEA: pulmonary endarterectomy; RAP: right atrial pressure; PVR: pulmonary vascular resistance.

periods (Table 2). Nevertheless, the median (IQR) number of procedures per patient and dilated vessels per procedure were lower during the 'initial period': 4 (3–4) vs. 4.5 (4–6) ($P=0.03$) and 3.5 (3–4) vs. 4 (3.5–5) ($P=0.002$), respectively. The haemodynamic benefits were also less during the 'initial period' than during the 'recent period': median (IQR) relative change in mPAP was –22% (–31% to –14%) vs. –37% (–44% to –29%) ($P=0.001$) and relative

Table 2 Select parameters in the 119 patients with CTEPH who had a complete invasive evaluation available in the database both before BPA and 3–6 months after the last BPA procedure.

	Complete cohort (n = 119)			Initial period (n = 59)			Recent period (n = 60)		
	Pre-BPA	Post-BPA	<i>P</i> ^a	Pre-BPA	Post-BPA	<i>P</i> ^a	Pre-BPA	Post-BPA	<i>P</i> ^a
PAH therapies			0.35			0.90			0.23
0	43 (36.2)	29 (24.4)		23 (39.0)	19 (32.2)		20 (33.4)	10 (16.7)	
1	55 (46.2)	58 (48.7)		23 (39.0)	25 (42.4)		32 (53.3)	33 (55.0)	
2	21 (17.6)	32 (26.9)		13 (22.0)	15 (25.4)		8 (13.3)	17 (28.3)	
NYHA functional class			< 0.001			< 0.001			< 0.001
I	1 (0.8)	30 (25.2)		1 (1.7)	10 (16.9)		0 (0.0)	20 (33.3)	
II	41 (34.5)	74 (62.2)		18 (30.5)	38 (64.4)		23 (38.3)	36 (60.0)	
III	66 (55.5)	14 (11.8)		33 (55.9)	10 (17.0)		33 (55.0)	4 (6.7)	
IV	11 (9.2)	1 (0.8)		7 (11.9)	1 (1.7)		4 (6.7)	0 (0.0)	
NT-proBNP (pg/mL)	807 (251–2751)	172 (112–316)	< 0.001	624 (271–2276)	197 (158–379)	0.002	927 (179–2934)	122 (83–245)	< 0.001
6-minute walk distance (m)	373 (290–437)	435 (312–513)	0.003	400 (290–420)	450 (302–550)	0.12	360 (298–443)	430 (318–506)	0.002
Haemodynamic parameters									
mPAP (mmHg)	42 (35–48)	30 (24–36)	< 0.001	44 (36–50)	34 (29–40)	< 0.001	41 (34–47)	26 (22–31)	< 0.001
Cardiac index (L/min/m ²)	2.3 (2.0–2.7)	2.6 (2.2–3.0)	< 0.001	2.3 (1.9–2.6)	2.3 (2.0–2.6)	0.29	2.5 (2.0–2.7)	2.8 (2.4–3.2)	< 0.001
PVR (Wood units)	7.4 (5.1–10.5)	3.5 (2.8–5.1)	< 0.001	8.0 (6.2–10.6)	5.0 (3.6–6.8)	< 0.001	7.2 (4.9–10.5)	3.0 (2.4–4.0)	< 0.001
SvO ₂ (%)	63 (58–68)	68 (65–72)	0.010	60 (59–66)	69 (60–71)	0.56	64 (58–68)	67 (66–72)	0.002

Data are expressed as median (interquartile range) or number (%). BPA: balloon pulmonary angioplasty; CTEPH: chronic thromboembolic pulmonary hypertension; mPAP: mean pulmonary artery pressure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; SvO₂: mixed venous oxygen saturation.

^a *P* < 0.0025 was considered significant (Bonferroni correction).

Table 3 BPA procedure-related complications in the 156 patients in the ‘safety/radiation analysis’.

	Complete cohort	Initial period	Recent period	<i>P</i> ^a
Procedure-based analysis	<i>n</i> = 646	<i>n</i> = 235	<i>n</i> = 411	
Haemoptysis	23 (3.6)	12 (5.1)	11 (2.7)	0.17
Lung injury	19 (2.9)	7 (3.0)	12 (2.9)	0.96
NIV post-procedure	4 (0.6)	1 (0.4)	3 (0.7)	1.00
Patient-based analysis	<i>n</i> = 156	<i>n</i> = 61	<i>n</i> = 95	
Haemoptysis	18 (11.5)	10 (16.4)	8 (8.4)	0.21
Lung injury	18 (11.5)	6 (9.8)	12 (12.6)	0.56
NIV post-procedure	4 (2.6)	1 (1.6)	3 (3.2)	0.95
≥ 1 BPA-related complication	26 (16.7)	11 (18.0)	15 (15.8)	0.88
Peri-procedural death	1 (0.6)	0 (0.0)	1 (1.1)	1.00

Data are expressed as number (%). BPA: balloon pulmonary angioplasty; NIV: non-invasive ventilation.

^a *P* < 0.0015 was considered significant (Bonferroni correction).

change in PVR was −38% (−51% to −8%) vs. −53% (−69% to −33%) (*P* = 0.002). The improvement in NYHA functional class was similar during both periods (Table 2).

BPA procedure-related complications

A total of 646 procedures were analysed in 156 patients (Table 3). Complications related to BPA occurred in 46 procedures (7.1% of all procedures). Twenty-six patients (16.7%) developed at least one BPA-related complication and one peri-procedural death occurred. The rate of complications was similar during the two periods (9.3% of procedures during the ‘initial period’ and 5.7 during the ‘recent period’; *P* = 0.38).

Radiation exposure

Detailed radiation exposure data are described in Table 4. Compared with the ‘initial period’, radiation exposure per procedure was lower during the ‘recent period’ (despite the number of dilated vessels per procedure being higher). Similarly, despite a higher number of procedures per patient during the ‘recent period’, radiation exposure per patient was lower during the ‘recent period’ than during the ‘initial period’.

Discussion

In a statement published very recently by the European Respiratory Society, it has been recognized that patients with CTEPH who are not eligible for PEA (or who have incomplete response to PEA) can benefit from BPA [27]. By analysing our large single-centre series, we have confirmed that BPA produced improvements in pulmonary haemodynamics, 6-minute walk distance and NYHA functional class in selected patients with CTEPH. By comparing the haemodynamic effects of BPA, the complication rates and the radiation exposure between patients treated during a ‘recent period’ and those treated during an ‘initial period’, we found that patients had better haemodynamic improvements in the ‘recent period’, confirming previous observations that have suggested a learning curve period for this procedure [9]. We

also found a higher number of BPA procedures per patient and a higher number of dilated vessels per BPA procedure during the ‘recent period’. Nevertheless, radiation exposure per procedure and per patient were lower during the ‘recent period’ than during the ‘initial period’. Finally, in our series, we did not find a significant decrease in procedure-related complications over time.

After a single case report in 1988 [24], it was reported in 2001 – in a series of 18 patients – that pulmonary angioplasty was feasible and effective to improve pulmonary haemodynamics, 6-minute walk distance and NYHA functional class in patients with CTEPH [4]. These encouraging results were confirmed a decade later by a Norwegian team [25] and then by several Japanese teams [5–7]. Our team performed the first French case of BPA in a patient with CTEPH in 2013 [21]. Since then, we have treated an increasing number of patients each year, with an average of 36 new patients referred per year during the last 3 years. For all patients, eligibility for BPA was decided on the basis of a consensus among a multidisciplinary team. The median haemodynamic improvements observed after BPA in our ‘initial period’ were 22% and 38% for mPAP and PVR, respectively. These values are in line with most ‘initial experiences’, including very recent ones [9,15,18,20]. In contrast, results observed in the second half of our cohort (that we called our ‘recent period’) were much better, with median drops in mPAP and in PVR that were as high as 37% and 53%, respectively. These haemodynamic improvements were in line with results of centres with a recognized experience with BPA, including Japanese ones, which have reported reductions in mPAP and PVR of 31–49% and 45–69%, respectively, as recently summarized in a review by Coghlan et al. [26].

Our study was not designed to determine the optimal number of patients and/or procedures to be performed before reaching a plateau in terms of optimal haemodynamic improvements, and there is currently no definition of such ‘optimal haemodynamic improvements’. In addition, there are no published data available to determine, scientifically, the number of procedures or patients needed for an operator to reach their optimal level, i.e. to treat patients with good results and without excessive morbidity or mortality [27]. Our results reinforce the existence of a learning curve for

Table 4 Radiation exposure in the 156 patients in the 'safety/radiation analysis'.

	Complete cohort	Initial period	Recent period	<i>P</i> ^a
Data per procedure	<i>n</i> = 632	<i>n</i> = 222	<i>n</i> = 410	
Kerma area product (cGy.cm ²)	6047 (3403–10,306)	9294 (5433–14,410)	4730 (2823–7890)	< 0.001
Effective dose (mSv)	12.1 (6.8–20.6)	18.6 (10.9–28.8)	9.5 (5.6–15.8)	< 0.001
Reference air Kerma (mGy)	661 (394–1091) ^b	910 (612–1392) ^b	556 (356–920)	< 0.001
Fluoroscopy time (minutes)	37.9 (27.8–47.2) ^c	41.4 (31.5–51.1) ^c	35.4 (26.2–45.7)	< 0.001
Data per patient	<i>n</i> = 155	<i>n</i> = 60	<i>n</i> = 95	
Kerma area product (cGy.cm ²)	26,614 (16,719–38,643)	33,920 (23,942–50,955)	21,949 (15,777–33,267)	< 0.001
Effective dose (mSv)	53.2 (33.4–77.3)	67.8 (47.9–101.9)	43.9 (31.6–66.5)	< 0.001
Reference air Kerma (mGy)	2690 (1853–4328)	3353 (2204–4441)	2381 (1695–3916)	0.02
Fluoroscopy time (minutes)	147 (107–190)	147 (115–177)	152 (106–198)	0.75

Data are expressed as median (interquartile range).

^a *P* < 0.0015 was considered significant (Bonferroni correction).

^b Data were missing for 2 patients.

^c Data were missing for 1 patient.

the magnitude of haemodynamic improvements after BPA in patients with CTEPH.

As CTEPH is a rare condition, and the definition of a 'BPA centre' cannot be based solely on procedural volume [27], such a learning curve for haemodynamic improvements is worthy of consideration for the definition of any new BPA centres. We suggest that criteria and/or outcome thresholds for starting a BPA programme should be the following: (1) demonstration of a territorial need: the number of 20 patients per year referred for BPA should be considered the minimum for a new BPA centre to be approved; (2) training of operators: a direct mentorship from a high-volume centre followed by experience of ≥ 50 procedures is considered the minimum for an operator to treat patients with good results and without excessive morbidity or mortality and (3) appropriate patient selection: the setting up of a multidisciplinary discussion with the participation of a thoracic surgeon experienced in PEA for CTEPH (gold standard for operable forms) is considered mandatory.

Owing to the rarity of CTEPH and the need for specific management of this disease, many countries have chosen a pyramidal organisation of patient management. Such organisation comprises one (or a few) reference centres, several competence centres (located mostly in university hospitals), local specialists and general practitioners. However, there is no legal text in France defining the number of sites (reference centres or competence centres) where specific treatments such as BPA can be performed. We believe that in the framework of a pyramidal network organisation, the number of centres performing BPA in a given country could be adjusted according to: (1) the capacity of the network to identify patients with CTEPH (bearing in mind that this disease is currently considered under-diagnosed); (2) the evolution of treatment recommendations for these patients (bearing in mind that the role of PH-targeted medical therapy in relation to BPA still has to be better defined and that treatment goals and key endpoints for completing BPA interventions still need to be better identified) and (3) the policy of the countries involved (one centre in one country versus several centres treating a minimum of 20 BPA patients per year).

The reasons why haemodynamic effects may vary from one centre to another remains questionable. Our study suggests that with increasing experience, both the number of procedures per patient and the number of treated vessels per procedure may increase. It is therefore plausible that better haemodynamic improvements in some centres are at least in part a consequence of: (1) better identification of vessels to be dilated (presumably, at least in part, thanks to an improved use of imaging techniques such as dual energy computed tomography); (2) shortening of procedures (allowing one to dilate an increased number of vessels during a procedure, as discussed below) and/or (3) application of technical refinements introduced from expert centres [27]. Another hypothesis for variable results between centres concerns patient baseline characteristics. There are increasing arguments in favour of a relationship between the magnitude of peripheral pulmonary vasculopathy (that exists before BPA) and residual PH after BPA [28]. Thus, it is highly plausible that the importance of peripheral pulmonary vasculopathy mitigates the haemodynamic effects of upstream vascular dilatation after BPA [1].

Safety concerns have regularly been raised regarding BPA. The most frequent complication associated with BPA is lung injury, which is now – by consensus – considered a consequence of mechanical vascular injury during wire manipulation or balloon overdilation and not a reperfusion pulmonary oedema (the latter being observed after PEA) [29]. In the pivotal study published in 2001, the prevalence of lung injury was as high as 61% and 17% of patients needed mechanical ventilatory support [4]. Complication rates in the new era are much lower. In German and French BPA series, complications occurred in 9% and 11% of procedures, respectively [9,18]. The complication rate in our complete cohort is similar, at 7.1%. Of note, although the rate of complications tended to be lower during the most recent period than during the initial one in our study (5.7% vs. 9.3% of procedures), this difference was not significant. These results contrast with those of Brenot et al., who reported a per procedure complication rate that decreased significantly from 16% to 8% between their initial and their most recent period [9]. These differences between the study of Brenot

et al. [9] and ours is unlikely to be related to patients' severity because baseline patient data were similar in these two studies. Our opinion is that some complications (particularly haemoptysis) were much more frequent and severe during the first year of BPA in our centre, but that the total duration of the 'initial period' did not allow this information to appear in our analysis.

A parameter that has been largely neglected in patients undergoing BPA is radiation exposure. We report three radiation dose metrics that were collected automatically (KAP, fluoroscopy time and air kerma) and one metric (effective dose) that was calculated from the KAP. One important and original result is that although the number of dilated vessels per BPA procedure was higher during the 'recent period' than during the 'initial period' of our study, radiation exposure (including fluoroscopy time) per procedure was much lower during the 'recent period'. In other words, the fluoroscopy time needed to dilate one single vessel was reduced with experience. In addition, although total fluoroscopy times per patient were similar during the two periods, radiation exposure metrics (KAP, air kerma and effective dose) were all lower during the recent period. Although we did not perform a specific analysis on the causes of this lowering radiation exposure, several plausible explanations might be considered. First, a contribution of pulsed radiation frequency during fluoroscopy and fluorography (cine and DSA modes) is very unlikely in our series because pulsed fluoroscopy and fluorography frequencies did not change over the study period. Second, for a given procedure, the dose accumulates more rapidly in patients with a higher body mass index, as the dose rates are higher in these patients. Nevertheless, patients had similar body mass index during the two periods in our series (data not shown). Third, the better the radiation protection practices, the lower the dose received by the patients [30]. These protective practices include avoiding high beam angles, keeping the flat panel detector as close to the patient as possible, collimating the radiation field to the area of interest and using low-dose protocols. Further research is needed to assess the influence of these factors on our data. Fourth, a likely hypothesis is that the number of images made per session has decreased over time with operator experience, as a consequence of the learning curve. Limiting the number of images acquired (DSA plus cine) does not change the fluoroscopy time but reduces the overall dose. Indeed, the total radiation dose received by the patient depends on the dose delivered by both fluoroscopy and fluorography (cine or DSA mode).

Study limitations

Our study has several limitations. Firstly, the functional and haemodynamic parameters (6-minute walk distance, NYHA functional class and haemodynamic parameters) as well as the complication rates and the radiation exposure were not obtained by blinded study personnel. Our results might therefore have been biased. Secondly, a high proportion (about two thirds) of our patients were receiving at least one PH-targeted therapy at the time of the first BPA procedure. Although this may have had an impact on post-procedural outcomes, our study does not allow us to analyse this issue as patients were not randomly assigned to receive or not receive a PH-targeted drug. Thirdly, as there is no

consensus criterion for defining the efficacy of pulmonary artery angioplasty treatment, we did not perform a sample size calculation. We decided to include all patients with CTEPH who were treated with pulmonary artery angioplasty at our centre and who met the inclusion criteria during the study period. Nevertheless, we assessed the statistical power of what are considered the most clinically relevant outcomes (i.e. PVR and mPAP) and they were >0.90 for these two parameters (data not shown). Fourthly, of the 192 patients who underwent BPA during the study period, the 73 who were not included in either the 'efficacy analysis' or the 'safety/radiation analysis' had significantly lower baseline mPAP and PVR than those who were included. This was due, at least in part, to the fact that 12 patients who received BPA did not have PH. Nevertheless, we cannot exclude that selection bias influenced our results.

Conclusions

We report here our 8-year experience and provide data from a large series including patients with CTEPH treated by BPA. Although we confirm a learning curve regarding haemodynamic effects, we did not confirm such a learning curve regarding the complication rate of BPA in highly selected patients with CTEPH. We report for the first time that radiation exposure can improve with growing BPA experience. We believe that our data may provide a realistic perspective on the risks and benefits associated with the introduction of a BPA programme in referral centres.

Acknowledgements

We are indebted to our colleagues who trusted us with referrals and helped us collect follow-up data of their patients: Julie Traclet (Lyon), Arnaud Bourdin (Montpellier), Sébastien Renard (Marseille), Claire Dauphin (Clermont-Ferrand), Marie-France Séronde (Besançon), Paméla Mocéri (Nice) and Laurent Bertoletti (Saint-Étienne).

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.acvd.2022.02.010>.

References

- [1] Gerges C, Gerges M, Friewald R, Fesler P, Dorfmueller P, Sharma S, et al. Microvascular disease in chronic thromboembolic pulmonary hypertension: hemodynamic phenotyping and histomorphometric assessment. *Circulation* 2020;141:376–86.
- [2] Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2019;53:1801915.

- [3] Mahmud E, Madani MM, Kim NH, Poch D, Ang L, Behnamfar O, et al. Chronic thromboembolic pulmonary hypertension: evolving therapeutic approaches for operable and inoperable disease. *J Am Coll Cardiol* 2018;71:2468–86.
- [4] Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. *Circulation* 2001;103:10–3.
- [5] 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 Interv* 2013;6:725–36.
- [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;5:748–55.
- [7] Kataoka M, Inami T, Hayashida K, Shimura N, Ishiguro H, Abe T, et al. Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv* 2012;5:756–62.
- [8] Ghofrani HA, D'Armini AM, Kim NH, Mayer E, Simonneau G. Interventional and pharmacological management of chronic thromboembolic pulmonary hypertension. *Respir Med* 2021;177:106293.
- [9] Brenot P, Jaïs X, Taniguchi Y, Garcia Alonso C, Gerardin B, Mussot S, et al. French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2019;53:1802095.
- [10] Kikuchi H, Goda A, Takeuchi K, Inami T, Kohno T, Sakata K, et al. Exercise intolerance in chronic thromboembolic pulmonary hypertension after pulmonary angioplasty. *Eur Respir J* 2020;56:1901982.
- [11] Fukui S, Ogo T, Morita Y, Tsuji A, Tateishi E, Ozaki K, et al. Right ventricular reverse remodelling after balloon pulmonary angioplasty. *Eur Respir J* 2014;43:1394–402.
- [12] Taniguchi Y, Jais X, Jevnikar M, Boucly A, Weatherald J, Brenot P, et al. Predictors of survival in patients with not-operated chronic thromboembolic pulmonary hypertension. *J Heart Lung Transplant* 2019;38:833–42.
- [13] Kriechbaum SD, Wiedenroth CB, Wolter JS, Hütz R, Haas M, Breithecker A, et al. N-terminal pro-B-type natriuretic peptide for monitoring after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. *J Heart Lung Transplant* 2018;37:639–46.
- [14] Darocha S, Pietura R, Pietrasik A, Norwa J, Dobosiewicz A, Pitka M, et al. Improvement in quality of life and hemodynamics in chronic thromboembolic pulmonary hypertension treated with balloon pulmonary angioplasty. *Circ J* 2017;81:552–7.
- [15] Sepúlveda P, Hameau R, Backhouse C, Charne G, Pacheco F, Ramirez PA, et al. Mid-term follow-up of balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: an experience in Latin America. *Catheter Cardiovasc Interv* 2021;97:E748–57.
- [16] 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:e001144.
- [17] Sablinskis M, Sablinskis K, Skride A. Pulmonary endarterectomy in Latvia: a national experience. *Medicina (Kaunas)* 2019;55:18.
- [18] 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 Respir J* 2017;49:1602409.
- [19] Taniguchi Y, Matsuoka Y, Onishi H, Yanaka K, Emoto N, Nakai H, et al. The role of balloon pulmonary angioplasty and pulmonary endarterectomy: is chronic thromboembolic pulmonary hypertension still a life-threatening disease? *Int J Cardiol* 2021;326:170–7.
- [20] Godinas L, Bonne L, Budts W, Belge C, Leys M, Delcroix M, et al. Balloon pulmonary angioplasty for the treatment of nonoperable chronic thromboembolic pulmonary hypertension: single-center experience with low initial complication rate. *J Vasc Interv Radiol* 2019;30:1265–72.
- [21] Bouvaist H, Thony F, Jondot M, Camara B, Jais X, Pison C. Balloon pulmonary angioplasty in a patient with chronic thromboembolic pulmonary hypertension. *Eur Respir Rev* 2014;23:393–5.
- [22] Rehani MM, Ciraj-Bjelac O, Vaňo E, Miller DL, Walsh S, Giordano BD, et al. ICRP Publication 117. Radiological protection in fluoroscopically guided procedures performed outside the imaging department. *Ann ICRP* 2010;40:1–102.
- [23] Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ* 1995;310:170.
- [24] Voorburg JA, Cats VM, Buis B, Brusckhe AV. Balloon angioplasty in the treatment of pulmonary hypertension caused by pulmonary embolism. *Chest* 1988;94:1249–53.
- [25] Andreassen AK, Ragnarsson A, Gude E, Geiran O, Andersen R. Balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. *Heart* 2013;99:1415–20.
- [26] Coghlan JG, Rothman AM, Hoole SP. Balloon pulmonary angioplasty: state of the art. *Interv Cardiol* 2020;16:e02.
- [27] Delcroix M, Torbicki A, Gopalan D, Sitbon O, Klok FA, Lang I, et al. ERS statement on chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2021;57:2002828.
- [28] Ruigrok D, Meijboom LJ, Nossent EJ, Boonstra A, Braams NJ, van Wezenbeek J, et al. Persistent exercise intolerance after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2020;55:2000109.
- [29] Ejiri K, Ogawa A, Fujii S, Ito H, Matsubara H. Vascular injury is a major cause of lung injury after balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv* 2018;11:e005884.
- [30] Valentin J. Avoidance of radiation injuries from medical interventional procedures. *Ann ICRP* 2000;30:7–67.