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RESEARCH ARTICLE

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Balloon pulmonary angioplasty for proximal chronic thromboembolic pulmonary hypertension in patients ineligible for pulmonary endarterectomy

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Abstract

Balloon pulmonary angioplasty (BPA) to treat chronic thromboembolic pulmonary hypertension (CTEPH) is generally reserved for distal obstruction precluding pulmonary endarterectomy (PEA) but can be used in patients with proximal disease who are at high surgical risk or refuse surgery. This single-center retrospective study compared BPA efficacy in patients with proximal versus distal CTEPH. Of the 478 patients, 36 had proximal disease, follow-up was 11.6 months and mean number of BPA 6. After BPA, PVR, and mean pulmonary artery pressure decreased significantly in the proximal and distal groups (from 6.5 to 4.0 WU and 39 to 31 mmHg and from 7.6 to 3.8 WU and 44 to 31 mmHg, respectively, $p < 0.001$ for all comparisons). NYHA class also improved significantly in both groups, from 3 to 2, whereas the 6-min walk distance, cardiac output, and serum NT pro-BNP showed significant improvements only in the distal group. Thus, when PEA for CTEPH is technically feasible but not performed due to severe comorbidities or patient refusal, BPA can produce significant hemodynamic improvements, albeit less marked than in patients with distal disease. Better patient selection to BPA might improve outcomes in patients with proximal disease who are ineligible for PEA.

KEYWORDS
morbidity, pulmonary endarterectomy

Abbreviations: 6MWD, 6-min walking distance; BNP, brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association class; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

INTRODUCTION

After pulmonary embolism, obstruction of the pulmonary arteries by nonresolving organized fibrotic clots can lead to chronic thromboembolic pulmonary hypertension (CTEPH) with an elevation in pulmonary vascular resistance (PVR) that can cause pulmonary hypertension (PH), right heart failure, and ultimately, death.[1–5] Pulmonary endarterectomy (PEA) is the reference standard treatment for patients with proximal obstructions.[6–12] However, up to 40% of patients have either distal obstructions that are not accessible to PEA or comorbidities posing an unacceptable surgical risk.[10] Moreover, PEA is a major surgical procedure that some patients are unwilling to receive. Balloon pulmonary angioplasty (BPA) has recently emerged as a safe, effective, and reproducible technique for treating CTEPH in patients ineligible for PEA.[13–20] We previously reported good clinical and hemodynamic outcomes of BPA in over 90% (148/160) of patients with juged technically inoperable CTEPH.[16] In 2020, the European Respiratory Society recommended BPA for CTEPH ineligible to surgery.[21,22]

In patients with proximal obstructions accessible to PEA who have severe comorbidities or who refuse surgery, BPA may be a valid option. A comparison of 16 patients with proximal CTEPH and 54 with distal CTEPH showed similar improvements and survival after BPA.[23] At our center, BPA is used chiefly in patients with distal CTEPH but is also offered to those with proximal (technically operable) CTEPH who either have severe comorbidities or do not want surgery.

The objective of this retrospective study done at our center was to assess the outcomes of BPA for proximal CTEPH in patients with severe comorbidities or an unwillingness to undergo surgery.

MATERIALS AND METHODS

Study design and patients

In this single-center retrospective study, we identified adults (aged 18 years or older) who underwent BPA between January 2014 and December 2020 for distal (technically inoperable) CTEPH or for proximal (technically operable) CTEPH. In the group with proximal CTEPH, we separated patients who had severe comorbidities associated with an unacceptably high surgical risk from patients who refused surgery. We excluded patients who had PEA on one side and BPA on the other or BPA after PEA.

All patients referred for BPA to our French national referral center for CTEPH have their cases reviewed by a multidisciplinary panel including a surgeon highly experienced in PEA, interventional radiologists/cardiologists, radiologists experienced in pulmonary vascular imaging, and pulmonologists with expertise in PH. The CTEPH multidisciplinary panel classifies observed lesions as proximal or distal and determines the indications for intervention based on clinical severity, estimated risks of perioperative morbidity and mortality, and expected clinical benefits. Proximal lesions were defined by involvement of the pulmonary artery dow to subsegmental level. When intervention is indicated, BPA is offered to patients with distal disease and to patients with proximal disease whose comorbidities carry unacceptably high perioperative risks. Patients with proximal disease who refuse surgery are also offered BPA. All patients are informed about the potential risks and expected benefits of the intervention, for which they provide written informed consent.

Data collection

The data listed in Table 1 were collected by medical-chart review, using standardized forms. Before BPA, each patient underwent a pulmonary ventilation/perfusion scan, spiral computed tomography (CT) with biplanar reconstructions, digital subtraction pulmonary angiography, and right heart catheterization. Clinical and hemodynamic evaluations were conducted just before the first BPA session (baseline) and 6 months after the last BPA session; they included the New York Heart Association (NYHA) functional class, 6-min walk distance (6MWD), serum level of N-terminal pro-brain natriuretic peptide (NT pro-BNP), and full right-heart catheterization.

Among severe comorbidities precluding PEA, we defined morbid obesity as a body mass index (BMI) > 40, left ventricular failure as a left ventricular ejection fraction below 50% by echocardiography, and respiratory failure as dyspnea at rest shown by lung function testing to be due to a cause other than CTEPH. Histological documentation was required to record cirrhosis and malignancies as comorbidities. Cognitive function impairment (MMSE < 24) was recorded.

Balloon pulmonary angioplasty technique

The previously described standard procedure was used.[16,18] Under local anesthesia, the pulmonary arteries were approached through the right femoral vein using a peripheral guiding sheath (6 French Destination 65 cm; Terumo; 7 French ArrowFlex 80 cm; Teleflex). Vitamin K

TABLE 1 Baseline characteristics of the 36 patients with proximal disease, 378 patients with distal disease, and 64 patients with residual pulmonary hypertension (PH) after pulmonary endarterectomy (PEA).

	Distal disease $n = 378$	Residual PH after PEA $n = 64$	Proximal disease, ineligible for PEA $n = 36$	p Value
Age, years, mean ± SD	65 ± 14	59 ± 12	75 ± 6	<0.001
Females/males, *n*	198/180	34/30	18/18	NS
Risk factors for CTEPH, *n* (%)	107 (28)	7 (10.9)	11 (31)	NS
Splenectomy	35 (9.2)	0	3 (8)	NS
Ventriculoatrial shunt	2 (0.5)	0	2 (6)	NS
Pacemaker	6 (1.6)	0	2 (6)	NS
Port-a-Cath	30 (7.9)	1 (1.5)	0	NS
Myeloproliferative disease	26 (6.9)	5 (8.0)	4 (13)	NS
Sickle-cell disease	8 (2.1)	1 (1.5)	0	NS
Antiphospholipid syndrome, *n* (%)	10 (2.6)	8 (12.5)	0	NS
Deep venous thrombosis, *n* (%)	222 (58.7)	44 (68.7)	27 (75)	NS
PH-specific pharmacotherapy, *n* (%)	232 (61.4)	46 (71.8)	17 (47)	NS
Reason for not performing PEA, *n* (%)				
Severe comorbidities[a]			27 (75)	
Patient refused surgery			9 (25)	
mPAP, mmHg, mean ± SD	45 ± 10	39 ± 9	41 ± 9	0.01
CO, L/min, mean ± SD	4.6 ± 1	5.35 ± 1	4.6 ± 1	NS
PVR, WU, mean ± SD	8.7 ± 2.7	5.6 ± 2.4	6.5 ± 2.6	0.03

Abbreviations: CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary artery pressure; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

[a]Morbid obesity, $n = 6$; respiratory failure, $n = 6$; cognitive impairment, $n = 5$; left ventricular failure, $n = 4$; cirrhosis, $n = 3$; and active cancer, $n = 2$.

antagonist therapy was maintained in a dosage that produced an International Normalized Ratio of about 3. Right heart catheterization was performed at the beginning of the procedure to measure the mean pulmonary artery pressure (mPAP) and the cardiac output (CO) by thermodilution. A 6 French guide catheter (Launcher, Multipurpose, Judkins right and left 4.0, Amplatz right and left; Medtronic) was inserted through the peripheral guiding sheath and advanced to the target vessels. Heparin (2000–3000 units) was then administered. Selective pulmonary angiography images served to guide the passage of a 0.014-inch guidewire (Whisper MS or Pilot 50–150; Abbott Vascular; PT2; Boston Scientific) across each target lesion. Given the relatively high pulmonary blood flow in the lower lobes, the lesions at this site were dilated preferentially, to lower mPAP. The lesions were dilated to an appropriate size using balloon catheters of 2.0-mm to 9.0-mm, depending on vessel diameter (NC TREK or Viatrac 14 Plus; Abbott Vascular; Ryujin Terumo). We treated 2–10 segmental or subsegmental arteries during each BPA session, depending on clinical severity and amount of contrast medium injected, and to keep the procedure duration below 2 h. Two BPA sessions were performed 2 or 3 days apart during the same hospital stay. Catheterization was repeated 3–4 weeks later and additional BPA sessions were done until the mPAP was below 30 mmHg and/or PVR was below 4 WU and/or all accessible lesions were considered to have been treated. Six months after the last BPA session, all patients underwent an assessment that included a full right heart catheterization.

Endpoints

The primary objective was to compare the clinical and hemodynamic effectiveness of BPA for treating proximal (technically operable) CTEPH versus distal (technically

inoperable) CTEPH. The primary endpoint was the PVR change induced by BPA at last evaluation recorded (minimum 6 months). The secondary endpoints were the NYHA class and 6MWD changes observed after BPA at last evaluation recorded.

Statistical analysis

Variables were described as mean ± standard deviation (SD) if continuous and as n (%) if categorical. Comparisons were with Student's t-test for continuous variables and with the χ^2 test or Fisher's exact test, as appropriate, for categorical variables. Among the 36 patients managed by BPA despite having proximal disease, none had missing data and none were lost to follow-up. p values less than 0.05 were considered significant, and all p values were reported. The statistical analysis was performed using GraphPad Prism (version 7; Dotmatics).

RESULTS

Patient characteristics (Table 1)

Figure 1 is the patient flowchart. Table 1 compares the baseline characteristics in the groups with proximal disease, distal disease, and residual PH after PEA. The reasons for not doing PEA and the comorbidities are in Table 1. The patients with proximal disease were significantly older and had significantly lower PVR and mPAP values compared to the other groups. The proportions of patients taking pharmacological treatment for CTEPH and having conditions associated with CTEPH were similar. Figure 2 shows the location of the lesions and Figure 3 examples of patients with proximal disease and either severe comorbidities or refusal of surgery.

Balloon pulmonary angioplasty features and safety data

Table 2 reports the main features of the lesions in the group with proximal disease. In this group, the mean number of BPA sessions was 6 ± 2 per patient and the mean number of treated pulmonary-artery segments was 14 ± 5 per patient. Maximum balloon diameter was 9 mm. Of the 216 BPA sessions, 8 (4%) were associated with postprocedural complications. Catheterization failed for 10 of the 481 targeted lesions, due to an intravascular web ($n = 5$) or to occlusion or subocclusion ($n = 5$); of these 10 lesions, 5 were in the lower lobe and 5 in the upper lobe; 5 were in the left lung and 5 in the right lung. None of the patients died or where lost within 6 months after the last BPA session.

Effectiveness of balloon pulmonary angioplasty (Table 3)

Mean follow-up was 11.6 months among patients treated by BPA for CTEPH with proximal lesions In the group with proximal lesions, the mean NYHA class improved significantly, whereas the 6MWD improvement was not significant. Significant decreases occurred in both PVR and mPAP. The improvements were not significant for CO or serum NT pro-BNP (from 371 to 289 ng/L, $p = 0.17$). All six efficacy parameters improved significantly in the group with distal disease. Angiography indicated a greater number of totally occluded PA segments in the group with proximal disease than in the group with distal disease. In the group with proximal disease, 17 patients were on specific drug therapy for PH before BPA. Among them, five took a single drug (riociguat, $n = 3$; phosphodiesterase type 5 inhibitor [PDE5I], $n = 1$; endothelin receptor antagonist [ERA], $n = 1$) and 12 two drugs (riociguat and ERA, $n = 4$; and PDE5I and ERA, $n = 8$). After BPA, one patient on dual therapy stopped the ERA but continued riociguat, while none of the other patients changed their pharmacotherapy regimen.

DISCUSSION

Of 660 patients referred for proximal CTEPH over 7 years, 36 (5.5%) were unable to undergo PEA because they had severe comorbidities or did not want surgery. At last follow-up after BPA, several major effectiveness parameters were significantly improved in this group, including PVR, mPAP, and the NYHA class. However, the 6MWD, CO, and serum NT pro-BNP level improved but the gains were not statistically significant, in contrast to the group with distal disease, in which all efficacy parameters improved significantly. This contrast may, however, be ascribable to the limited statistical power related to the small number of patients with proximal disease. Of note, the baseline 6MWD was considerably shorter in the proximal than in the distal group (321±127 m vs. 397±117 m), probably because most patients with proximal disease also had severe comorbidities.

PEA is the reference standard treatment of CTEPH with lobar and segmental obstructions.[8,10,11] Nonetheless, PEA raises substantial technical challenges and is a major procedure generally performed with deep hypothermic circulatory arrest. The indications therefore depend in part on the patient's clinical status and willingness to accept the surgical risk. BPA has emerged over the last decade as a challenging but safe and effective treatment for patients with

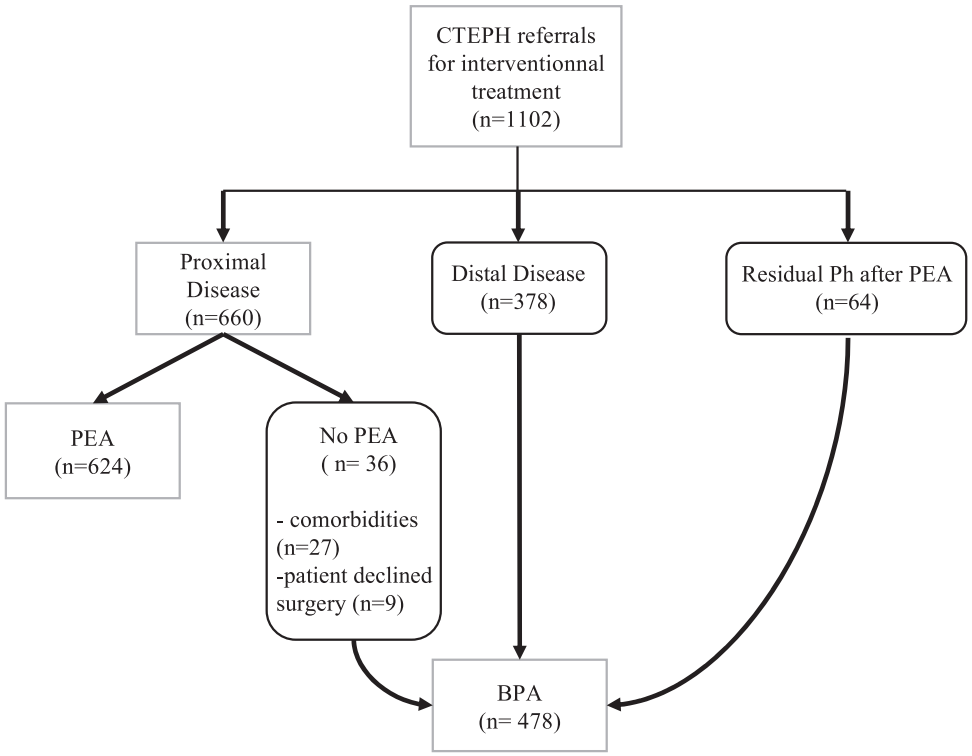

FIGURE 1 Patient flowchart.

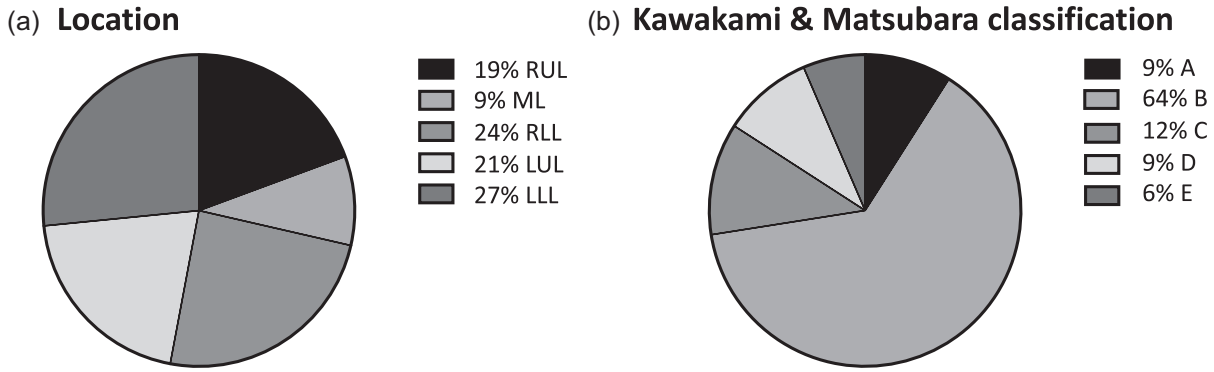

FIGURE 2 Location and distribution of the lesions of patients presenting a proximal CTEPH treated by BPA, according to the Kawakami and Matsubara classification. LLL, left lower lobe LUL, left upper lobe; ML, middle lobe; RLL, right lower lobe; RUL, right upper lobe.

CTEPH who have distal lesions or recurrent or persistent PH after PEA.[12,22,24-28] Many groups have reported good safety and effectiveness of BPA performed at expert centers to treat technically inoperable CTEPH.[15,16,18,26-30] However, to our knowledge, no study specifically addressed the potential benefits of BPA in patients with technically operable disease but an unacceptably high surgical risk or an unwillingness to undergo surgery. Patients with proximal lesions were typically excluded from studies of BPA due to concern that this procedure might induce extensive pulmonary edema and higher morbidity and mortality compared to PEA. Thus, reperfusion pulmonary edema developed in 11 of 18 and 19 of 28 patients in two studies, respectively.[31,32] Over time, however, high-volume centers came to view BPA as a possible treatment option for proximal CTEPH in patients at high surgical risk. The first report was in 2013, in a 76-year-old woman with proximal stenosis of the right pulmonary artery and a combination of poor general health and severe chronic obstructive pulmonary disease.[33] Two BPA sessions decreased mPAP from 41 to 23 mmHg, with no reperfusion edema or other complications. Subsequently, two studies compared outcomes after BPA for proximal versus distal disease and found similar significant improvements in both groups, which were small (16 vs. 54 and 10 vs.

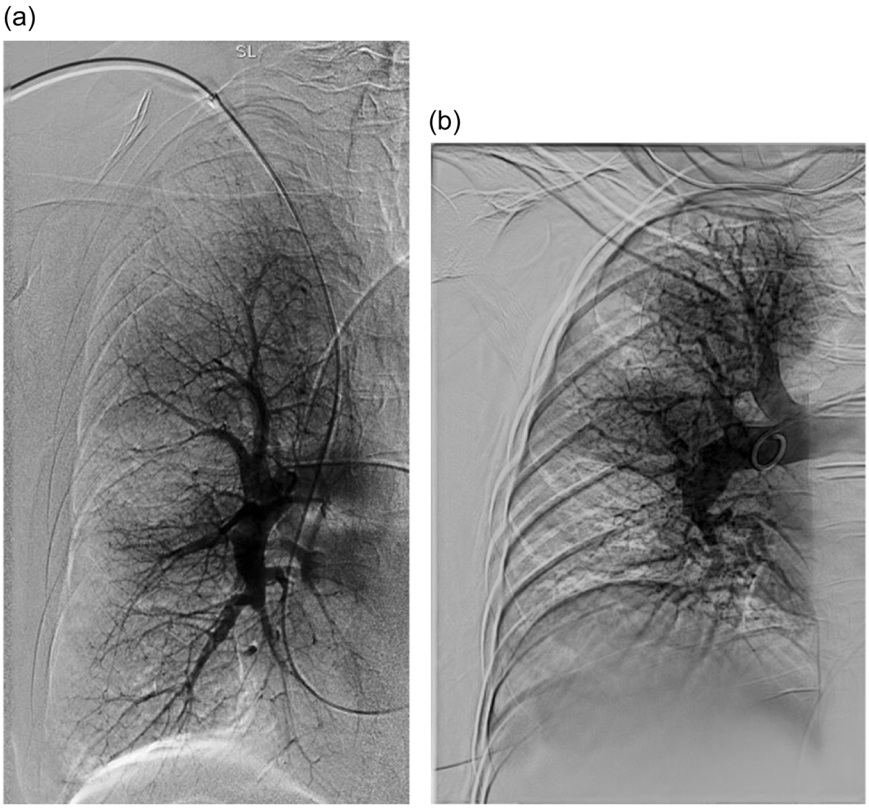

FIGURE 3 Pulmonary angiography examples in two patients. (a) Proximal lesions at the segmental level in a patient with severe comorbidities. (b) Proximal lesions at the lobar level (occlusion of the right lower lobar pulmonary artery) in a patient who refused surgery.

TABLE 2 Angiography features in the 36 patients with proximal disease managed by balloon pulmonary angioplasty.

	Proximal disease, ineligible for PEA[a] $n = 36$
BPA sessions, mean ± SD	6 ± 2
Number of treated segments, mean ± SD	14 ± 5
Kawakami and Matsubara classification, *n* (%)	
A	49 (9)
B	344 (62)
C	63 (12)
D	51 (11)
E	35 (6)
Location, *n* (%)	
Right upper lobe	105 (19)
Middle lobe	50 (9)
Right lower lobe	132 (25)
Left upper lobe	111 (22)
Left lower lobe	144 (25)
BPA failure, *n* (%)	10 (5)
Maximum balloon diameter (mm), mean ± SD	7 ± 2

Note: Kawakami and Matsubara classification, A: Ring-like stenosis; B: Web; C: Subocclusion; D: Occlusion; E: Tortuous artery

Abbreviation: BPA, balloon pulmonary angioplasty.

[a]Ineligibility was due to severe comorbidities entailing an inacceptable surgical risk in 27 patients and to patient unwillingness to have PEA in 9 patients.

TABLE 3 Outcomes of balloon pulmonary angioplasty: Comparison of patients with proximal disease who were ineligible for pulmonary endarterectomy vs. patients with distal disease.

	Distal disease $n = 378$			Proximal disease, ineligible for PEA[a] $n = 36$		
	Baseline	Last follow-up	*p* Value	Baseline	Last follow-up	*p* Value
NYHA, mean	3 ± 0.6	2 ± 0.7	<0.001	3 ± 0.6	2 ± 0.7	0.005
6MWD, m, mean	397 ± 117	441 ± 109	0.002	321 ± 127	388 ± 131	0.11
mPAP, mmHg, mean	44 ± 10	31 ± 9	<0.001	39 ± 9	31 ± 8	<0.001
PAOP, mmHg, mean	10 ± 3	11 ± 4	0.007	9 ± 5	12 ± 4	0.18
CO, L/min, mean	4.9 ± 1	5.7 ± 1	<0.001	5 ± 1	5.4 ± 2	0.27
CI, L/min/m^2, mean	2.7 ± 0.6	3 ± 0.6	<0.001	2.7 ± 0.4	2.9 ± 0.5	0.45
PVR, WU, mean	7.6 ± 3	3.8 ± 1	<0.001	6.5 ± 3	4.0 ± 3	<0.001
PTR, WU, mean	9.7 ± 4	5.8 ± 2	<0.001	8.4 ± 3	6.5 ± 4	<0.001
NT pro-BNP, ng/L, mean	619 ± 86	268 ± 63	<0.001	371 ± 88	289 ± 124	0.17

Abbreviations: 6MWD, 6-min walking distance; CI, cardiac index; CO, cardiac output; mPAP, mean pulmonary artery pressure; NT pro-BNP, serum level of pro-brain natriuretic peptide; NYHA, New York Heart Association class; PAOP, pulmonary artery occlusion pressure; PTR, pulmonary total resistance; PVR, pulmonary vascular resistance.

[a]Ineligibility was due to severe comorbidities entailing an inacceptable surgical risk in 27 patients and to patient unwillingness to have PEA in 9 patients.

33 patients, respectively).[22,33] Another study reported that the reason for BPA was the presence of severe comorbidities in 11/153 (7%) patients and refusal of PEA in 5/153 (3%) patients but did not compare outcomes in these groups to those in the group with distal disease.[34] A very recent study assessed BPA outcomes in 344 patients, including 81 with proximal disease who either refused surgery ($n = 41$) or had comorbidities, poor health, or very advanced age.[35] BPA was effective, although less so than in patients with distal lesions, in keeping with our findings. The number of BPA sessions was five to six per patient in the four previous studies.[22,33–35] Overall, the previously published data agree with ours showing significant post-BPA improvements in patients with proximal disease with, however, smaller gains than in patients with distal disease.

The dramatic improvements in CTEPH outcomes achieved over the last two decades are ascribable to new pathophysiological insights, advances in diagnostic tools, the introduction of targeted vasodilators and BPA, and progress in PEA techniques. CTEPH is being increasingly diagnosed worldwide.[22] Pharmacotherapy and BPA are readily available in many high-income countries. PEA, in contrast, is a challenging procedure performed only in expert centers. Due to its long learning curve, PEA is often viewed as putting patients at very high risk. This belief exists even in countries where expert centers have mortality rates below 3%.[8,36–39] Thus, in France, the current mortality rate is 2% (data not shown) but many patients who are good candidates for PEA refuse the procedure out of concern that it may be unduly hazardous. This situation raises a challenge for healthcare teams, which must strive to deliver optimal information, including a realistic picture of the risks.

Known risk factors for CTEPH[40,41] were identified in 31% of the patients with proximal disease in our study. These risk factors tend to produce more PA obstructions located more distally compared to those caused by proximal pulmonary embolism. Both segmental and subsegmental lesions were classified as proximal CTEPH by the expert multidisciplinary panel. Conceivably, theses lesions, induced by CTEPH risk factors, may have predominated at more proximal sites (main artery and lobar arteries) in the group with proximal disease than in the group with distal disease. This possibility is consistent with the higher number of totally occluded PA segments in the proximal group. In addition, BPA repermeabilised arterial lumen without removing the fibrous cast. Inproximal CTEPH, the cast is thicker and stiffens the artery, reducing its compliance. Repermeabilisation alone may not be sufficent to correct artery stiffening and compliance in order to improve these patients hemodynamics data.

One limitation of our study is the small number of patients with proximal disease, which limited our ability to detect improvements in functional parameters over time. Nonetheless, the demonstration of several significant improvements in the proximal group despite its

small size supports the effectiveness of BPA. Another limitation is the short follow-up. Conceivably, further BPA sessions might have been helpful in the refusal group. Finally, the design was retrospective and information bias may therefore have occurred.

CONCLUSION

BPA may deserve to be considered in patients with proximal CTEPH who have severe comorbidities creating an unacceptably high surgical risk. Multicenter studies to produce a larger sample are needed to further assess the safety risk and effectiveness of BPA for proximal CTEPH in patients who cannot, or refuse to, undergo PEA.

AUTHOR CONTRIBUTIONS

Concept and design: Justin Issard, Elie Fadel, and Philippe Brenot. *Acquisition, analysis or interpretation of data*: Justin Issard, Elie Fadel, Samuel Dolidon, Benoit Gerardin, Dominique Fabre, Delphine Mitilian, Olaf Mercier, Mitja Jevnikar, Xavier Jais, Marc Humbert, and Philippe Brenot. *Drafting the manuscript*: Justin Issard. *Critical revision of the manuscript for important intellectual content*: Justin Issard, Elie Fadel, Samuel Dolidon, Benoit Gerardin, Dominique Fabre, Delphine Mitilian, Olaf Mercier, Mitja Jevnikar, Xavier Jais, Marc Humbert, and Philippe Brenot. *Statistical analysis*: Justin Issard. *Supervision*: Elie Fadel and Philippe Brenot. All authors read the final version of the manuscript and approved its submission. Philippe Brenot and Justin Issard are the study guarantors, had full access to all the study data, and take responsibility for the integrity of the work reported in this manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The study was approved by the ethics committee of the French Society for Thoracic and Cardiovascular Surgery (SFCTCV, #IRB0012919, 24/01/2023). The requirement for informed patient consent was waived in keeping with French law on retrospective studies of deidentified healthcare data.

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