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Advances in the Management of Chronic Thromboembolic Pulmonary Hypertension

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Abstract Chronic thromboembolic pulmonary hypertension (CTEPH), a potentially curable form of pulmonary hypertension with pulmonary thromboendarterectomy surgery, has been the focus of significant medical advances. In addition to new imaging modalities that are now used to help recognize and diagnose CTEPH, additional treatment options have emerged for inoperable cases. These include a newly approved medical therapy for inoperable disease or persistent/recurrent CTEPH as well as percutaneous balloon angioplasty of the pulmonary arteries. In this article, we summarize these recent advances in the field and review the related literature.

Keywords Pulmonary hypertension · Chronic thromboembolic pulmonary hypertension · Pulmonary thromboendarterectomy · Pulmonary endarterectomy · Balloon pulmonary angioplasty · Riociguat

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially curable form of pulmonary hypertension (PH). The treatment of choice is surgical removal of chronic, obstructing thromboembolic material from the pulmonary artery lumen via pulmonary thromboendarterectomy (PTE) surgery. Although the precise incidence or prevalence is unknown, estimates as high as 4–5 % [1••, 2•] have been reported following acute pulmonary embolism. However, the true prevalence of CTEPH may be higher considering the under-utilization of ventilation perfusion scanning in the work-up of pulmonary hypertension patients [3•], and that in one large registry, 25 % of CTEPH patients did not have a history of pulmonary embolism [4•].

Although PTE remains the treatment of choice for CTEPH, there are patients who cannot receive surgery due to numerous reasons. There is also a subset of patients who have residual and symptomatic pulmonary hypertension following PTE for whom additional treatment may be necessary. We will address recent advances in the field pertaining to operability assessment and novel alternative treatments for CTEPH when PTE is not feasible.

Determining Operability and the Role of Imaging Studies in CTEPH

Operability assessment in CTEPH combines multiple factors including objective imaging compared with hemodynamic data. One key hurdle in correctly screening for CTEPH still remains—the lack of routine use of the lung ventilation/perfusion scan (VQ). Despite advances in multi-detector computer tomography pulmonary angiograms (CTPA), Tunariu and colleagues [5••] reported a dismal 51 % sensitivity in detecting CTEPH using CTPA in their experienced center. Comparatively, VQ scan sensitivity was in the 96–97.4 % range. Recently, data from the Queri registry showed that 43 % of patients diagnosed with pulmonary arterial hypertension (PAH) never had a VQ scan to exclude CTEPH [6]. This raises the concern that the diagnosis of CTEPH will be excluded from many cases of pulmonary hypertension by imaging studies other than VQ scan and that many patients with

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CTEPH will be misclassified as having other forms of pulmonary hypertension. Thus, there will be missed opportunities for treating CTEPH. VQ scan also has multiple benefits when compared with CTPA, including less radiation, no intravenous contrast dye, less incidental findings, and not requiring additional training for interpretation, as CTEPH findings in CTPA may be more subtle [7, 8]. Based on the above, VQ remains the screening test of choice for CTEPH despite ongoing advances in imaging modalities [9•].

While acknowledging the important role of VQ scan in the diagnostic algorithm, recent reports of pulmonary vascular imaging and the increasing awareness of the condition have yielded promising advances in the field of CTEPH diagnostics. More recent studies comparing CTPA to VQ in the diagnosis of CTEPH, using digital subtraction pulmonary angiography (DSPA) as the gold standard, are showing a significant narrowing of the sensitivity gap previously reported by Tunariu et al. [5, 10, 11] Moreover, CT images allow for the visualization of additional details of the surrounding structures and tissues, and can reveal other findings that are consistent with CTEPH, such as bronchial artery collaterals and mosaic perfusion pattern [12], which are not seen on DSPA or VQ scans. Additionally, Liu and colleagues reported that CTPA measurements of cardiovascular structure anatomic characteristics (such as right to left ventricular diameter ratio, right ventricular anterior wall thickness, and main pulmonary artery trunk diameter) may be independently associated with pulmonary artery pressure measurements [13].

A recent study evaluating 320-slice CTPA using DSPA as the gold standard in patients with suspected CTEPH based on VQ and echocardiographic work-up, showed a 97 % sensitivity and specificity for chronic thromboembolic findings in main and lobar pulmonary arteries [14]. The CTPA sensitivity and specificity dropped to 86 and 95 %, respectively, when more distal segments were evaluated, with a concomitant decrease in inter-observer agreement for the two modalities. Interestingly, these results are in accordance with data from a prior study comparing 64-detector row CT and DSPA [15].

Dual-energy CTPA uses the photoelectric absorption properties of iodinated contrast media to derive a relative regional blood volume map, which can then be used as a surrogate for relative regional blood flow. The latter is in addition to traditional CTPA data provided by this modality. Hoey and colleagues reported on this technique in patients with known CTEPH [diagnosed with echocardiography, right heart catheterization (RHC) and VQ scans] [16]. Although they showed a positive correlation between mosaic attenuation pattern on lung windows and dual-energy CT-derived perfusion, there are no other data on using this technique as a screening or diagnostic tool [16]. An example of dual-energy CTPA is shown in Fig. 1. Rossi et al. [17] used a non-contrast high-resolution CT technique called minimum intensity projection (MinIP), in which an algorithm uses all the data in a volume of interest to create a single two-dimensional image, projecting the voxel with the lowest attenuation. When applied to patients with PH, they noted an 85 % concordance between lung attenuation patterns on CT and perfusion patterns on VQ scans. When specifically looking for inhomogeneous patterns, which in this group of patients would be consistent with CTEPH, the sensitivity and specificity of the MinIP technique was reported as similar if not better than that of VQ scans. Of note, the gold standard for the diagnosis in this series was CTPA and not DSPA [17].

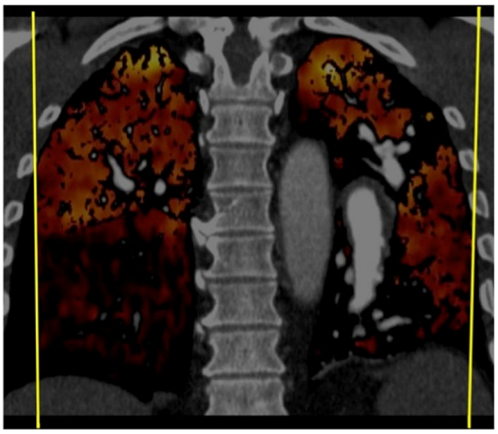

Fig. 1 Dual-energy CT coronal image. Multiple bilateral perfusion defects, with lower zone predominance, as well as a segmental perfusion defect in the left upper lobe are shown

In a recent study [11], three imaging techniques were compared in the evaluation of patients with PH and possible CTEPH identified from the ASPIRE registry [18]. Sensitivity, specificity, negative and positive predictive values for VQ, magnetic resonance (MR) three-dimensional contrast-enhanced perfusion imaging, and CTPA were all relatively comparable and above the 90th percentile. The gold standard for diagnosis was based on clinical assessment, RHC, MR angiography (without the 3D perfusion analysis noted above), CTPA, and VQ. Contrast-enhanced MR imaging, without additional perfusion algorithms, has been evaluated in CTEPH diagnosis in the past with reported specificity of 98 %, and slightly lower sensitivity of 83 and 88 % at lobar and segmental level, respectively [12]. In the same study, DSPA had the best specificity but relatively low sensitivity, with CTPA having the best sensitivity and maintaining a high specificity. The gold standard in these cases was joint interpretation of all three techniques [12]. Finally, similar results have been reported previously on contrast-enhanced MR angiography (sensitivity and specificity of 98 and 94 % for proximal and distal disease), but with lower sensitivity for central vessel disease (50 %), that significantly improved (88 %) when images were analyzed with unenhanced proton MR angiography [19]. An example of MR pulmonary angiography is shown in Fig. 2.

Cone-beam computed tomography (CBCT) is based on divergent x-rays that take the form of a cone and is usually

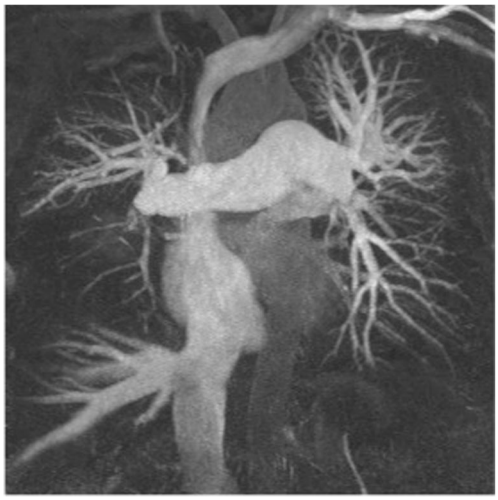

Fig. 2 Magnetic resonance pulmonary angiogram showing proximal occlusion of the right middle lobe, right lower lobe as well as a tight proximal stenosis/web of the left lower lobe. Also shown distended right atrium and hepatic veins due to tricuspid regurgitation and elevated pulmonary artery pressures. Figures provided and used with permission by: Deepa Gopalan, Cardiovascular Radiologist Cambridge University Hospital, Cambridge, and Imperial College Hospital, London

paired with a rotating axis in order to take images from various angles. It is often used in dentistry and interventional radiology, and was recently applied in the evaluation of patients with known CTEPH to assess segmental and sub-segmental pulmonary arterial lesions. This modality was compared to CTPA, which detected all segmental lesions noted with CBCT, but missed 30 % of the sub-segmental lesions [20].

Despite the advances in medical imaging, RHC with selective pulmonary angiography still offers unique advantages in the pre-operative assessment of CTEPH in most cases. The critical advantage of combining imaging at the time of hemodynamic assessment is the comparison of radiographic disease burden with the degree of hemodynamic derangement, which is a key factor in determining operability [21]. Nevertheless, these radiographic modalities add to our CTEPH evaluation armamentarium and can be useful in challenging cases where questions of disease level or burden remain. Regardless of the imaging modality used for the evaluation of CTEPH, a fundamental and critical aspect is having experience with the technique and awareness of CTEPH.

Medical Treatment

Although surgical treatment can be curative for CTEPH, a recent registry from experienced centers in Europe and Canada reported 36 % of CTEPH were not operable [4]. Moreover, up to 35 % may be left with residual PH after surgical treatment [22]. To this extent, there have been multiple clinical trials, including four randomized-controlled trials [23, 24, 25••, 26••], testing PH-targeted medications for inoperable CTEPH. Of these, only two [25••, 26••] included an operability adjudication process, highlighting the importance of surgery and care in patient recruitment. In the BENEFIT study, bosentan was compared to placebo and although a significant decrease in pulmonary vascular resistance (PVR) was noted (24 % reduction in the treatment group, $p<0.0001$), the other co-primary endpoint of 6-min walk distance (6MWD) was unchanged [25••]. In the more recent CHEST study, multiple key endpoints were achieved in patients with inoperable CTEPH using the soluble guanylate cyclase stimulator riociguat compared to placebo. Significant improvements included a 46-m relative increase in 6MWD, 31 % relative decrease in PVR, as well as improvement in pro-b natriuretic peptide (pro-BNP) and WHO Functional Class (FC) values compared to patients treated with placebo [26••]. Although there was no significant effect observed on time to clinical worsening and the treatment effect was less pronounced in the subgroup of patients with residual PH after surgery, the study resulted in regulatory approval for treatment of inoperable CTEPH or persistent/recurrent PH after PTE. A recently published open-label extension of this study [27] noted sustained improvement in 6MWD and WHO FC up to 1 year after enrollment, although these were pre-defined exploratory efficacy endpoints without a comparator group. Of note, safety and tolerability of the medication, which were the extension trial's primary endpoints, were also confirmed.

Although a medical therapy is now approved for a select group of CTEPH patients deemed inoperable or with persistent/recurrent PH after PTE, there are still unanswered questions regarding the general role of medical therapy in CTEPH. Prior to the approval of riociguat, the use of PAH-targeted therapies for patients with operable CTEPH led to delays in surgery [28] without appreciable benefits. It is unclear whether a bridging therapy approach (currently not the indication) offers safety, benefit, or harm. Until that is carefully studied, the recommendation is for early referral of all CTEPH for surgical evaluation without delay [9]. Furthermore, for cases deemed inoperable, consideration should be given for a second opinion from an experienced CTEPH center for possible PTE in recognition of the subjectivity of operability assessment.

Patients with persistent/recurrent PH after PTE represent unique challenges and opportunities as well. There is no consensus on clinically significant level of residual PH and hemodynamic definition following PTE. Borrowing PAH hemodynamic definitions may not accurately identify patients in need of additional targeted therapy. The CHEST trial recruited post-PTE patients using a PVR inclusion defined over 300 dyn·s/cm^5, a value that has not traditionally been a threshold criterion for PAH [29]. Moreover, early post-operative hemodynamics may be affected by multiple and potentially transient factors related to post-operative care (vasopressors,

positive pressure ventilation, etc.)—therefore, caution and recognition of such limitations should be exercised when considering medical therapy acutely following PTE. Lastly, some cases of residual PH after PTE may be related to inadequate or incomplete endarterectomy. In cases of recurrent thrombosis or inadequate endarterectomy, repeat surgery may be warranted [30].

Balloon Pulmonary Angioplasty

Percutaneous transcatheter balloon angioplasty has been a mainstay for coronary artery interventions for a few decades and its first use in pulmonary arteries of CTEPH patients was reported in 1988 [31]. This was followed by a larger series in 2001 with report of 18 selected cases of inoperable CTEPH [32•]. Patients deemed inoperable, either due to inaccessible disease or due to comorbidities, underwent as many as 5 procedures and 12 dilations (on average 3 per procedure). Overall, the results were promising, with significant improvements in WHO FC, mean PA pressures, and 6-min walking distance, but with a very high reperfusion lung injury rate (11 of 18 patients), some requiring mechanical ventilation (3 patients) and one death [32•]. Although another small case series of two patients published in 2003 had similar results [33], only recently has balloon pulmonary angioplasty (BPA) emerged as a viable option in CTEPH management [34•, 35•, 36••].

Sugimura and colleagues [34•] reported on 12 prospectively recruited patients with "distal-type" CTEPH (defined as disease more distal than within arteries proximal to upper lobe branches or between upper lobe branches and lower lobe segmental branches) [37] and 2 cases with residual PH after PTE. Eleven patients were female and WHO FC ranged from II to IV. These patients were initially treated with PAH-targeted therapies (monotherapy or combination of epoprostenol, beraprost, bosentan, or sildenafil) and anticoagulated and then treated with BPA under imaging guidance with optical coherence tomography and angiography. BPA was repeated every 4–8 weeks until the mean PAP was less than 30 mmHg. At the end of the study, significant improvements in FC, 6MWD, hemodynamic variables (PAP, PVR, and cardiac index) and 1-year survival as compared to historical controls were reported. Six of the 12 patients had post-procedure hemoptysis treated conservatively with non-invasive positive pressure ventilation and/or oxygen therapy.

Kataoka and colleagues [35•] performed BPA in 29 patients, one of which died from a procedure-related complication. This group of patients had mostly lobar, segmental, or subsegmental lesions that, per the authors, would have been accessible with PTE and although both procedures were offered to the patients, the ones included in the study either refused PTE or were recommended BPA due to advanced age or poor physical condition. Patients with post-PTE persistent PH were also included. Most patients received more than one session of BPA and on average, more than six vessels were treated. Although hemodynamics immediately after the procedures were almost identical to the ones prior to the BPA, at approximately 6 months after the interventions, there were significant improvements in WHO FC, hemodynamics, and BNP levels. In addition to one death, one pulmonary artery dissection, and one case of extravascular leak, almost 70 % of the initial BPA procedures were followed by reperfusion lung injury. Post hoc data analysis identified patients with lower cardiac outputs as the high risk group for this complication. Severity of lung injury ranged from mild (requiring oxygen therapy via nasal cannula) to severe (one patient required intubation and percutaneous extracorporeal membrane oxygenation), and was also described in subsequent BPA sessions.

Mizoguchi et al. [36••] have reported the largest prospective trial of BPA, with a total of 68 patients. In this study, patients deemed inoperable for PTE were selected to undergo BPA. Inoperability was adjudicated by a surgical team with PTE experience, based on lesion location and accessibility, as well as patient age and comorbidities. Patients were FC III or IV and all were being treated with intravenous epoprostenol therapy prior to BPA. The procedure was performed in a staged fashion in order to minimize reperfusion injury and each patient received four sessions on average, with approximately three vessels being treated at a time with the help of intravenous ultrasound imaging. FC, BNP, 6MWD, and hemodynamic parameters improved after the final interventions and sustained reduction in mean PAP was noted (approximately 1 year after BPA). A correlation was noted between the number of treated pulmonary artery segments and PAP reduction. Reperfusion injury was again a factor, with 60 % of patients developing some level of lung injury post-BPA, and four patients requiring mechanical ventilation. Interestingly, a large number of these cases were diagnosed based on CT scan criteria for reperfusion lung injury alone (i.e., increased density in the area of the treated vessel) in otherwise asymptomatic patients. There were five incidents of pulmonary artery perforation, two requiring emergent coil embolization. One patient died 28 days after BPA due to right heart failure, but 66 of 68 patients were alive at 2.2 years post-procedure mean follow-up.

In 2013, a group from Norway [38•] reported on their experience with BPA in inoperable CTEPH patients or patients with persistent PH after PTE. Most of the patients included were deemed poor operative candidates by a team of surgeons and cardiologists due to distal and inaccessible disease (n= 16). The rest of the patients had comorbidities, refused the surgery, or had persistent/recurrent PH after surgery. Again, there were significant improvements in hemodynamics, FC, pro-BNP levels, and cardiopulmonary exercise testing after

Table 1 Summary of recent reports on percutaneous balloon pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension

Study	Demographics: No. of patients (*N*) Female/male (F/M) Age (mean±SD)	Procedures per patient (*P*), dilations (*D*), lesions (*L*), vessels (*V*), vessels per procedure (VP) [mean±SD; (range)]	Patient selection and adjudication process	Pre-procedure PH-specific therapy	Follow-up (mean±SD where applicable)	BPA outcome measures (6MWD in meters; mPAP in mmHg; CO in L/min; CI in L/min/m^2; TPR in WU m^2; PVR in dyn·s/cm^5; BNP in pg/mL; proBNP in pmol/L; Peak VO2 in ml/kg/min). Values are mean±SD			Complications
						Measure	Pre-BPA	Post-BPA	
Feinstein et al. 2001 [32•]	*N*=18 F/M=NA Age=52±12 years (range 14–75)	*P*=2.6±1; (1–5) *D*=6±3; (1–12) *L*=NA *V*=NA VP=NA	Deemed inoperable due to: inaccessible disease (*n*=16); comorbidities (*n*=2). Adjudication by CTEPH team and 2nd opinion in 50 % of cases.	NA	36 months (range 0.5–66 months)	FC 6MWD mPAP CI TPR	3.3 (mean) 209 43±12 2.0±0.4 22±9	1.8 (mean)† 497† 34±10† 2.1±0.6 17±8	RPE=11 cases (61 %) Mech. Vent=3 PA perforation=1 Deaths=1 (1 week post-BPA); 1 (16 months post-BPA, unrelated)
Sugimura et al. 2012 [34•]	*N*=12 F/M=11:1 Age=58±13 years	*P*=5.2±2 *D*=NA *L*=14±7 *V*=NA VP=NA	Deemed inoperable due to: "distal" CTEPH (*n*=10); post-PTE persisting PH (*n*=2)	All subjects: Initiated1–3 months prior to BPA with some outcome improvement	12 months (up to 24 months)	FC 6MWD mPAP CI PVR BNP	II–IV (range) 340±112 43±10 2.66±.0.47 672±236 78±113	II only† 441±76† 25±5† 2.79±.0.37 310±73† 16±11	Hemoptysis=6 Deaths=0
Kataoka et al. 2012 [35•]	*N*=29 (28 analyzed) F/M=23:6 Age=62±12 years	*P*=1.8±0.9 *D*=NA *L*=NA V=6.5±3; (1–6) VP=3.6±1.4	Refused PTE or deemed high risk due to: age or poor physical condition (*n*=26); post-PTE persisting PH (*n*=3). [Authors note that majority of subjects had lesions also amenable to PTE]	All subjects: a. Oral mono- or combination therapy (ERA, PDE5i and/or beraprost) b. Pre-BPA dobutamine (2 μg/kg/min)	6±6.9 months	FC 6MWD mPAP CO PVR BNP	II–IV (range) NA 45±10 3.6±1.2 NA 306±271	I–III† (range) NA 32±10† 4.6±1.7† NA 98±197†	RPE=53 % of all procedures; 68 % of all patients Mech. Vent=3 (2 NIPPV), 1 on ECMO Deaths=1 (2 days post-BPA, with wire perforation; excluded from analysis) Other=1 dissection, 1 extravascular leak
Mizoguchi[#] et al. 2012 [36••]	*N*=68 F/M=53:15 Age=62±12 years (range 38–82)	*P*=4; (2–8) [255 total] *D*=NA *L*=NA *V*=558 (total) VP=3; (1–14)	Deemed inoperable due to: lesion location, age, or comorbidities. Adjudication by "experienced surgeons"	All subjects: a. Oral mono- or combination therapy b. Had IV epoprostenol (± dobutamine) initiated c. Post-BPA steroids	53±17 months (2.2±1.4 years)	FC 6MWD mPAP CI PVR BNP	III mean (range III–IV) 296±108 45±10 2.2±0.7 942±367 330±444	II mean† (range I–III) 368±83† 24±6† 3.2±0.6† 327±151† 35±55†	RPE=41 patients (60 %) Mech. Vent=4; 2 on ECMO PA perforation=5 Deaths=1 (28 days post-BPA), 1 (during long-term follow-up; unrelated)
Andreassen et al. 2013 [38•]	*N*=20 F/M=10:10 Age=60±15 years	*P*=3.7±2.1; (2–9) *D*=NA *L*=NA *V*=18.6±6.1 VP=3; (1–14)	Deemed inoperable due to: lesion location (*n*=16); age or comorbidities (*n*=2). Rejected surgery (*n*=3); post-PTE persisting PH (*n*=1). Adjudication by	10 % of patients (*n*=2)	51±30 months	FC 6MWD mPAP CO/CI	3±0.5 NA 45±11 4.9±1.6/ 2.3±1.6	2±0.5† NA 33±10† 5.4±1.9†/2.8±1.9†	RPE=7 Deaths=2 early (2 h and 9 days post-BPA); 1 unrelated (15 months post-BPA; unable to be transplanted)

Table 1 (continued)

Study	Demographics: No. of patients (*N*) Female/male (F/M) Age (mean±SD)	Procedures per patient (*P*), dilations (*D*), lesions (*L*), vessels (*V*), vessels per procedure (VP) [mean±SD; (range)]	Patient selection and adjudication process	Pre-procedure PH-specific therapy	Follow-up (mean±SD where applicable)	BPA outcome measures (6MWD in meters; mPAP in mmHg; CO in L/min; CI in L/min/m^2; TPR in WU m^2; PVR in dyn·s/cm^5; BNP in pg/mL; proBNP in pmol/L; Peak VO2 in ml/kg/min). Values are mean±SD			Complications
						Measure	Pre-BPA	Post-BPA	
			"qualified team of thoracic surgeons and cardiologists"			PVR	8.8±4	5.9±3.6†	
						proBNP	194±182	90±119†	
						Peak VO_2	13.6±5.6	17±6.5†	
Fukui et al. 2014 [39]	*N*=20 F/M=15:5 Age=67±9 years (range 44–82)	*P*=3.2±0.9; (2–5) *D*=NA *L*=NA *V*=NA VP=NA	Deemed inoperable due to: lesion location (*n*=16); comorbidities (*n*=2). Post-PTE persisting PH (*n*=1); rejected surgery (*n*=1). Adjudication by "CTEPH team … with PTE experience"	75 % of patients on oral mono- or combination therapy	4±0.8 months (range 3–6) after final BPA session	FC	2.8 (mean)	2.0 (mean)†	RPE=0 Mech. Vent=0 Deaths=0
						6MWD	361±104	463±76†	
						mPAP	39±8	27±9†	
						CI	2.2±0.7	2.4±0.5†	
						PVR	889±365	490±201†	
						BNP	175±135	56±49†	
						CMR	Improved RV function and remodeling post-BPA		
Taniguchi# et al. 2014 [40•]	*N*=29 F/M=22:7 Age=67±11 years	*P*=2.97 *D*=NA *L*=NA *V*=NA VP=2.74	Deemed inoperable due to: lesion accessibility (*n*=13); patient age (*n*=6); comorbidities (*n*=8). Post-PTE persisting PH (*n*=2). Adjudication by CTEPH team consensus	83 % of patients on oral mono- or combination therapy; 24 % of sessions required vasopressors/ epoprostenol	13.8±9.72 months (1.15±0.81 years)	FC	II to IV	I to III†	RPE=64 % (33 % without symptoms) Deaths=1 in-hospital; 1 unrelated (cancer, during follow-up) Other=4 wire perforations
						6MWD	295±95	397±117†	
						mPAP	39±7	21±6†	
						CO/CI	3.5±0.8/ 2.2±0.5	4.3±1.2†/ 2.7±0.6†	
						PVR	763±308	284±128†	
						BNP	210±240	41±37†	

SD standard deviation, *CTEPH* chronic thromboembolic pulmonary hypertension, *PTE* pulmonary thromboendarterectomy, *PH* pulmonary hypertension, *BPA* balloon pulmonary angioplasty, *6MWD* 6-min walk distance, *mPAP* mean pulmonary artery pressure, *CO* cardiac output, *CI* cardiac index, *TPR* total pulmonary resistance, *PVR* pulmonary vascular resistance, *BNP* B-type natriuretic peptide, *proBNP* N-terminal pro-B-type natriuretic peptide, *peak* VO_2 peak oxygen consumption, *FC* functional class, *RPE* reperfusion pulmonary edema, *Mech. Vent* requiring mechanical ventilation, *PA* pulmonary artery, *NIPPV* non-invasive positive pressure ventilation, *ECMO* extracorporeal membrane oxygenation, *CMR* cardiovascular magnetic resonance imaging

Sustained hemodynamic responses at 1 year mean follow-up

† Denotes statistical significance with $p<0.05$

the procedures. However, in this study, there was a 10 % peri-procedural mortality with two deaths immediately or shortly after the first procedure. In this series, reperfusion pulmonary injury was less frequent at approximately 35 %.

Another study looked retrospectively at 20 patients with CTEPH deemed inoperable by a team of surgeons and radiologists based on distal, surgically inaccessible disease or the presence of comorbidities, who had BPA after undergoing cardiovascular MRI. Imaging was repeated on average 4 months after the last BPA procedure and multiple RV function parameters were compared. It was noted that after BPA, RV systolic and diastolic indices, RV ejection fraction, RV mass, and interventricular septal bowing all improved. This was also accompanied by hemodynamic improvements, increased 6MWD, reduced levels of BNP and improved WHO FC [39].

Taniguchi and colleagues [40•] also looked retrospectively at 53 CTEPH patients that were either assigned to BPA or PTE based on operability. The latter was assessed by a group of cardiologists and cardiovascular surgeons with CTEPH experience and was based on lesion distribution (distal segmental and subsegmental lesions), intimal thickening at the lesions, comorbid conditions, and patient age. Twenty-four patients underwent PTE and 29 had BPA using intravascular ultrasound. Approximately three BPA procedures were performed per patient over a few weeks, with approximately three vessels treated per session. The BPA group was significantly older, had longer median time from diagnosis to procedure, had lower pulmonary artery occlusion pressures on RHC, and had a much higher rate of vasodilator use compared to the PTE group. Post-BPA reperfusion lung injury was evaluated using chest CT within 6 h of the procedure, and in most cases, non-invasive positive pressure ventilation (NIPPV) was used pre-emptively (for at least 24 h) post-BPA to decrease its incidence. Hemodynamic results and FC improved in a similar fashion in both groups, but the incidence of post-procedure reperfusion lung injury was much higher in the BPA group (even after excluding asymptomatic patients with only CT evidence of reperfusion injury) and there was one additional death in the PTE group compared to the BPA group. These results were maintained at 1 year post-BPA and 5 years post-PTE [40•].

Based on these recent reports from multiple centers (summarized in Table 1), BPA may benefit a select group of CTEPH patients, improving clinically significant outcomes including hemodynamics. Nevertheless, despite the promising results from these studies, there are still some unanswered BPA-related questions. More specifically, despite multiple groups reporting on the procedure, the technique is not standardized. The number of vessels per BPA procedure, the number of total sessions, the time between these sessions, the use of vasodilator therapy, and its significance or the use of inotropes, have not been well established or studied. Moreover, there seems to be a high incidence of post-BPA lung injury, which in some cases, is diagnosed only radiographically but can frequently be symptomatic and severe, requiring mechanical ventilation. Whether these are related to reperfusion injury or mechanical vascular injury from BPA is also unclear. Follow-up has been limited to 1 year, and it is not known whether these results are maintained for longer periods of time, similar to results obtained by PTE [41].

In addition, the paramount question with BPA remains patient selection. Since operability is center-dependent, a case deemed inoperable at one site may be operable at another with more surgical experience. Therefore, the BPA patient selection based on inoperability as deemed by a single center has been an ongoing criticism of BPA since the early series. Unlike the BENEFIT [25••] and CHEST [26••] studies, the numerous BPA reports did not have cases adjudicated by high volume-experienced PTE centers. Moreover, the role of BPA in the current setting of approved medical therapy for inoperable CTEPH has not been evaluated and requires investigation. Accordingly, with these additional therapies introduced into the treatment of CTEPH, more work and challenges remain in properly identifying the best therapy when PTE is not an option.

Conclusions

Chronic thromboembolic pulmonary hypertension is an uncommon but possibly curable form of pulmonary hypertension that is under-recognized and may be more prevalent than currently thought. In recent years, there have been major advances in CTEPH treatment, including approval of medical therapy for persistent/recurrent CTEPH or inoperable CTEPH and the emergence of BPA as a viable option for select CTEPH patients not deemed amenable to PTE surgery. Despite these advances, and although global PTE experience is increasing, clinical barriers in CTEPH remain. Timely and accurate diagnosis followed by operability assessment by a medical team well experienced with the diagnosis and treatment of CTEPH remain key priorities.

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Compliance with Ethics Guidelines

Conflict of Interest Dr. Papamatheakis has received speaking honoraria by Actelion Pharmaceuticals. Dr Kim has received consultancy and speaking honoraria from Actelion Pharmaceuticals and Bayer HealthCare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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