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ORIGINAL STUDIES

Mid-term follow-up of balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: An experience in Latin America

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Abstract

Objectives: To describe the characteristics of patients who undergo balloon pulmonary angioplasty (BPA) for inoperable chronic thromboembolic pulmonary hypertension (CTEPH) and report the mid-term outcomes.

Background: BPA has been recently introduced in Latin America. Mid-term results have not been published.

Methods: Prospective Chilean Registry of inoperable CTEPH patients who underwent BPA. Clinical variables were analyzed at baseline, after each procedure and at follow-up. Hemodynamic variables were recorded before and after the last BPA.

Results: Between August 2016 and September 2019, 22 patients (17 women), 59 ± 12.7 years, underwent 81 BPA and were followed for as long as 33.1 months (mean 17.3 ± 7.5). Mean pulmonary artery pressure decreased by 17.4% (51.1 ± 12 vs. 42.2 ± 13 mmHg, p = .001), pulmonary vascular resistance by 23.9% (766.7 ± 351 vs. 583 ± 346 dynes/s/cm^{-5}, p = .001), cardiac index increased by 8% (2.3 ± 0.54 vs. 2.5 ± 0.54 L/min/m^2, p = .012), N-terminal pro-B-type natriuretic peptide decreased by 73.8% (1,685 ± 1,045 vs. 441.8 ± 276 pg/dl, p = .006), and 6-min walk distance improved by 135 m (316.7 ± 94 vs. 451.1 ± 113 m, p = .001). One patient (4.5%) developed lung reperfusion injury and four patients (18.2%) had minor bleeding (hemoptysis), after the procedure. There was no mortality associated with BPA.

Conclusions: Our results confirm that BPA for inoperable CTEPH is a relatively safe procedure that improves clinical and hemodynamic parameters in the mid-term. This

Abbreviations: 6MWD, 6-min walk distance; BPA, balloon pulmonary angioplasty; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; FC, World Health Organization functional class; FU, follow-up; LRI, lung reperfusion injury; mPAP, mean pulmonary artery pressure; OFDI, optical frequency domain imaging; PAG, pulmonary angiography; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; Pro-BNP, N-terminal pro-B-type natriuretic peptide; PVR, pulmonary vascular resistance; RHC, right heart catheterization; V/Q scan, ventilation/perfusion lung scan; VC, vascular complications.

therapy should be considered as an alternative, mainly in places where access to PAH therapy or surgery is restricted.

KEYWORDS
angioplasty, chronic thromboembolic pulmonary hypertension, pulmonary hypertension, registry

1 | INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease caused by persistent thrombi after an acute embolism that leads to fibrotic obstructions and microvascular changes in the pulmonary circulation.[1-6] As a consequence of this process, pulmonary arterial hypertension (PAH), right heart failure, and death ensue in the course of 3–5 years after diagnosis.[1-4] Pulmonary endarterectomy (PEA) is still considered the first line treatment according to recent guidelines, provided patients and lesion characteristics are adequate for surgery and surgical expertise is available.[7] Nevertheless, up to 40% of CTEPH patients are excluded from surgery, due to distal lesions or comorbidities.[8,9] Balloon pulmonary angioplasty (BPA) is increasingly becoming a therapeutic option for patients with CTEPH who are ineligible for PEA, or in cases of recurrent or residual PAH after surgery. Current guidelines and expert consensus endorse BPA with or without the use of concomitant specific PAH drugs in this subset of patients.[6,7]

In Chile, access to PAH target therapies is limited mainly due to economic constraints. The national health system only supports treatment for idiopathic, heritable, or connective tissue disease-related PAH. Moreover, PEA is performed in few low-volume centers, whose results are largely unpublished. Our group has pioneered the use of BPA in our country, following the Japanese-modified approach to the technique.[10-15] We have recently published an initial single-center experience with short-term follow-up (FU) in a small series of patients, showing positive and consistent results compared with other similar experiences.[16]

There is still a gap in knowledge regarding the mid- and long-term results of BPA, although some registries have reported hemodynamic, clinical and survival benefits similar to PEA, up to 43 months of FU.[17-21] Moreover, no mid-terms FU of BPA have been reported in our country, nor experiences from other centers compiled in a single data set. The objective of this study is to report the mid-term results of BPA for inoperable CTEPH, based on a Chilean multicenter prospective registry.

2 | METHODS

2.1 | Patients selection

Between June 2016 and September 2019, 25 patients with CTEPH—previously excluded from PEA by a multidisciplinary team—were evaluated at three PAH reference centers in Chile: Hospital San Juan de Dios (Santiago), Hospital Naval (Viña Del Mar), and Hospital Clínico Pontificia Universidad Católica de Chile (Santiago). A comprehensive evaluation of clinical data and historical imaging studies was undertaken, including chest radiography, echocardiography, ventilation-perfusion lung scan (V/Q scan), computed tomography pulmonary angiography (CTPA), right heart catheterization (RHC), and pulmonary angiography (PAG), provided they were less than 3-month-old. Otherwise, they were updated to be reviewed by three of the authors (interventional cardiologists), performing the procedures at each center (P. S., G. C., C. B.).

The inclusion criteria were:

1. Symptomatic patient with WHO functional class (FC) II or more, despite maximal tolerated medical therapy.
2. Vascular lesions suitable for BPA, assessed by PAG.
3. High or intermediate risk prognostic factors for PAH according to current guidelines.[6]

The exclusion criteria were:

1. Asymptomatic patients without high or intermediate risk prognostic factors.
2. Comorbidities that prevented repeated PAG or interventional procedures.
3. Unwilling to sign the informed consent.

After this initial selection, 22 patients were considered adequate BPA candidates and included in this registry. Three patients were excluded on the basis of severe comorbidity and frailty: One patient with chronic kidney disease (Stage 4) and two patients with advance COPD (Gold 3–4).

Targeted areas to intervene were chosen if perfusion defects seen in V/Q scan correlated with lesions seen at CTPA or PAG. For patients without optimal medical therapy at the time of screening, the recommendation was to titrate PAH specific medications—mainly sildenafil—up to maximum tolerated doses and keep them stable for at least 3 months before BPA. If more than 3 months were required to reach a stable dose, RHC and PAG were repeated to re-assess angiographic eligibility for BPA. The study was approved by each institution's IRB or Ethics Committee. Informed consent was obtained according to the ethical norms of the declaration of Helsinki of 2013, and to comply with local regulations regarding clinical registries.

2.2 | Medical therapy

Treatment for PAH was decided by the treating physician. All patients received oral anticoagulant, oxygen therapy as needed and sildenafil,

titrated to the maximal tolerated dose. Medical therapy was not modified after BPA, in order to properly assess the effect of the intervention.

2.3 | BPA procedure

Equipment and technical details for BPA were previously described in our preliminary report.[15] Briefly, anticoagulation was withdrawn 24 hr before the procedure for patients on direct oral anticoagulants; and 48 hr before for patients on warfarin or acenocoumarol. Under local anesthesia (lidocaine 2%, 10 cc), an 8F short sheath (Arrow®) was installed. We favored the right jugular vein to access the right lung circulation, and the right femoral vein to access the left lung circulation. In case of failure to access both veins, the right brachial vein was used to access both lungs. After the access site was secured, a bolus of 2,000 IU of unfractionated heparin was given intravenously, with 1,000 IU boluses every hour thereafter until the end of the

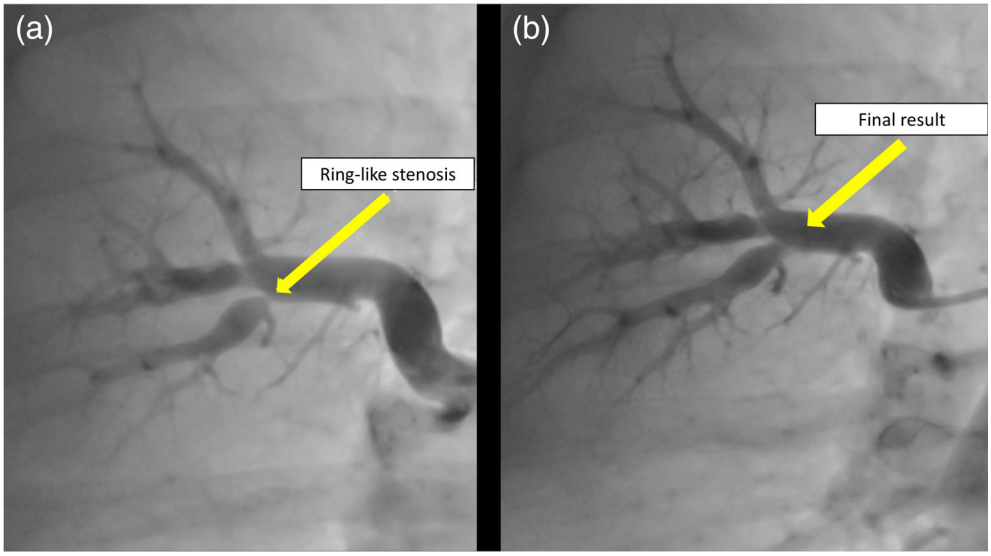

FIGURE 1 Balloon pulmonary angioplasty. (a) Pulmonary angiography showing a type A (*ring-like*) stenosis at the right upper lobe artery (A3 segment). (b) Post procedural results [Color figure can be viewed at wileyonlinelibrary.com]

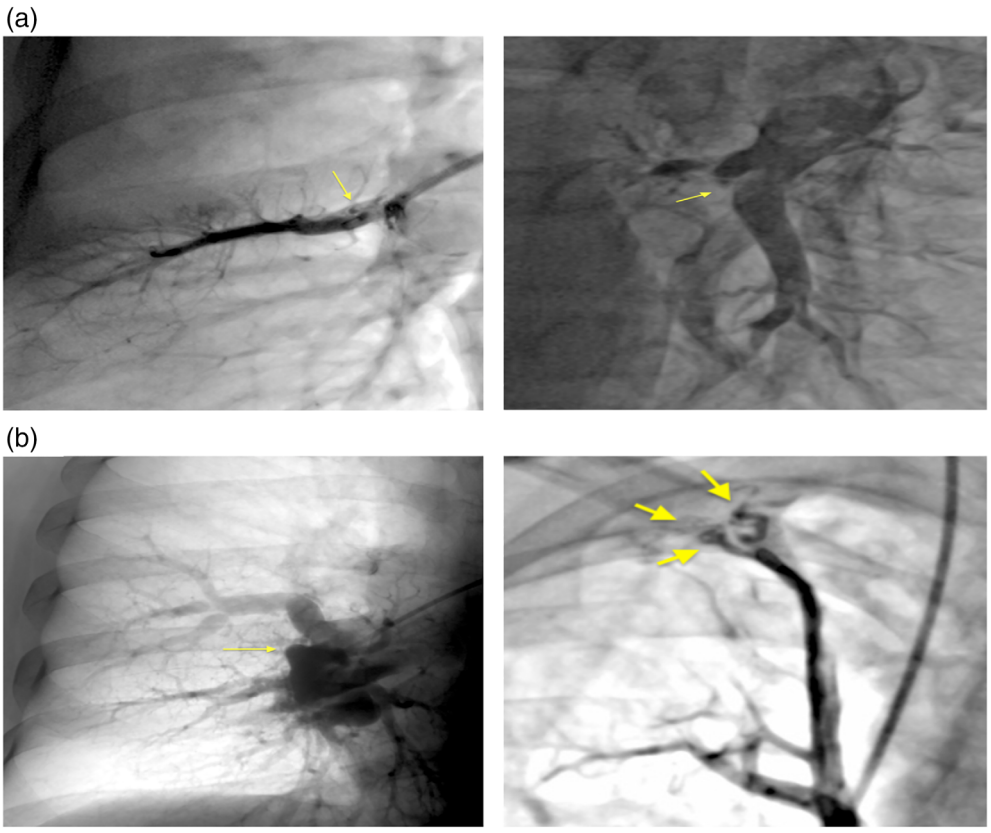

FIGURE 2 Angiographic classification of chronic thromboembolic pulmonary hypertension lesions and eligibility for balloon pulmonary angioplasty (BPA). (a) Types of lesions that were *selected* for BPA: Left, Type B (web lesion); Right, Type C (subtotal lesion). Type A lesions (ring-like stenosis lesion, shown in Figure 1) were also selected. (b) Types of lesions that were *excluded* for BPA: Left, type D (total occlusion lesion); Right, Type E (tortuous lesion) [Color figure can be viewed at wileyonlinelibrary.com]

intervention. Oxygen was given during the procedure at a flow rate of 3 L/min. First of all, an RHC was performed using a Swan-Ganz catheter (7F, 110 cm, Edwards Lifesciences®) and cardiac output calculated using the thermodilution method. Then, the Swan-Ganz catheter was exchanged over a Hi-Torque Steelcore wire (0.018″, 300 cm, Abbott®), and a pigtail catheter (6F Launcher 100 cm, Medtronic®) was advanced. PAG was done in the main branch of the pulmonary artery at each side, with anteroposterior and oblique contralateral (50–65°) projections acquired for each lung. The pigtail catheter was then exchanged over a 0.035″ wire (J-tip fixed core exchange guide wire, Medtronic®) and a peripheral guiding sheath—Destination (7F, 45 cm for jugular access, 90 cm for femoral access, Terumo®)—was positioned in the trunk of the pulmonary artery or one of its main branches. A guiding catheter JR-4 (6F, 100 cm, Medtronic®) or MP-1 (6F, 100 cm, Terumo®) was selectively engaged in the targeted segmental or subsegmental artery.

Based on the current angiographical classification, we opted to intervene lesions type A (ring-like stenosis lesion, Figure 1), type B (web lesion, Figure 2a-left) and type C (subtotal lesion, Figure 2a-right), over type D (total occlusion lesion, Figure 2b-left) or type E (tortuous lesion, Figure 2b-right).[22] Where available, evaluation with intravascular imaging—optical frequency domain imaging (OFDI)—was used to identify type B lesions not clearly visible by selective angiography. After crossing the lesion with a floppy wire—Runthrough NS Hypercoat (0.014″, 180 cm, Terumo®)—, a semicompliant balloon 1.5–4.0 mm (0.8:1.0 balloon to artery ratio) was inflated at nominal pressure.

BPA was considered successful if the target vessel was reopened, with restoration of antegrade flow and increase in venous return in the intervened segment, along with a decrease in mean pulmonary artery pressure (mPAP) assessed by RHC performed at the end of the procedure. In this protocol, no more than two segments were treated in the first BPA session and ≤3 in the following ones. After BPA, all patients were admitted to the cardiac intensive care unit for monitorization over a 24-hr period. A predischarge chest radiograph was taken to exclude lung reperfusion injury (LRI). Subsequent BPA sessions were scheduled at 4–6 weeks intervals.

2.4 | Follow-up

Evaluations were performed between sessions assessing pro-BNP, FC and 6MWD, and every 6 months (or less upon treating physician decision) after the final BPA. Clinical response to BPA was defined as improvement in FC or 6MWD, or a reduction of >10 mmHg in mPAP, after at least two sessions with at least one BPA in each lung. The criteria for stopping the BPA sessions were: (a) Futility: Absence of clinical response; (b) Patients unable or unwilling to tolerate more procedures; (c) Improving mPAP below 30 mmHg, considered the "curative" threshold.

2.5 | Efficacy analysis

This protocol evaluated two groups of variables:

1. Hemodynamic parameters: mPAP, cardiac index (CI), and pulmonary vascular resistance (PVR), at baseline (i.e., before the first BPA) and after the final BPA session.
2. Clinical parameters: 6-min walk distance (6MWD), N-terminal pro-B-type natriuretic peptide (Pro-BNP), and FC, at baseline and at the last FU available.

TABLE 1 Clinical characteristics of the study cohort

N patients	22
Age, years	59 ± 12.7
Female sex, *n* (%)	17 (77)
Cardiovascular risk factors, *n* (%)	
Hypertension	12 (54.5)
Obesity	5 (22.7)
Hypercholesterolemia	5 (22.7)
Current smoker	3 (13.6)
Diabetes	2 (9.1)
Heart failure	2 (9.1)
Previous DVT, *n* (%)	11 (50)
Previous PE, *n* (%)	18 (81.8)
Previous PEA, *n* (%)	1 (4.5)
Vena cava filter implanted *n* (%)	4 (18)
Time from PEA exclusion to BPA, months	24.0 ± 11.1
FC, 1–4	3.0 ± 0.5
6MWD, m	316.7 ± 94
Pro-BNP, pg/dl	1,685 ± 1,045
PAPs-echo, mmHg	83 ± 13.7
TAPSE, mm	19 ± 4.4
V/Q scan positive, *n* (%)	19 (86)
CTPA positive, *n* (%)	16 (73)
PAH treatment, *n* (%)	
Sildenafil, mg/day	127.3 ± 51.1
Riociguat	1 (4.5)
Oral anticoagulation	22 (100)
Oxygen	6 (27)
Indication for BPA, *n* (%)	
Distal lesions	18 (82)
Comorbidity	2 (9)
Persistence of PAH after PEA	1 (4.5)
PEA refusal	1 (4.5)

Note: Results presented as *n*, *n* (%) or mean ± *SD*.

Abbreviations: 6MWD, 6-min walk distance; BPA, balloon pulmonary angioplasty; CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; FC, World Health Organization functional class; PAH, pulmonary artery hypertension; PAPs-echo, systolic pulmonary artery pressure estimated by echocardiography; PE, pulmonary embolism; PEA, pulmonary endarterectomy; Pro-BNP, Pro-brain natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion; V/Q scan, ventilation/perfusion lung scan.

2.6 | Safety analysis

Any kind of procedure-related complications were registered, with special attention to vascular complications (VC). VC were classified as perforations (wire or balloon) or dissections, with or without hemoptysis. Need for mechanical ventilation and the presence of LRI in the predischarge chest radiograph were also considered as safety outcomes. Vital status (dead or alive) was assessed in September 2019, by queries to the National Civil Registry.

TABLE 2 Procedural and angiographic characteristics

Number of segments treated	81
Success, *n* patients (%)	21 (95)
Mortality during the procedure or at 30 days	0
Right lung segments treated, *n* (%)	48 (59.3)
Left lung segments treated, *n* (%)	33 (40.7)
Segments/patient	3.7 ± 2.2
Sessions/patient	2.7 ± 1.4
Use of intravascular imaging (OFDI)[a]	8 (36.4)
Procedural-related complications, *n* (%)	
Vascular complications with hemoptysis	5 (6.2)
4 wire perforation	
1 balloon overdilatation (life-threatening bleeding)	
Vascular complications without hemoptysis	2 (2.5)
1 wire perforation	
1 disection	
Lung reperfusion injury	1 (1.2)
Pericardial tamponade	1 (1.2)

Note: Results presented as *n*, *n* (%) or mean ± *SD*.
Abbreviation: OFDI, optical frequency domain imaging.
[a]Only the first eight consecutive patients.

2.7 | Statistical analysis

Data were stored in a cloud-based spreadsheet. Safety and efficacy of BPA were evaluated for the overall population. The current analysis was performed when all patients had at least one BPA in each lung and at least 6 months of FU, regardless if they had reached their final session. Categorical variables are expressed as absolute frequency and proportions. Continuous variables are expressed as mean ± *SD*. The Shapiro–Wilk test was used to evaluate the distribution of the variables. We used the Chi-square test to compare categorical variables and the Wilcoxon signed rank test for continuous non-parametric variables. A *p* value of <.05 was considered statistically significant. All analyses were performed using the STATA 14.0 software (StataCorp LLC, TX).

3 | RESULTS

Between August 2016 and September 22, 2019 patients with inoperable CTEPH were included in a multicenter registry and followed for as long as 33.1 months (mean 17.3 ± 7.5 months). The number of patients [n(%)] reaching the 6-, 12-, 18-, 24-, and 30-months FU visit at the time of this analysis were: 22 (100); 18 (82); 12 (55); 7 (32); 1 (4.5), respectively. Three patients—all of them alive at the time of this evaluation—had not had their last BPA session performed but were included in this analysis because they had >10 mmHg decrease

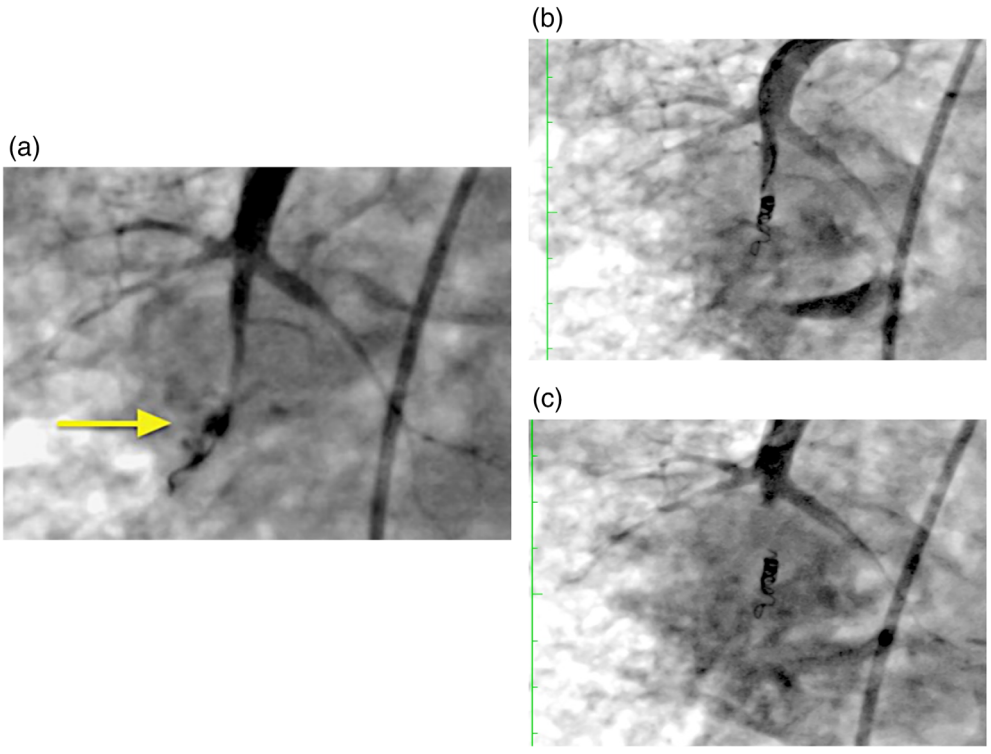

FIGURE 3 Acute vascular complication during balloon pulmonary angioplasty (BPA). Life-threatening vessel perforation due to balloon overdilatation, in a 69-year-old man with inoperable chronic thromboembolic pulmonary hypertension. (a) The arrow shows perforation and pulmonary hemorrhage after balloon inflation in a subsegmental artery in the right lower lobe. (b,c) Implantation of microcoils to control bleeding [Color figure can be viewed at wileyonlinelibrary.com]

in mPAP and sufficient clinical data were available (i.e., in between sessions' 6MWD, pro-BNP, FC).

3.1 | Clinical characteristics

The clinical characteristics of the study population are given in Table 1. Importantly, history of pulmonary embolism, and deep vein thrombosis was present in 81 and 50% of the patients, respectively. The main indication for BPA was lesion distality (i.e., not accessible by PEA) in 82% of the patients. Baseline functional evaluations revealed a high-risk population with mean 6MWD 316.7 ± 94 m, Pro-BNP 1,685 ± 1,045 pg/dl, and mPAP 51.1 ± 12 mmHg. All patients were under oral anticoagulation (11 on acenocoumarol, 9 on rivaroxaban and 3 on warfarin). Sildenafil was the only PAH specific medication used, except for one patient treated with Riociguat. Almost all of the patients were in FC III or IV (68.2 and 27.7%, respectively). Only one patient had a previous PEA and was considered for BPA, due to residual PAH.

3.2 | Procedural results

The procedural results are presented in Table 2. A total of 81 BPA were performed with a success rate of 95%. The number of sessions per patient were 2.7 ± 1.4 with a mean of 3.7 ± 2.2 segments treated per patient. The fluoroscopic time was 52.3 ± 16.7 min. Only 45% of the study population had >3 BPA sessions. OFDI was used in 36.4% of the patients, mainly in the early period of our experience. There were 9 procedural-related complications (40.9% of all patients, 11.1% of all procedures), 7 of those being VC (31.8% of all patients, 8.7% of all the procedures). The most common VC were wire perforations with hemoptysis (18.2% of all patients, 6.2% of all procedures). Most of these bleeding events were self-limited and low risk, without

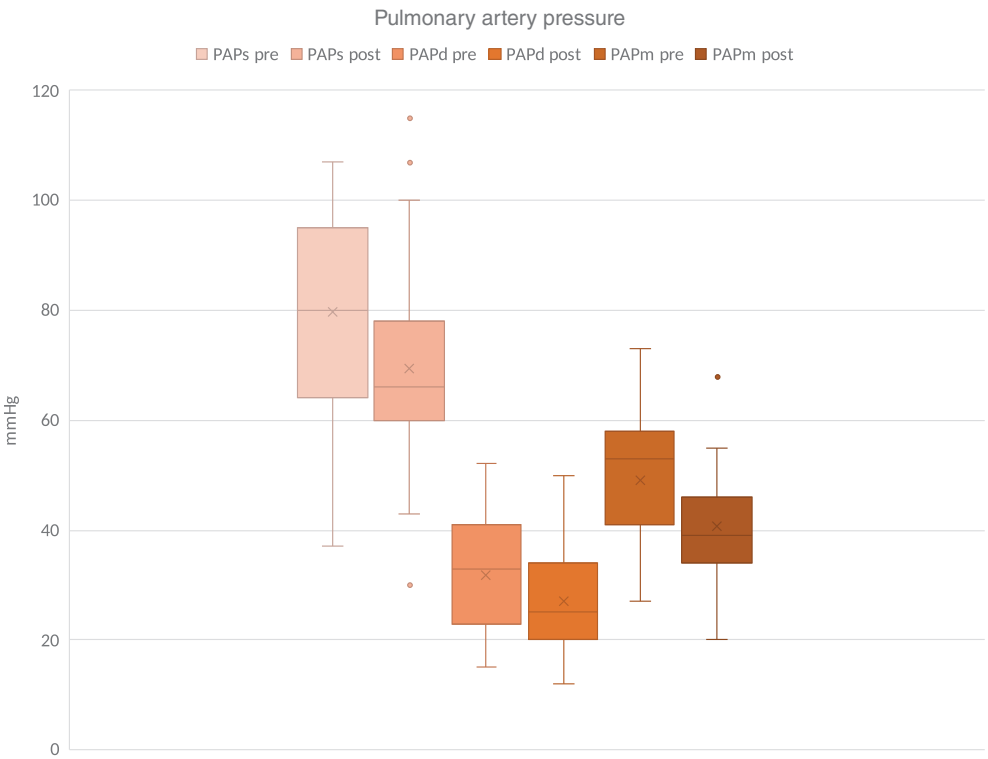

FIGURE 4 Change in pulmonary artery pressure after balloon pulmonary angioplasty (BPA). Box and whisker plot showing the results of BPA on pulmonary artery pressure (systolic, diastolic, and mean). Comparison is between baseline and last BPA. PAP, pulmonary artery pressure [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Change in hemodynamic parameters

Parameter	Pre-BPA	Post-BPA	% change	*p*-values
mPAP (mmHg)	51.1 ± 12	42.2 ± 13	17.4	.001
PVR (dyn/s/cm^{-5})	766.7 ± 351	583.4 ± 346	23.9	.001
CI (L/min/m^2)	2.3 ± 0.54	2.5 ± 0.54	8	.012

Note: Results presented as mean ± *SD*. Pre: Baseline right heart catheterization before the first BPA session; Post: Right heart catheterization, immediately after the last BPA session.
Abbreviations: BPA, balloon pulmonary angioplasty; CI, cardiac index; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance.

hemodynamic instability. Only one patient had a life-threatening bleeding due to balloon overdilatation that needed urgent coil implantation (Figure 3). One patient (4.5%) developed LRI, which was successfully treated with non-invasive mechanical ventilation. There were no periprocedural deaths (in-hospital or at 30 days).

3.3 | Hemodynamic results

The hemodynamic results are presented in Figure 4 and Table 3. BPA resulted in a significant 17.4% reduction in mPAP, 23.9% reduction in PVR, and a slight increase in CI by 8%. Two patients (10%) reached the prespecified goal of mPAP <30 mmHg after the first BPA. 77.3% of the patients had at least 10 mmHg reduction in mPAP, considered also a therapeutic target.

3.4 | Clinical results

The clinical results are presented in Figure 5 and Table 4. Overall survival at the end of FU was 86%. Three deaths occurred: one due to advanced right heart failure and two secondary to respiratory failure. By the end of FU, 6MWD increased by 29.7%, Pro-BNP levels were reduced by 73% and half of the patients were on FC II.

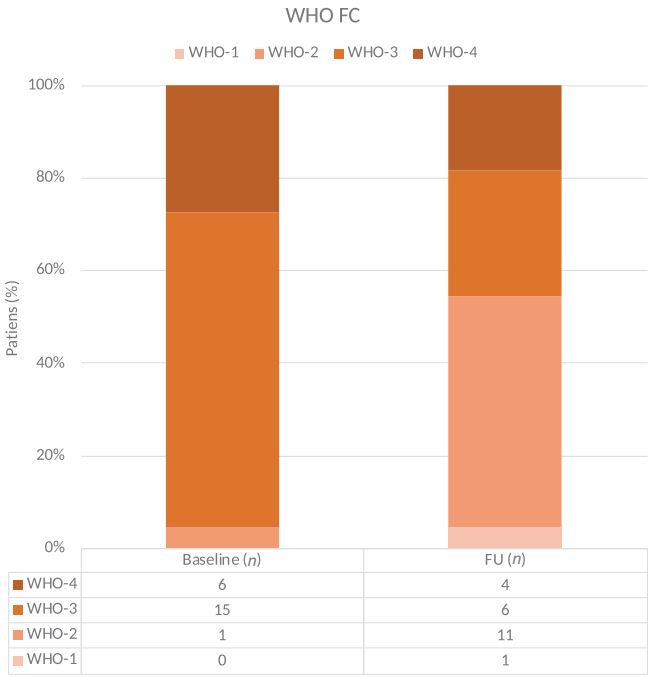

FIGURE 5 Change in functional class after balloon pulmonary angioplasty (BPA). Bar graph with the distribution of patients according to the reported FC before and after BPA. Comparison is between baseline and last follow-up visit. FC, World Health Organization functional class [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

We report the results of a multicenter prospective BPA registry in Chile that, to the best of our knowledge, is the largest series of inoperable CTEPH patients treated with BPA in Latin America. In this experience of 81 procedures, BPA significantly reduced mPAP and PVR, by the end of the last session, while also improving 6MWD, pro-BNP, and FC at FU. No in-hospital or 30-day mortality was observed.

Our Chilean population showcased some unique features regarding baseline clinical characteristics and risk factors for CTEPH. More than 75% of the patients were women, with a mean age of 59 ± 12.7 years, similar to what has been reported in Asian population and slightly younger than the European cohorts.[9,17,18,21] On the other hand, >80% of the patients had a history of thromboembolic events, which is similar to what is observed in other Western countries.[9,19-21] Most patients were highly symptomatic, with 25% of them in functional class IV and 27.3% needing permanent oxygen therapy, clear indicators of a very sick population.

The overall immediate BPA success rate was 95%, achieving a significant 17.4% reduction in mPAP and 23.9% reduction in PVR. Only 10% of the population reached the prespecified target mPAP <30 mmHg. Nevertheless, 77.3% showed >10 mmHg reduction, achieving a mean mPAP of 42 mmHg in the whole cohort. Although it could be argued that this result might be far from what has been

TABLE 4 Change in clinical parameters

Parameter	Baseline	Follow-up	% change	*p*-values
FC	I 0%	I 4.55%	—	.01
	II 4.55%	II 50%		
	III 68.8%	III 27.27%		
	IV 27.27%	IV 18.18%		
Pro-BNP (pg/dl)	1,685 ± 1,045	441 ± 276	73.8	.006
6MWD (m)	316.7 ± 94	451.1 ± 113	29.7	.001

Note: Comparison is between baseline and last FU visit.
Abbreviations: 6MWD, 6-min walk distance; FC, World Health Organization functional class; FU, follow-up; Pro-BNP, Pro-brain natriuretic peptide.

traditionally considered the "curative threshold" (<30 mmHg), new evidence coming from PAH patients in Japan consider this exact value (42 mmHg) as a treatment target to ensure >80% survival at 10 years.[23] This has not been proven in CTEPH, but we can hypothesize that the favorable impact in clinical parameters seen in our cohort might have been driven by the reduction in mPAP to this "palliative" threshold.

VC were frequent, but not different to what has been described in other registries.[9,19,20] Only one patient (4.5%) developed LRI and was successfully treated without the need for invasive mechanical ventilation. It has been suggested that LRI is less dependent on flow, as it is the case in PEA, and more closely related to iatrogenic vascular injury.[24,25] Therefore, experience with the technique is pivotal to achieve optimal results. A recently published single-center experience from France (the largest outside Japan) has clearly shown that the rate of complications tends to be reduced over time (15.8% in the initial period to 7.7% in the later period).[21] Indeed, as our experience with the technique increased, VC and LRI became less frequent. In fact, the severe complications in this registry (one life-threatening bleeding and one LRI) occurred within the first 10 patients, probably related to the learning curve. Our results reflect that an adequate level of expertise has been achieved by local interventionalist since the introduction of BPA in 2016.

Even though OFDI was used in almost one third of the cases, its use decreased over time. In this registry, OFDI was limited to the confirmation of type B lesions, if PAG did not clearly reveal its presence. With increasing operator's experience, PAG seems to be an adequate tool to select target lesions. Nevertheless, we think OFDI might also aid in preventing VC (i.e., balloon-mediated perforations) as it can reliably detect the proper vessel diameter—especially at the subsegmental level of the pulmonary circulation—to determine the best balloon-to-artery ratio, therefore avoiding potentially severe complications.

Timely referral to specialized PAH tertiary centers is a key aspect in the treatment of CTEPH.[6,10,13,24] It is known from the surgical literature that results of PEA are highly dependent on baseline hemodynamics.[26,27] In this registry, delay between PEA exclusion and the first BPA session was almost 2 years. This could partially explain the high baseline mPAP observed (51.1 mmHg) and may have blunted the treatment effect of BPA in our cohort. In the three most successful and comprehensive series published up to date, mPAP was on average 41.7 mmHg before BPA.[17,18,21] Moreover, recently, baseline mPAP has also been identified as a strong predictor of LRI after BPA.[21] Therefore, it could be argued that access to BPA at earlier stages of the disease could potentially increase its efficacy and safety. We believe, however, that our data reflects the reality of patient's care in the region and provides evidence that albeit intervening sicker patients, BPA can still be beneficial in less developed health systems.

The results of this registry are consistent with other similar publications, which included the learning curve. A BPA registry of 46 patients, from a PAH reference center in Spain, showed significant reductions in PVR by 44% (10.1 ± 4.9 vs. 5.6 ± 2.2 WU; $p < .001$) and mPAP by 23.6% (49.5 ± 12 vs. 37.8 ± 9 mmHg; $p < .001$).[20] They also reported an improvement in 6MWD by 74 m (394 vs. 468 m; $p = .001$). LRI developed in 5.8% of the interventions. Our study population was sicker, with 27% of the patients in functional class IV at baseline, as compared to 17% in the Spanish cohort. Of remark, we were able to show a greater improvement in 6MWD—almost twofold increase—, with less BPA sessions performed. On the other hand, our results almost replicate the initial German experience from two centers, reporting on 56 consecutive patients who underwent 266 BPA.[19] In that registry, reductions of 18% in mPAP and 26% in PVR were achieved; in our case, 17.4 and 23.9%, respectively, with similar rates of VC (≈8%). Nevertheless, none of the studies mentioned, including ours, were able to replicate the Japanese results, where improvements in mPAP and PVR in modern series are over 50 and 70%, respectively.[14,15,17,18]

An important difference, between the European and Japanese populations from the Chilean (i.e., Latin American population), is access to PEA. This is a key aspect, because in places were resources are limited, BPA is the only feasible alternative that can be offered. It is plausible that some of the patients in this experience who were excluded from PEA, might have been deemed operable in other countries. Current guidelines recommend expert opinion before considering inoperable a patient with CTEPH.[6,7] This expertise implies being able to perform more than 50 PEA per year (with less <5% mortality), something that, in a restricted and limited health system as the Chilean, seems unrealistic at this moment. For all these reasons is that BPA, which is technically less demanding than PEA, has been rapidly embraced by the interventional community in our country, showing encouraging results.[16] Still, the role of BPA in subjects with technically operable disease has not been established.

The development of reference centers for the management of CTEPH has improved awareness, patient selection and access to specific therapies like BPA. Nevertheless, guideline-directed medical treatment, according to international standards, is not available for everyone in some regions of the world. A recent report from Latin America clearly demonstrates these inequalities in access to PAH therapies.[28] Even in a high-income country like Chile, access to CTEPH evidence-based treatment is limited mainly due to its prohibitive cost and lack of reimbursement. In our registry, only one patient received Riociguat (a Class I indication according to current guidelines), while the standard of care in other countries consider access to PAH target therapies in patients excluded from surgery as well as in those bridging to PEA.[11] This lack of guideline-recommended PAH therapy gave us the unique opportunity to assess the independent impact of BPA in disease progression. In this setting, a clear benefit of BPA is shown in our registry, without the need for specific PAH therapies, as assessed by the significant improvements in clinical parameters.

The study has several limitations. First, it is an observational prospective registry with no control group. Second, only mid-term clinical FU is reported, and hemodynamic data are currently incomplete to confirm the persistence of the acute results in an extended FU. Third, the number of sessions and segments treated are less than what has been described in other registries. Fourth, three patients (13.6%) have not reached their final BPA and are still undergoing active treatment. Fifth, LRI can develop up to 2 weeks after BPA, and although a predischarge

chest radiograph was used to rule it out, it might probable have underestimated its real incidence, as shown in studies where computed tomography was used to asses LRI.[25] Sixth, there is no information regarding the proportion of time in the therapeutic INR range in the 14 patients of this series prescribed acenocoumarol or warfarin. Finally, most patients were not able to reach a "curative" status regarding PAH; so, for a better understanding of the real impact of BPA in quality of life, dedicated patient-oriented and self-administered questionnaires could have been used to complement clinical data.

Recent guidelines recommend that patients need to be educated in order to actively engage in the decision process when it comes to determine the best available treatment options in PAH.[29] In this regard, this study provides sufficient evidence to reassure them that BPA is a useful and safe alternative to treat inoperable CTEPH, especially in health systems like ours, where other evidence-based treatments are not readily available.

5 | CONCLUSION

At mid-term FU, this multicenter registry in Chile—and also the largest published to date in Latin America—confirms that BPA for inoperable CTEPH is a relatively safe procedure that achieved significant improvements on hemodynamic and clinical parameters. BPA should be considered as a valid alternative where access to specific PAH therapy or PEA is restricted.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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