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Review Article

Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

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Abstract: Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension (PH) caused by thromboembolic disease with the secondary remodeling of the pulmonary vessels. The primary treatment of CTEPH is pulmonary thromboendarterectomy (PTE). However, some patients are not candidates for PTE because of surgically inaccessible thrombi or high operative risk and can be candidates for balloon pulmonary angioplasty (BPA), an emerging, lower risk treatment. This review discusses the patient selection, the technique, and comprehensive review of reported outcomes following BPA. BPA techniques have improved over the years, and so has its safety profile. Recent data show that after several sessions of BPA, patients who were not eligible for PTE had improvement in their hemodynamic profile, functional capacity, and 6-minute walk distance. Studies have shown that compared to riociguat, BPA has shown significant improvement in the functional capacity and hemodynamic measurements. Reperfusion pulmonary edema is a common complication after PTE and BPA, which may be due to vessel injury rather than pulmonary extravasation. Rates of complications have decreased especially after the use of optical coherence tomography, which helps in proper sizing of the balloons. Patients with CTEPH who are ineligible for PTE should be evaluated for BPA. In addition to medical therapy, BPA has shown promising clinical and hemodynamic outcomes in patients with CTEPH.

Keywords: Chronic thromboembolic pulmonary hypertension, pulmonary thromboendarterectomy, pulmonary hypertension, balloon pulmonary angioplasty

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pre-capillary pulmonary hypertension (PH), classified as World Health Organization (WHO) group 4, that occurs due to obstruction of pulmonary arteries by non-resolving thromboemboli and secondary remodeling of pulmonary vessels [1-4]. The diagnosis of CTEPH requires a mean pulmonary artery pressure (mPAP) >20 mmHg without elevated pulmonary capillary wedge pressure (PCWP <15 mmHg), and evidence of pulmonary perfusion defects evaluated with a radionuclide ventilation-perfusion scan or by imaging such as computed tomography (CT) or pulmonary angiography with digital subtraction angiography. About 500 to 2,500 new cases of CTEPH are reported annually in the United States (US) with the incidence being higher (2.8%-4.8%) in patients with history of pulmonary embolism [5-8]. Surgical pulmonary thromboendarterectomy (PTE) is the preferred treatment for CTEPH. Nonetheless, some patients are deemed inoperable because of distal distribution of thrombi and/or prohibitive surgical risks. Balloon pulmonary angioplasty (BPA) is a minimally invasive intervention for inoperable cases and is becoming popular, especially with newer techniques that have improved the safety and outcomes of the procedure. Whether used alone or in combination with PTE or BPA, medical therapy remains a viable treatment option. BPA, once preformed almost exclusively in Japan, has now emerged as an attractive treatment alternative to PTE or as rescue therapy after PTE. Its place in the current treatment algorithm for CTEPH is evolving and in this

review, we will summarize the current experience with BPA in CTEPH and highlight potential avenues of its utilization.

Invasive treatment options for CTEPH

CTEPH is the only type of PH which is potentially "curable" with surgical PTE. Complete surgical removal of the fibrotic thrombi causing obstructive vasculopathy with PTE is the definitive treatment of CTEPH, and results in the most significant and immediate improvement in hemodynamics and clinical status of the patient, assuming the lesions are operable, and the surgical team is experienced. The University of California-San Diego Jamieson classification of CTEPH lesions is based on location and accessibility of the thromboembolic obstruction in post-PTE surgical specimens [9]. Obstructive lesions in the main pulmonary artery and lobar arteries are classified as type I and II, respectively. Type III lesions are located in segmental and subsegmental arteries. Any disease distal to subsegmental branches (type IV) may be suggested by discrepancies between pulmonary vascular resistance (PVR) elevation and the number of accessible occlusions and often leads to residual disease after PTE.

A significant portion of patients are deemed inappropriate for PTE. Apart from surgical inaccessibility of distal lesions (which can be due to discrepancy between PVR elevation and the number of accessible occlusions), there are other factors that may make the candidates not ideal for PTE, such as patient factors like age, comorbidities, and patient preference [10-12]. In a large international CTEPH registry, 37% patients were considered inoperable due to surgical considerations or medical comorbidities [11]. PTE has been shown to increase the 5-year survival rate in eligible patients from 53% to 83% [13]. Persistent or recurrent PH is reported in 25 to 45.4% of patients after PTE and is associated with recurrent symptoms and decline in functional capacity [14, 15]. Available treatment modalities for inoperable cases are PH medications and percutaneous BPA when feasible [4].

First described in 2001, BPA or percutaneous transluminal pulmonary angioplasty is an interventional angiographic procedure in which stenotic segmental and subsegmental pulmonary arteries are dilated using a standard balloon angioplasty technique [16]. Initially, this procedure was associated with unacceptable mortality risk. However, with refinements in technique and experiential learning, this procedure is gaining popularity in recent years as several observational studies have shown acceptable risk and improvement in hemodynamics and functional capacity after BPA.

History of BPA

BPA was previously used for the treatment of congenital vascular disease [17]. A description of this procedure for treating a case of PH secondary to pulmonary embolism was provided by *Voorburg et al.,* in 1988 [18]. A decade later, *Feinstein et al*., published a report of successful use of this procedure in 18 patients with CTEPH [16]. The authors adapted the technical advances from the congenital heart disease catheterization laboratory and used modified pigtail catheters, soft tip maneuverable guidewires, low profile balloons, and peri-operative anticoagulation. The authors reported significant improvement in pulmonary hemodynamics, New York Heart Association (NYHA) functional class, and 6-minute walk distance (6MWD). However, the procedure was complicated by reperfusion pulmonary edema (RPE) in 61.1% of patients and a 30-day mortality of 5.6% [16].

A decade later, several investigators from expert centers reported their experiences with this experimental technique. *Andreassen et al.,* performed multiple sessions of BPA at 6 to 8 weeks intervals in 20 patients with inoperable disease or persistent PH after PTE, and reported an RPE incidence of 35% and peri-procedural mortality of 10% [19]. In another study of 68 inoperable CTEPH patients, *Mizoguchi et al.,* reported a further decrease in the 30-day mortality rate to 1.5% as a result of using a revised BPA technique with intravascular ultrasound (IVUS) for balloon size estimation. BPA was performed in a staged fashion over multiple separate procedures to maximize efficacy and reduce the risk of reperfusion pulmonary injury. This study reported 60% incidence of mild RPE and injury, and only 5.9% of patients needed mechanical ventilation. Risk of RPE was highest during the first session. At 2.2±1.4 years follow up, 66/68 (97%) patients were alive [20].

Since then, several studies have shown that patients undergoing BPA have favorable clinical and hemodynamic outcomes, reduced complication rates, and better survival (**Table 1**). More recent meta-analyses of observational studies confirmed these findings (**Table 2**). The BPA technique has evolved with time at these expert centers and local institutional protocols have been established [21, 22].

Indications for BPA and patient selection

It is reported that patients with even distal CTEPH based on intra-operative findings may respond very well to PTE [23]. Operability for CTEPH depends on the surgical experience of the team and should be assessed by a multidisciplinary team at referral centers for CTEPH. The 2015 European Cardiology Society/European Respiratory Society (ECS/ERS) guidelines state that BPA should be considered for all inoperable cases and should only be performed at referral centers [24].

Previously 37% of the cases were reported as inoperable in an international registry with a large variation between countries [11]. A study from a multicenter registry in Japan reported that 80% of inoperable cases were due to lesion anatomy or unacceptable risk/benefit ratio [25]. Another retrospective study of CTEPH patients at a multidisciplinary treatment center in Europe reported 68% inoperable cases (29% due to high-risk comorbidities and 39% due to surgical inaccessibility) [26]. After excluding the patients with peripheral subsegmental lesions, approximately half of inoperable patients were successfully treated with BPA (with or without medical therapy) [26]. BPA has been safely used in elderly patients [27, 28], patients with residual PH after PTE [15, 19, 29, 30], patients with inoperable lesions [28], patients with acutely decompensating CTEPH as a rescue procedure [31, 32], and patients with symptomatic chronic thromboembolic pulmonary disease (CTED) without pulmonary hypertension [33]. However, patients who underwent BPA due to high-risk comorbidities, despite having surgically accessible lesions, had higher number of totally occluded lesions and required more BPA sessions than inoperable patients [28]. BPA has also been performed concurrently with PTE in three patients with operable lesions on one side, and inoperable lesions on the contralateral side, during the rewarming phase of cardiopulmonary bypass [34].

Clinical outcomes with BPA

The outcomes of BPA have improved significantly over time (**Table 1**). Various interventionalists reported temporal improvement in terms of number of vessels treated per session, and decreased complication rate with BPA as they became more familiar with the procedure [35-37]. Recent studies of newly established BPA centers that reported their initial BPA experience had fewer vessels treated per BPA session than more established, experienced centers [30, 38-40]. As the pulmonary hemodynamic improvement is proportional to the number of lesions treated, the efficacy of the procedure can be expected to improve with experience and the number of vessels treated.

Therapeutic objectives for BPA vary among different studies. Goals of BPA may be hemodynamically driven by a resulting mPAP less than 25, 30 or 35 mmHg, or anatomically directed with complete treatment of all identified lesions. Hemodynamic improvement after BPA may not be apparent until months after the procedure [41, 42]. Thus, BPA sessions are usually performed over an extended period of time to allow hemodynamic changes to be evident during interval clinical follow-up.

Some patients may continue to have residual functional impairment post BPA, despite improvement in mPAP and PVR. In a small group of patients that had undergone conventional BPA resulting in the normalization of mPAP, *Shinkura et al*., described additional improvement in functional capacity after further extensive revascularization by repeat BPA (angioplasty of all the residual stenotic lesions) [43]. In addition, *Yanaka et al*., performed BPA in patients with residual symptoms after PTE with a mPAP of 26.9±3.1 mmHg and reported significant improvement in functional status [15]. Similarly, BPA has been shown to improve symptoms in CTED patients without PH [33]. Thus, better outcomes may be expected by treating as many obstructive lesions as possible and achieving a mPAP as close to physiologically normal as possible.

Table 1. Studies reporting the outcomes following balloon pulmonary angioplasty (BPA)

Study	Patients (N; mean age in years)	BPA interventions	PH targeted medical therapy before BPA	Hemodynamic improvement (mPAP in mmHg)	Functional improvement	Complications and peri-procedural mortality
Anand, 2019 [30]	31, including 5 post-PTE patients, women 41.9%; 59.7±16.7	75 sessions, median 2 (IQR 1-3) sessions per patient, 3 (IQR 2-3) vessels per session	Pulmonary vasodilators 77.4%, riociguat 71%, sildenafil 3.2%, tadalafil 3.2%, bosentan 3.2%, macitetan 9.7%, treprostinil (inhaled) 3.2%	Median (IQR) 40 (29-48) to 29 (25-37) (P<0.001)	≥1 NYHA FC improvement 61.3%, no change 29% 6MWD-median (IQR) 402 m (311-439) to 439 m (366-510) (P=0.001)	Hemoptysis 9.7%, RPE 3.2%, cardiac tamponade 3.2%, MV 3.2%. Mortality-3.2%.
Andreassen, 2013 [19]	20, women 50%; 60±150	73 catheterizations, 371 BPAs, 3.7±2.1 procedures and 18.6±6.1 BPAs per patient	Sildenafil 2/20, stopped before BPA	45±11 to 33±10 (P<0.001)	NYHA-FC I/II/III/IV 0/3/14/3 to 4/11/3/0 (P<0.001)	7/20 RPE. Mortality-1 RVF on day 1, 1 acute PE on day 9.
Aoki, 2016 [82]	24, women 75%; Median (range, IQR) 70 (60-74)	113 procedures, mean 4.7 per patient	PDE-5i 71%, ERA 4%, oral PGIs 21%, Epoprostenol 8%, sGC activator 12%	Median (range) 37 (28, 45) to 23 (19, 27) (P<0.01)	WHO-FC I/II/III/IV 0/50/46/4% to 24/76/0/0% (P=0.04) 6MWD-Median (range) 390 (286, 484) m to 490 (411, 617) m (P<0.01)	
Aoki, 2017 [36]	77, women 82%; 65±14	Total 400 session, 5.0±2.5 procedures per patient	Pulmonary vasodilators 96%, PDE5i 73%, ERA 17%, Oral PGI2 44%, Epoprostenol 16%, sGC 17%	38±10 to 25±6 (P<0.01)	6MWD-380±138 to 486±112 m (P<0.01)	PA dissection 7%, hemoptysis 14%, pulmonary edema 1%, NPPV 8%, intubation <1% of procedures.
Brenot, 2019 [35]	184, women 49%; 63±14	Total 1006 sessions, 5.2±2.4 sessions per patient, treated segments per patient-14 during initial period, 16 during later period	sGC stimulator 32.1%, ERA 39.7%, PDE5-I 25.5%, Prostacyclin analogue 7.1%	43.9±9.5 to 31.6±9.0 (P<0.001)	NYHA FC % (I, II/III, IV)-35.3/64.7 to 78.7/21.3 (P<0.001) 6MWD-396±120 m to 441±104 m (P<0.001)	Lung injury 9.1%, severe lung injury 5.6%, hemoptysis 7.1%, perforation 2.8%, dissection 1.9%, NPPV 4.9%, MV 0.4%, ECMO 0.3%. Mortality-2.2% (severe lung injury).
Darocha, 2017 [83]	25, including 3 post-PTE, women 48%; 58.5±18.2	96 BPA sessions, mean 3.8±1.3 per patient, 447 vessels treated, mean 17.8±11.5 vessels per patient	Pulmonary vasodilators 76%, PDE5i 64%, sGCs 4%, PDE5i + PGI2 8%	51.7±10.6 to 35.0±9.1 mmHg (P<0.01)	WHO-FC III, IV-96% to 20% (P<0.05) 6MWD-323±135 to 410±109 m (P<0.001)	Self-resolving desaturation most common complication. hemoptysis 5.2%, guidewire injury 4.1%.
Feinstein, 2001 [16]	18, women NR; 52±12	Total 47 catheterizations, 107 dilations, mean 2.7±1 catheterizations, 2.3±1 dilations per patient		42.0±12 to 33±10 (P=0.002)	NYHA-FC 3.3 to 1.8 (P<0.001) 6MWD-209 to 497 yards (P<0.0001)	11/18 RPE, 3/18 MV, 1/18 PA perforation. Mortality-1 (5.6%) RPE and RHF, day 7.
Fukui, 2014 [53]	20, women 75%; 67±9.0	Mean 3.2±0.9 procedures per patient	ERA 5/20, PGI_2 analogue 13/20, PDE-5i 4/20, combination therapy 6/20	39.4±7.6 to 27.3±8.5 (P<0.001)	WHO-FC 2.8 to 2.0 (P<0.001) 6MWD-361±104 m to 463±76 m (P<0.001)	No major events.
Godina, 2019 [38]	18, women 56%; 61±19	91 procedure, median 4 (2-6) sessions	sGC 33%, ERA 55%, PDE5i 28%, IV prostanoid 11%	44±12 to 31±12 mmHg (P<0.01)	NYHA FC-2 (1-4) to 2 (1-3). 6MWD-412±167 to 402±196	Hemoptysis/wire perforation 3/91, BPA-related lung injury 2/91, Arrhythmia 2/91, Stress cardiomyopathy 1/91.
Hoole, 2020 [39]	30, women 27%; 63.5±11.6	Total 95 procedures, 198 vessels treated, median 3 (IQR 1-6) sessions per patient	PDE5-I 12/30, ERA 1/30, sGC 7/13, ERA + PDE5I 6/30, ERA + sGC 2/30	44.7±11.0 to 34.4±8.3 (P<0.0001)	WHO FC ≥3 -80% to 13% (<0.0001) 6MWD-366±107 to 440±94 (P<0.0001)	Access site hematoma 2/95, Mild hemoptysis 5/95, RPE 3/95.

Hosokawa, 2018 [84]	13, women 92%; 61±11	20 unilateral sessions, 5.4±1.9 sessions per patient	PDE5i, sGC 77%, ERA 54%, prostanoid 62%	37.4±8.2 to 25.6±4.6 mmHg		
Inami, 2014 [85]	68, women 18%; 62±14	178 sessions, 2.5±1.4 sessions per patient.	For BPA and PTE patients combined (n=107) prostanoids 60%, PDE-5i 66%, ERAs 55%.	42.9 to 25.0 (P=0.0004)	NYHA-FC improved (P<0.05) 6MWD-349±130 m to 424±111 m (P<0.0001)	RPE 7.0%, hemosputum 2.3%, hemoptysis 3.3%, dissection 2.3%, perforation 0.9%. Mortality-1.47% (wire perforation).
Inami, 2016 [46]	170, women 78%; median 66 (IQR 55-73)	Median 4 (IQR 2-4) session per patient, median 15 (IQR 10-20) vessels treated per patient	PH targeted drug-free rate-8.8%	mPAP-significantly reduced at 1, 3, and 5 years follow up		PA injury 1/170. Mortality 1/170, PA injury.
Inami, 2019 [33]	15 CTED patients, women 73%; median 58 (IQR 44-68)	median number of sessions-2 (IQR 1-3), median number of vessels treated per patient-9 (IQR 5-15)		20 (IQR 16-22) to 16 (IQR 13-17), P=0.001	WHO FC I/II/III/IV-0/15/0/0 to 14/1/0/0. 6MWD-408 (IQR 358-468) to 444 (IQR 380-566), P=0.03	none.
Isobe, 2018 [60]	45, women 60%; 62.2±15.1	269 procedures, 5.9±2.0 times per patient	PDE5i/sGC 58%, ERA 40%, PGI2 40%, CCB 24%	37.3±10.5 to 19.5±3.8 mmHg (P<0.001)	WHO-FC I or II/III or IV-7/38 to 45/0 (P<0.001) 6MWD-305.6±98.7 to 446.0±110.1 (P<0.001)	Hemoptysis 4.8%, Oxygen therapy required in 1.1% procedures.
Kataoka, 2012 [41]	29, women 79%; 62.3±11.5	Mean 1.8±0.9 procedures per patient, 3.6±1.4 vessels dilated per session, 6.5±3.0 vessels per patient	Bosentan 14/29, ambrisentan 2/29, sildenafil 20/29, tadalafil 4/29, beraprost 5/29	45.3±9.8 to 31.8±10.0 (P<0.01)	NYHA-FC significantly improved at 6 months (P<0.01)	27/51 procedures RPE, 1/29 patients MV, 2/29 patients NPPV, 1/51 vessel dissection. Mortality-1 (3.4%) PA wire perforation, day 2.
Kawakami, 2016 [72]	97, including 1 post-PTE, women 74%; 61.7±12.3	500 procedures, 1936 lesions, mean 5.2±3.1 per patient	Oral PGI_2 50.5%, i.v. PGI_2 9.3%, ERA 47.4%, PDE-5i 36.1%.	45.1±10.8 to 23.3±6.4 (P<0.01)	WHO-FC median 3 to 3 (P<0.01) 6MWD-276.3±123.2 m to 359.3±91.9 m (P<0.01)	Hemoptysis 19.6%, Pulmonary injury 26.0%, MV 2% of the procedures. Mortality-4.1% patient, RHF.
Kimura, 2016 [86]	67, including 5 post-PTE, women 67%; 63.2±13.2	446 procedures, mean 6.8±6.2 sessions, mean 13.1±2.4 vessels per patient	PDE-5i 55%, ERA 41%, Prostacyclins 29%, sGC stimulator 11%	39.2±10.5 to 20.9±5.4 (P<0.001)		Hemosputum 6.1%, RPE requiring NPPV 1.1% of procedures.
Koike, 2016 [87]	8, women 100%;70.8±8.6	16 procedures, mean 2 procedures per patient		30.4±11.0 to 25.6±8.2 (P=0.04)	6MWD-332.3±59.6 m to 352.1±64.1 m (P<0.0001)	
Kwon, 2018 [58]	15, including 6 post-PTE, women 47%, 53±18.04	52 BPA sessions	Sildenafil or macitentan 60%	41.07±13.11 to 32.07±9.54 (P<0.001)	NYHA-FC-2.87±0.83 to 1.67±0.62 (P=0.002) 6MWD-387±86.4 to 453.4±63.8 m (P=0.01)	Complications in 11.5% sessions, vascular dissection 3/52, hemoptysis 1/52, reperfusion injury 2/52.
Minatsuki, 2020 [28]	43, women 72%; 62.7±13.5	Total 212 BPA sessions, 1389 vessels treated, median 5 sessions	Riociguat 49%	43.3±7.8 to 23.9±4.7 (significant change)	WHO FC I/II/III/IV-0/0/35/8 to 9/30/3/0. 6MWD-370.0±107.4 to 443.8±101.4 m (significant change)	Lung bleeds 39/212 sessions, MV 4/43 patients, percutaneous cardiopulmonary support 2/43 patients. Mortality-2.3% (severe right heart failure).
Mizoguchi, 2012 [20]	68, women 78%; 62.2±11.9	Total 255 sessions, 558 arteries, 4 (2-8) sessions per patient, 3 (1-14) vessels per session	All >1 PH targeted drug, Epoprostenol for at least 5 days before BPA	45.4±9.6 to 24±6.4 (P<0.01)	WHO-FC 3.0 to 2.0 (P<0.01) 6MWD-296 to 368 m (P<0.01)	221/255 sessions RPE, 4/68 patients MV, 5/68 patients PA perforation. Mortality-1 RHF, day 28.

Ogawa, 2017 [25]	308, including 14 post-PTE, women 80%; 61.5±12.5	Total 1408 procedures, median of 4 (range 1-24) procedures per person	Oral monotherapy 24.7% Oral dual therapy 27.9% Oral triple therapy 15.9% Epoprostenol 0.6% Epoprostenol + oral monotherapy 0.6% Epoprostenol + oral dual therapy 2.3%	43.2±11.0 to 22.5±5.4 (P<0.001)	Median WHO-FC-3 to 2 (P<0.001) 6MWD-318.1±122.1 to 429.7±108.5 (P<0.001)	Complication rate 36.3%, pulmonary Injury 17.8%, hemoptysis 14%, PA perforation 2.9%. Mortality-2.6%.
Ogo, 2017 [88]	80, women 26%; Median (IQR) 68 (58-76)	Total 385 sessions, 1155 lesions, mean 4.8 per patient	PH targeted therapy 61%, ERA 33%, PDE-5i 25%, Oral prostacyclins 42%, i.v. epoprostenol 6%, sGC stimulator 6%	42±11 to 23±5 (P<0.01)	WHO-FC 3.0±0.4 to 1.7±0.5 (P<0.01) 6MWD-372±124 m to 495±107 m (P<0.01)	Wire perforation 7.5%, RPE 4.7%, Hemoptysis 4.7%, MV 0.5% of cases.
Olsson, 2017 [40]	56, women 61%; Median (IQR) 65 (55-74)	266 interventions, median 5 (range 3-8) interventions patient, median 2 (range 1-4) vessels targeted per intervention	Riociguat 14%, PDE5i 59%, ERA 18%, Prostacyclin i.v. 2%	40±12 to 33±11 (P<0.001)	WHO FC I/II/III/IV-0/15/70/15% to 13/60/25/0% (P<0.001) 6MWD-358±108 to 391±108 (P=0.001)	PA dissection without bleeding 0.8%, Vascular lesions with pulmonary bleeding without hemoptysis 1.1%, hemoptysis 5.6%, RPE 0.8% of interventions. Mortality-1.8%, hemothorax/ hemorrhagic shock.
Roik, 2016 [76]	11, 9 underwent BPA, 2 were excluded, women 36%; 76 (range 59-84) 6	27 sessions, mean 3 (range 1-5) sessions per patient, mean vessels 6 (range 3-9) per patient, 2.03 vessels per session.	Sildenafil 6/11	Median (range) 40 (32-54) to 34.5 (29-42) (P=0.01)	WHO-FC I/II/III/IV 0/0/6/3 to 0/7/2/0 (P=0.018) 6MWD-Median (IQR) 304 (135-450) to 384 (205-530) (P=0.03)	RPE 2/9, hemoptysis 1/9.
Roik, 2017 [27]	10, women 60%; median 81 (range, IQR 75-88)	39 BPA sessions, mean 3.9 (range 1-9) sessions per patient, 70 vessels dilated, mean 6.5 (range 1-14) vessels per patient	Riociguat 2/10, sildenafil 4/10	Median (range) 41 (31-53) to 23 (17-33) (P<0.01)	WHO-FC I/II/III/IV-0/0/7/3 to 2/8/0/0 (P<0.05) 6MWD median (range)-221 (80-320) to 345 (230-455) (P<0.01)	RPE 2/10, PA perforation 3%, dissection 1.5% of angioplasties.
Sepulveda, 2019 [89]	8, women 88%; 61±14	16 BPA, mean 2.3 (range 1-4) segments per patient, 1.6 (range 1-2) sessions per patient	Sildenafil 8/8	48.6±5.8 to 37.4±8.6 (P=0.02)	WHO FC-3.3±0.5 to 2.5±0.5 (P<0.01) 6MWD-331±92 to 451±149 (P=0.01)	RPE 1/8.
Shimura, 2015 [29]	9 post-PTE, women 78%; Median (IQR) 55.1 (44.9-61.7) (post-PTE patients)	44 BPA sessions in 9 post-PTE patients, 5 (3-7) sessions per patient		Median (IQR) 43 (30-52) to 26 (21-29) (P<0.05)	NYHA-FC I/II/III/IV 0/3/5/1 to 7/2/0/0 (P<0.05)	Vessel injury 0.6% of vessels treated, RPE 2.3% of 44 sessions.
Sugimura, 2011 [45]	12, 2 post-PTE, women 92%; 58±13	5±2 procedures for 14±7 lesions	Epoprostenol 7/12, beraprost 5/12, sildenafil 11/12, bosentan 5/12	47.8±11.6 to 24.8±4.9 (P<0.01)	WHO-FC II/III/IV 33/42/25% at baseline; 100% FC II at follow-up. 6MWD-350±105 m to 441±76 m (P<0.05)	6/12 hemoptysis.
Tatebe, 2016 [90]	55, women 76%; 64±13	3.5±1.5 sessions per patient	Epoprostenol 2%, oral prostanoids 51%, PDE5i 65%, ERA 16%, combination therapy 45%	35±9 to 24±6 (P<0.001)	WHO-FC I/II/III/IV-0/22/12/1 to 7/28/0/0 (P<0.01) 6MWD-408±181 m to 482±146 m (P<0.01)	
Tsugu, 2016 [59]	26, women 76%; 63±16	Mean 6±2 sessions per patient	PDE-5i 72%, ERA 46%, Prostanoid 40%, CCBs 20%	38.3±8.4 to 18.5±4.2 (P<0.01)	WHO-FC 2.9±0.6 to 1.2±0.4 (P<0.01) 6MWD-326.8±83.7 m to 400.3±77.4 m (P<0.01)	

Velazquez Martin, 2015 [91]	7, women 71%; 61	22 BPA, mean 3 procedures per patient; mean 2.4 segments and 1.2 lobes per procedure	ERA + sildenafil + epoprostenol 6/7	56±17 to 36±10 (P<0.06)	NYHA-FC 3.8±0.2 to 2.3±0.2 (P<0.001)	RPE 2/7, MV + ECMO 1/7. Mortality-1/7, CVA day 8.
van Thor, 2020 [92]	38, including 1 patient with CTED, women 61%; 65±15	Total 172 procedure, 4.5±1.3 BPA sessions per patient	sGC stimulator 21%, PDE5-i 9%, ERA 13%, sGC stimulator + ERA 18%, PDE5-i + ERA 21%	39.5±11.6 to 30.6±8.2 (P=0.0001)	WHO FC I/II/III/IV (%)-0/63/34/3 to 39/50/11/0 (P=0.014) 6MWD-374±124 to 422±125 (P=0.007)	Mild hemoptysis 8%, temporary conduction/rhythm disturbances 2%, PA dissection 1%, perforation 1%.
Wiedenroth, 2018 [51]	36, women 39%; Median (IQR) 62 (IQR 50-71)	195 interventions, median 5 (range 5-6) sessions per patient, median 11 (range 8-13) pulmonary segments targeted per intervention	Riociguat 100% for 3 months pre-BPA	43±12 to 34±14 (P=0.0001)	WHO FC I/II/III/IV 0/19.4/50/30.6% to 50/44.4/5.6/0 (P=0.0001) 6MWD-409±102 to 467±95 m (P=0.0001)	13.8% of interventions, wire perforation most common complication, RPE 7/36, NPPV after any severity of hemorrhage 11/36.
Yamasaki, 2017 [54]	20, women 80%; 61.9±10.6	Mean 2.71.6 sessions per patient	ERA 9/20, Oral prostacyclins 8/20, PDE-5i 10/20, sGC stimulator 9/20	42.6±11.0 to 30.0±6.6 (P<0.0001)	6MWD-391±75 m to 437±68 m (P<0.0001)	
Yanagisawa, 2014 [44]	≥65 years: 31, women 67%, <65 years: 39, women 90%; Median age (IQR) <65 years: 54 ≥65 years: 70 (69-74), <65 years: 54 (42-60)	≥65 years: median 4 (IQR 3-5) sessions, 13 (IQR 9-19) target vessels per patient. <65 years: median 3 (IQR 2-4) sessions, 11 (IQR 8-14) target vessels. (P>0.05)	PDE-5i 79%, ERAs 53%, PGI_2 53% in all patients. Non-significant difference between groups	≥65 years: 41 to 23.5, <65 years: 42 to 26.0 (P=0.11)	Improved in both groups (P<0.05), age ≥65 years (P<0.0001) 6MWD-≥65 years: 310 to 409 m, <65 years: 380 to 441 m (P=0.553)	≥65 years vs. <65 years group: RPE 26.3 vs. 23.4%, vessel injury 8.1 vs. 5.7% of the session (P>0.05). Mortality-3.2%, wire perforation, RHF in ≥65 years group. (over-all 1.4%).
Yanaka, 2018 [15]	10, all with residual PH after PTE, women 90%; 63.9±2.5	Total 24 sessions, average 2.4±0.3 BPA sessions, 7.8±1.2 target segments per patient, total 155 target vessels	ERA 1/10, sGC 1/10	25.0±2.2 to 16.7±1.8 (P=0.002)	WHO FC I/II/III/IV-0/5/4/1 to 7/3/0/0 (P<0.001) 6MWD-338±62 to 429±38 m (P=0.160)	Reperfusion pulmonary injury 33.3%, (hemosputum 12.5%, only CT findings 20.8%), wire perforation 8.3%, NPPV 8.3%.

Abbreviations: BPA: balloon pulmonary angioplasty; CCB: calcium channel blocker; CI: confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; CVA: cerebrovascular accident; ERA: endothelin receptor antagonist; ECMO: extracorporeal membrane oxygenation; IQR: interquartile range; mPAP: mean pulmonary artery pressure; MV: mechanical ventilation; 6MWD: 6-minute walk distance; NPPV: non-invasive positive pressure ventilation; NYHA-FC: New York heart association functional class; PA: pulmonary artery; PCA: prostacyclin analogue; PDE5i: phosphodiesterase 5 inhibitor; PGI_2: prostacyclin; PE; pulmonary embolism; PEPSI: pulmonary edema predictive scoring index; PTE: pulmonary thromboendarterectomy; PWG: pressure wire guidance; RHF: right heart failure; RPE: reperfusion pulmonary edema; RVF: right ventricular failure; sGC: soluble guanylate cyclase; USA: United States of America; WHO-FC: World Health Organization functional class.

Table 2. Meta-analysis and systematic reviews

Study	Included studies and patients	Reduction in mPAP	Increase in 6MWD	Peri-procedural (≤30 days) mortality and complications	Long-term mortality
Tanabe, 2018 [47]	13 observational BPA studies, 493 patients	39.4-56 to 20.9-36 mmHg	191-405 to 359-501 m		2-year mortality: 1.3% with BPA vs. 13.2% with medical therapy, RR 0.14 (95% CI 0.03-0.76)
Phan, 2018 [67]	BPA: 6 observational sites, 252 patients, background medical therapy used in 10-100% and history of prior PTE in 0-16.7%. Medical therapy: 12 observational studies, 333 patients, history of prior PTE in 0-32%	-44.4% with BPA vs. -5.2% with medical therapy (P=0.002)	26.5% with BPA vs. 22.8% with medical therapy (P=0.001)	Mortality 1.9%, Vascular injury/perforation 6.8%, severe RPE 1.9%, mild-moderate RPE 22%	
Khan, 2019 [68]	17 observational BPA studies, 670 patients	-14.2 mmHg (95% CI: -18.9, -9.5)	67.3 m (95% CI: 53.8, 80.8)	1.90%	5.7% at median follow up of 9 months (IQR 1-51 months)
Zoppellaro, 2019 [93]	14 observational BPA studies, 725 patients	43 (IQR 40.5-49.25) to 32.5 mmHg (IQR 25-33.5)	345 (IQR 322-369) to 442 m (IQR 403-466)	Mortality 2.1% of patients (95% CI 0.8-4.1), RPE 9.3% (95% CI 3.1-18.4), pulmonary vascular injury 2.3% (95% CI 0.9-4.5) of BPA sessions	
Wang, 2019 [66]	BPA: 17 observational studies, 631 patients. Riociguat: 6 observational studies, 823 patients	-15.02 mmHg with BPA (95% CI -17.32, -12.71) vs. -4.19 mmHg with Riociguat (95% CI -5.58, -2.8)	71.66 m wit BPA (95% CI 58.34-84.99) vs. 45.25 m with Riociguat (95% CI 36.51-53.99)	Pulmonary injury 0.3-5.6%, RPE 0.8-28.6%	

Abbreviations: BPA: balloon pulmonary angioplasty; CI: confidence interval; IQR: interquartile range; m: meters; mPAP: mean pulmonary artery pressure; 6MWD: 6-minute walk distance; PTE: pulmonary thromboendarterectomy; PRE: reperfusion pulmonary edema.

Few studies have reported the long-term effects after BPA. Nonetheless, observed survival has improved over the years. Most recent studies have reported 1-5 years of survival of greater than 95% [20, 25, 27, 36, 44-46]. A meta-analysis showed comparable 2-year mortality between BPA and PTE {2.1% vs. 4.8%; RR 0.74, [95% confidence interval (CI), 0.16-3.48], P=0.7} [47].

Improvement in pulmonary artery compliance

Afterload of the right ventricle (RV) is determined by static (PVR) and dynamic components [pulmonary artery (PA) compliance]. PA compliance depends on the elastic properties of the vessel wall but also has an inverse hyperbolic relation with PVR. Thus, in severe CTEPH, a significant decrease in PVR may not lead to a significant increase in PA compliance. PA compliance is one of the independent predictors for exercise capacity in patients after PTE [48]. No or minimal improvement in PA compliance after PTE is associated with worse clinical improvement and higher prevalence of distal CTEPH [49]. The correlation of functional improvement with increased PA compliance has not yet been studied in BPA; nonetheless, patients undergoing successful BPA experience significant increase in PA compliance [38, 50, 51].

Cardiac imaging after BPA

Cardiac magnetic resonance (CMR) imaging is frequently used for non-invasive assessment of the RV after BPA. Imaging parameters such as an increased RV end-diastolic volume (RVEDV), reduced left ventricle (LV) end-diastolic volume (LVEDV), and a low stroke volume at baseline are associated with poor outcomes in idiopathic PAH patients [52]. Similar to PTE, BPA has been shown to significantly ameliorate RV dilation, improve RV ejection fraction (RVEF), RV hypertrophy (ventricular mass index) and interventricular septal bowing [53]. BPA is also shown to improve interventricular dyssynchrony [54]. Lack of improvement in RVEDV and RVEF after BPA is associated with worse functional status despite favorable hemodynamic changes, possibly indicating an irreversible RV remodeling and fibrosis [55]. This suggests that positive changes in RVEDV and RVEF on imaging after BPA may have prognostic significance.

Echocardiographic assessment of RV is difficult because of its complex geometrical shape. However, tricuspid annular plane systolic excursion (TAPSE), tricuspid annular systolic velocity (TASV), RV longitudinal strain, and 3D echocardiography are being used and can be valuable parameters for assessing treatment response after BPA. Measurements of RV volume were comparable with real-time 3D-echocardiography and CMR in patients with PH, and had less than 17% inter and intra-observer variability for various parameters [56]. TAPSE, right atrial area, and RV fractional area changes have prognostic value in CTEPH [57]. Various studies have shown significant change in these echocardiographic parameters after BPA [40, 58-60]. TTE may be used as an alternative for post-BPA assessment of the RV in patients with contraindications for CMR (such as metallic implants, medication pumps) and in patients who are unable to lie still for prolonged periods.

BPA versus medical therapy for CTEPH

BPA and medical therapy target different parts of the pulmonary vasculature. Specifically, BPA targets segmental and subsegmental pulmonary arteries down to 2-5 mm, and medical therapy targets pre-capillary arterioles and post-capillary venules. Thus, medical therapy can be a complementary treatment both before and after BPA in patients that are not candidates for PTE.

CHEST-1 (A study to evaluate efficacy and safety of oral BAY63-2521 in patients with CTEPH) was a randomized, double-blinded phase III trial investigating the efficacy and safety of riociguat in patients with inoperable and persistent/recurrent CTEPH. At 16 weeks of follow up, there was an increase in 6MWD (mean 39 m) in the riociguat group compared to a decrease (mean 6 m) in the placebo group (P<0.001). PVR decreased by 226 dyn·sec·cm^{-5} in the riociguat group and increased by 23 dyn·sec·cm^{-5} (P<0.001) in the placebo group [61]. These improvements in the clinical endpoints were sustained in the extension trial (CHEST-2; BAY63-2521 - long-term extension study in patients with chronic thromboembolic pulmonary hypertension) [62]. MERIT-1 (Clinical Study to Assess the Efficacy, Safety and Tolerability of Macitentan in Subjects With

Inoperable Chronic Thromboembolic Pulmonary Hypertension) was a 16-week phase II trial investigating macitentan-a dual-endothelin receptor antagonist-that reported a decrease in geometric mean PVR to 73% of baseline compared to 87.2% in the placebo group (P=0.041). Patients in this study had inoperable CTEPH, and those with functional class III and IV symptoms were concomitantly treated with other PAH therapies [63]. The BENEFiT study (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension) was a 16-week double-blind, randomized, placebo-controlled study investigating bosentan, an endothelin antagonist in patients with inoperable CTEPH or persistent/recurrent PH after PTE. This study showed a statistically significant decrease in PVR (-24.1% of baseline) in the bosentan group over placebo (P<0.0001). 6MWD increased but was not significant (mean + 2.2 m; P=0.5449) [64].

Ambrisentan was tested in patients with inoperable CTEPH in a double-blind placebo-controlled study. However, the study was terminated due to futility after enrollment of 30 patients. Trends of improvement in primary and secondary endpoints were observed [65]. BPA combined with medical therapy has been frequently used as a hybrid strategy to maximize the improvement in functional capacity, 6MWD, and hemodynamic parameters. Sequential treatment with riociguat and BPA was studied in 36 patients and showed that after at least 3 months of riociguat therapy, there was improvement in functional class by at least one class in 13 (36.1%) patients (P=0.01), mPAP (49±12 mmHg vs. 43±12 mmHg; P=0.003), PVR (956±501 dyn·s·cm^{-5} vs. 517±279 dyn·s·cm^{-5}; P=0.0001), and 6MWD (389±108 m vs. 409±102 m; P=0.88). After 3 months of therapy with riociguat, patients underwent BPA. Treatment with a combination of riociguat and BPA resulted in improvement in functional capacity in 34 (94.4%) patients, mPAP (43±12 mmHg vs. 34±14 mmHg; P=0.0001), PVR (517±279 dyn·s·cm^{5} vs. 360±175 dyn·s·cm^{-5}; P=0.0001), and 6MWD (409±102 m vs. 467±95 m; P=0.0001) [51].

A meta-analysis comparing BPA to medical therapy showed significantly lower mortality in BPA (1.3% vs. 13.2%; RR 0.14 [95% CI, 0.03-0.76], P=0.028) [47]. Another meta-analysis comparing BPA with medical therapy and riociguat without BPA has shown a greater improvement in pulmonary hemodynamics in the BPA subgroup [66]. Patients undergoing BPA also experienced more improvement in functional capacity compared to medical therapy with riociguat [66, 67]. The majority of patients included in these studies were women. However, after meta-regression analysis, the hemodynamic and functional improvement after BPA could not be attributed to the female gender [68].

Many randomized control trials for riociguat and macitentan have shown promising results in the treatment of CTEPH [61, 63], while the benefit of BPA is mostly supported by observational studies only. Presented as a late-breaking abstract at the 2019 CHEST conference, the results of a multicenter randomized control trial comparing riociguat to BPA in patients with inoperable CTEPH showed a reduction in PVR of 60% in the BPA group and 32% in the riociguat group. BPA showed an improvement in at least 1 WHO functional class, but the difference in 6MWD did not reach statistical significance. The study also showed 50% higher chance of serious adverse events in the BPA group compared to 26% in the riociguat group. Further data from this study are pending [69].

Predictors of treatment failure after BPA

The outcomes of BPA in terms of improvement in hemodynamic parameters and symptoms are variable. About 15-23% of patients have persistent PH after BPA [70, 71]. A longer duration of symptoms and higher diastolic PA pressure (indicator of pulmonary vascular remodeling) at baseline predicted treatment failure on multivariate analysis [71]. Long standing CTEPH may lead to development of microvascular arteriopathy which is one of the known poor prognosticators of outcomes after PTE, as well [2]. In some cases, CTEPH is caused by diffuse distal thrombosis where collaterals between pulmonary vessels and bronchial arteries fail to develop. This is seen as poor subpleural perfusion in the capillary phase in the pulmonary angiogram and is associated with poor outcomes post PTE. A retrospective study of 101 patients with inoperable CTEPH showed that poor subpleural perfusion predicted failure of hemodynamic improvement after

BPA [70]. Thus, early intervention with BPA and simultaneous treatment with medical therapy may lead to better treatment outcomes. *Kawakami et al.,* proposed imaging-based classification of occlusive lesions and reported that totally occluded and tortuous lesions had a lower success rate (52.2% and 63.6%, respectively) [72].

Safety and complications in BPA

Lung injury associated with BPA was initially described as RPE and the refinements in technique were primarily intended to reduce pulmonary injury. *Inami et al.,* developed the pulmonary edema predictive scoring index (PEPSI) for predicting the risk of RPE after BPA. The PEPSI is calculated by multiplying the sum total of Pulmonary Flow Grade (pulmonary equivalent of TIMI Grade Flow) with baseline PVR. A high Pulmonary Flow Grade post PTE, and baseline PVR (high PEPSI score) was associated with a high risk of RPE. A PEPSI value of less than 35.4 had a 92.3% negative predictive value for RPE after BPA [73]. RPE incidence was significantly lower for PEPSI score guided BPA, with or without additional pressure wire guidance to achieve pressure distal to lesion (Pd) of less than 35 mmHg, when compared to non-guided procedure [74]. Lower Pd after BPA is associated lower risk of RPE [75]. Achieving a complete flow in the target vessels is not necessary as perfusion usually improves with time because of higher proximal pressure.

In-vivo imaging with IVUS to determine the appropriate balloon size for dilation was safely used by *Mizoguchi et al*. They limited the balloon size to less than 90% of the vessel diameter, however 60% of patients experienced RPE and 5.9% needed mechanical ventilation [20]. *Roik et al*., performed the procedure using IVUS or optical coherence tomography (OCT) guidance. They also limited the number of vessels re-vascularized per session to 2-3 sub- or segmental lesions and further reduced in balloon size when mPAP was greater than 35 mmHg, leading to 18% incidence of RPE [76]. In-vivo imaging with OCT or optical frequency domain imaging (OFDI) provides higher resolution images of the obstructive segments of vessels. When used in CTEPH, mean pulmonary vessel diameter measured with OCT was 22% smaller when compared to IVUS, thus leading to smaller balloon size selection and 0% incidence of pulmonary injury in the study by *Ikeda et al*. However, in this study, the baseline mPAP was also lower at 28 mmHg [77].

With increasing experience with BPA, there is a rising consensus that the lung infiltrates after BPA are secondary to vascular injury instead of RPE [78-80]. Patients with lung infiltrates after BPA have a poor response to non-invasive positive pressure ventilation (NPPV), while RPE should respond favorably to NPPV [81]. *Ejiri et al*., have classified the lung infiltrates on multi-detector CT appearing within 24 hours after BPA into focal extravasation, stain and pooling type, and diffuse blooming type infiltrates. They also found that a high mPAP may predict the need for mechanical ventilation but does not predict the incidence of lung injury on imaging [78]. In another study of 35 patients, baseline mPAP higher than 35 mmHg was not associated with a higher pulmonary complication rate after multivariate analysis. However, occlusive lesions significantly increased the risk (OR 5.83, P=0.002) as also described by *Kawakami et al*. [72, 80].

Navigating the guide wire through completely occluded lesions requires guidewires with heavier tip load leading to a greater risk of extravasation of the wire and vessel injury.

Pulmonary vessel injury is managed with reversal of anticoagulation, inflating the balloon at the site of injury, embolization with bio-absorbable gelatin or a metallic coil, or stent placement in larger vessels. However, uncontrolled and critical bleeds may need urgent surgical intervention [79].

Compared to coronary angiography where incidence of contrast induced nephropathy is high, kidney injury is only reported in up to 2% of cases after BPA [25, 35, 44, 94, 95]. Some studies have reported an improvement in estimated glomerular filtration rate after BPA [51, 90].

Conclusion

When performed in a high-volume center, BPA has an important role in the treatment of patients who are not candidates for PTE or have persistent symptomatic PH after PTE, and are in need of the hemodynamic improvement

that medications like riociguat alone may fail to provide. Studies have shown that BPA improves functional status, hemodynamics, and RV systolic function. With the continued refinement of patient selection, technique, and peri- and post-procedural care, BPA is likely to help more and more people with CTEPH. Further studies are required to examine the benefit of medical therapy in addition to BPA for CTEPH. Additionally, given the potentially higher upfront mortality and morbidity of PTE over BPA, randomized controlled studies are needed to understand which CTEPH patients are best treated by each intervention.

Just as it was controversial twenty years ago to suggest transcatheter aortic valve implantation (TAVI) could compete with or even be superior to surgical aortic valve replacement (SAVR) for aortic stenosis, so to BPA may eventually compete with or supplant PTE. Current guideline recommendations that PTE is the ideal treatment for CTEPH reflect our historical treatment bias and collective experience. Similar to how the technology of transcatheter valve implantation was introduced in competition with the "gold standard" of SAVR, there should first be prospective, randomized trials comparing BPA to PTE in high risk CTEPH patients. If BPA is found to be superior or at least non-inferior, then BPA may subsequently be trialed in lower risk patients. By adding to medical and surgical treatment options, the care of patients with CTEPH can only improve as percutaneous techniques and technology of BPA grows.

Disclosure of conflict of interest

None.

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