Review

Pulmonary angioplasty: A step further in the continuously changing landscape of chronic thromboembolic pulmonary hypertension management

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A R T I C L E   I N F O

A B S T R A C T

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially fatal and frequently undiagnosed form of pulmonary hypertension (PH), classified within group 4 by the World Health Organization (WHO). It is a type of precapillary PH, which uncommonly develops as a peculiar sequel of acute pulmonary embolism due to the partial resolution of the mechanically obstructing thrombus with a coexisting inflammatory response from pulmonary vessels. CTEPH is one of the potentially treatable forms of PH whose current standard of care is surgical pulmonary endarterectomy. Medical therapy with few drugs in non-operable disease is approved and has shown improvement in patients' hemodynamic condition and functional ability. Recently, balloon pulmonary angioplasty (BPA) has shown promising results as a treatment option for technically inoperable patients, those with unacceptable risk-to-benefit ratio and in a case of residual PH after endarterectomy. Lack of meticulous CTEPH screening programs in post-pulmonary embolism patients leading to underdiagnosis of this condition, complex operability assessment, and diversity in BPA techniques among different institutions are still the issues that need to be addressed. In this paper, we review the recent achievements in the management of non-operable CTEPH, their outcome and safety, based on available data.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a subtype of pulmonary hypertension (PH) recognized as a separate entity within pulmonary arterial hypertension (PAH). CTEPH is a rare and potentially fatal complication of pulmonary embolism (PE) with a specific physiopathology and represents at least 19 % of patients with PH according to various registries [1–4]. The estimated overall annual incidence of CTEPH is 3–5 patients per 100,000 inhabitants [5]. Its frequency after pulmonary embolism has been shown in recent studies to vary between 0.4–3 % [6,7]. If untreated, long-term outcomes are relatively poor; 5-year survival rate of 30 % for those with a mean pulmonary arterial pressure (mPAP) > 40 mmHg and 10 % for those with mPAP > 50 mmHg [8,9]. Currently, pulmonary endarterectomy

(PEA) is the treatment of choice with an in-hospital mortality rate of 2.2 % for all eligible CTEPH patients at experienced centers [10]. PEA can potentially cure CTEPH disease, especially in cases with organized thrombi of the proximal branches of pulmonary arteries [11]. However, patient selection for PEA is a complex process, and based on a multidisciplinary team decision. Eligible patient rates vary wildly, even in expert centers with high volumes, ranging from 39 % to 88 % in recent reports [12].

Advances in medical therapy promote adjunctive drugs in CTEPH patients, especially for those with no surgical option or those with residual PH after PEA. To date, Riociguat, Macitentan, and subcutaneous Treprostinil are the only drugs proven by randomized control trials to be capable of improving the exercise capacity (6-min walking distance) of CTEPH patients [13–15]. The added value of targeted medical therapy –

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as well as the appropriateness of routine use – is still a matter of debate and calls for further trials and long-term outcome data [16,17].

Percutaneous balloon angioplasty is a minimally invasive technique routinely used as primary treatment for obstructive vascular disease in many conditions [18]. The first report of doing balloon pulmonary angioplasty (BPA) to treat CTEPH in a patient ineligible for PEA was published more than three decades ago [19]. In 2001, the first case series of BPA reported significant improvement of New York Heart Association class and 6-minute walking distance (6MWD) in 18 patients [20]. However, the high procedural and post-procedural complication rate (61 %) was discouraging for further studies. From then on, BPA had been particularly investigated and advanced in Japanese studies, which reported promising results in improving patients' hemodynamics, right ventricular (RV) systolic and diastolic function, respiratory and exercise capacity, and quality of life with fewer complications [21–23]. During the last few years, BPA refinement and development continued with improved outcome and safety data and currently carries a class IIb recommendation to treat inoperable CTEPH in the most recent European guidelines [24].

This manuscript reviews the diagnostic pathway of CTEPH and the various treatment options, especially the newer non-surgical strategies. The required knowledge to introduce a BPA program will be discussed, with a particular focus on patient selection and specificities of BPA for CTEPH patients.

2. CTEPH definition and physiopathology

PH was defined by European guidelines as a resting mPAP equal to or higher than 25 mmHg [24] and more recently by the 6th World Symposium on Pulmonary Hypertension as mPAP > 20 mmHg and pulmonary vascular resistance (PVR) ≥ 3 WU. CTEPH is a precapillary type of PH characterized by normal pulmonary artery wedge pressure ≤ 15 mmHg during resting right heart catheterization (RHC) and chronic thromboembolic evidence shown as mismatched perfusion defects in pulmonary arteries on computed tomographic pulmonary angiography (CTPA), lung perfusion scintigraphy or pulmonary angiography [25]. It is a rare, progressive pulmonary vascular disease that is usually the consequence of prior acute PE, with persistent obstruction of large to middle-sized arteries by organized thrombi. Fibrinolytic disorders, underlying hematological or autoimmune conditions, inflammation, and even infection likely play a substantial role [26,27]. Non-resolving PEs undergo firbrinotic transformation and cause partial or complete obstruction of large and middle-sized vessels, but micro-vessel diesase characterized by intimal proliferation and increased media thickness, often referred to as "microvascular remodelling", is now recognized as a contributing factor to PH in CTEPH [28]. However, the underlying mechanisms are not fully understood, and growing evidence indicates that small-vessel disease in obstructed territories is key to hemodynamic compromise, functional impairment, and disease progression, perhaps due to excessive collateral high-pressure systemic blood supply and increased shear stress [29].

Patients with CTEPH usually present with non-specific symptoms such as progressive dyspnea and exercise intolerance [12]. In more advanced disease, additional symptoms and signs related to RV dysfunction may be prominent, such as peripheral edema, exertional chest pain, or syncope. History of acute venous thromboembolic events before the onset of dyspnea may be absent in as many as 38 % of patients with surgically accessible disease. This should not dissuade from thinking about the diagnosis of CTEPH in patients with unexplained dyspnea [30], especially since post-PE screening programs are not usually recommended and implemented [31]. Clinical symptoms and, in particular non-resolving dyspnea, remain the main factor leading to suspicion and treatment of CTEPH [32]. Whenever PH is suspected, the distinction between CTEPH and other entities is crucial because CTEPH is the only entity potentially amenable to PEA or BPA.

3. CTEPH imaging and classification

Several imaging modalities find their place in the workup of suspected CTEPH (Fig. 1). Transthoracic echocardiography is a simple and effective means of assessing the right heart chambers and the probability of PH. RV hypertrophy (wall thickness >5 mm) and RV dilation are indicative of chronic RV loading and adaptive remodeling, and echocardiography can suggest elevated PVR before RHC [33]. According to the latest diagnostic algorithm from the European Society of Cardiology (ESC) [24], patients with intermediate or high probability of PH at echocardiography benefit from radionuclide ventilation-perfusion (V/Q) lung scintigraphy, which accurately detects suggestive abnormalities, typically large mismatched perfusion defects. Sensitivity and specificity are excellent (>90 %) with both planar V/Q, and V/Q single-photon computed tomography (SPECT) [34]. Additionally, due to its nearly perfect negative predictive value, V/Q can safely exclude CTEPH and avoid unnecessary additional diagnostic tests. On the other hand, in the presence of mismatched perfusion abnormalities, further diagnostic tests are required because of the limited specificity of V/Q scintigraphy.

CT pulmonary angiography has established itself as the principal non-invasive instrument to assess the pulmonary vasculature, with the ability to evaluate the pulmonary anatomy and cardiac morphology at the same time [35,36]. While the sensitivity of V/Q was long considered higher than that of CTPA for the detection of CTEPH, recent data show equivalent sensitivities for these two imaging tests, which has been attributed to technological improvements [3,37]. The sensitivity and specificity of CTPA to detect CTEPH findings are excellent at the main and lobar arterial segments (97.0 % and 97.1 %, respectively) and slightly lower at the segmental and subsegmental levels (85.8 % and 94.6 %) [38]. Besides the detection of typical CTEPH signs including increased right-to-left ventricular ratio, dilated main pulmonary artery, organized chronic emboli, peripheral tapering of pulmonary arteries, systemic collaterals, and mosaic attenuation pattern, CTPA has the potential to unveil alternative diagnoses (mimickers of CTEPH) such as systemic vasculitis, arterial sarcoma, fibrosing mediastinitis, or pulmonary veno-occlusive disease [39,40]. More recently, dual-energy CT systems have become available for clinical use, opening the door to a new era of combined morphological and functional vascular assessment. Dual-energy CT (Figs. 2,3 and 5) platforms acquire spectral X-ray attenuation data without additional radiation or iodine dose [41] and allow semi-quantitative evaluation of pulmonary perfusion [42,43], as well as blood volume (Fig. 3, panel b). Whereas iodine density maps show promising initial results as a surrogate marker of pulmonary perfusion [44], further evaluation with prospective studies is warranted to establish this technology as a clinical standard [45].

Recently, pulmonary magnetic resonance imaging has gained interest as a radiation-free alternative to other imaging techniques in CTEPH. It has limited spatial resolution compared to CTPA but offers the advantage of measuring cardiac and pulmonary hemodynamics. Drawbacks include the required level of training and expertise to perform it properly and its time-consuming nature [46,47].

Right heart catheterization is the final diagnostic procedure that will confirm PH with invasive hemodynamic assessment and remains the gold standard to diagnose PH. Care must be taken in patients with normal resting mPAP (< 20 mmHg) but high clinical or radiological suspicion of CTEPH because abnormal mPAP may become apparent only during exercise. This condition is named Chronic Thrombo-Embolic Disease (CTED), and its management remains poorly defined. RHC is usually combined with catheter-based pulmonary angiography, which helps determine the distribution and extent of thromboembolic burden, especially at the subsegmental level. Diagnostic angiography remains a mainstay in evaluating surgical accessibility, and the development of BPA restores the importance of accurate mapping of occlusive target lesions with transcatheter angiography. Findings include vessel narrowing (Fig. 4), webs and bands (Fig. 2), pouch defects, or occlusions
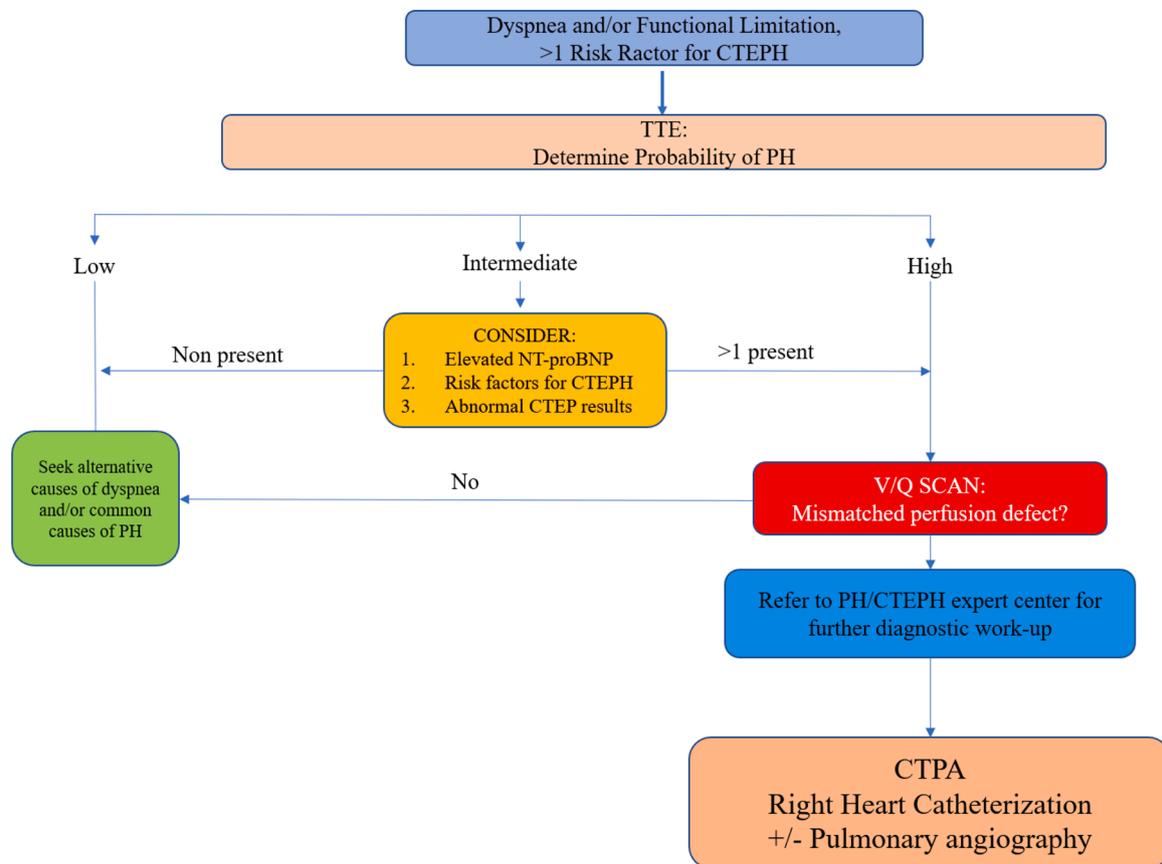
Fig. 1. Recommended diagnostic algorithm for chronic thromboembolic pulmonary hypertension (CTEPH). Adapted from the 2019 ESC pulmonary embolism guidelines [90]. TTE: Trans thoracic echocardiography, PH: Pulmonary hypertension, CTEP: Cardiopulmonary exercise testing, V/Q: ventilation/perfusion, PH: pulmonary hypertension, CTPA: computed tomography pulmonary angiography.

(Fig. 5). The latest proposed angiographic classification of pulmonary vascular lesions specifically tailored for BPA identifies five lesion types. Type A: ring-like stenosis lesion; type B: web lesion; type C: subtotal lesion; type D: total occlusion lesion; and type E: tortuous lesion [48]. The highest success rate and lowest complication rate of BPA were attributed to type A lesions followed by type B, while type D and E lesions had the least success rate, and the highest complication rate was noticed in type E lesions [49].

4. CTEPH management

Table 1 presents a comparison of available treatment strategies. Early referral for evaluation of pulmonary thromboendarterectomy is the rule for all patients and should not be delayed even with only mild symptoms. All patients with CTEPH should receive treatment because they are likely to develop progressive disease and have a high risk of dying from right heart failure [50]. A mPAP exceeding 30 mmHg is predictive of pulmonary vascular impairment and poor prognosis [51, 52]. Surgery involves deep hypothermic circulatory arrest and is the only definitive therapy for CTEPH. The decision to operate should be discussed in an expert center, primarily taking into account the four following parameters: the presence of hemodynamic and/or respiratory compromise; the surgical accessibility of the thrombi (main, lobar, or segmental arteries); the patient's comorbidities; and the willingness of the patient. However, it should be noted that a disproportionately high PVR associated with a limited extent of arterial occlusive disease is suggestive of micro-vessel disease, and such patients are unlikely to benefit from PEA or BPA. Radiologists play a crucial role during the preoperative workup by mapping both the severity and distribution of thrombi, characterizing lesion appearance, and the vessels' status

downstream. Fig. 3 shows a patient who was successfully treated with surgery. When PEA is not feasible, BPA – as a minimally invasive catheter-based technique – represents an acceptable alternative. Medical treatment is not curative, and its effects are relatively modest. Initiation of lifelong anticoagulant therapy to prevent recurrent venous thromboembolism and in situ pulmonary artery thrombosis is mandatory [53], usually with antivitamin K with a target INR between 2.0 and 3.0, but other options are currently available, including direct oral anticoagulants' (DOAC) administration. However, the latter have not been studied in detail for patients with CTEPH.

5. The rationale for pulmonary arterial angioplasty

Because lowering the pulmonary vascular resistance in CTEPH is critical, inoperable patients may benefit from endovascular treatment restoring blood flow in obstructed or stenotic arteries. The goal of BPA is to improve hemodynamics by increasing pulmonary perfusion and reducing RV afterload, eventually preventing RV failure. Over time, treatment with BPA induces RV reverse remodeling and improves systolic function [54]. In contrast to conventional angioplasty, BPA uses undersized balloons over guide wires, intending to relieve stenosis exclusively by breaking intraluminal webs and bands, without dissecting other vessel wall layers [48].

BPA should be offered to patients with inoperable CTEPH due to distal distribution of vascular obstructions; those with a poor risk-to-benefit ratio for surgery (e.g., few lesions but severe cardiac consequences, significant comorbidities); those with recurrent or persistent PH after surgical PEA; patients necessitating rescue angioplasty after early failure of PEA [55]. Another indication can be refractoriness to medical therapy with contraindication to surgery. Because of technical
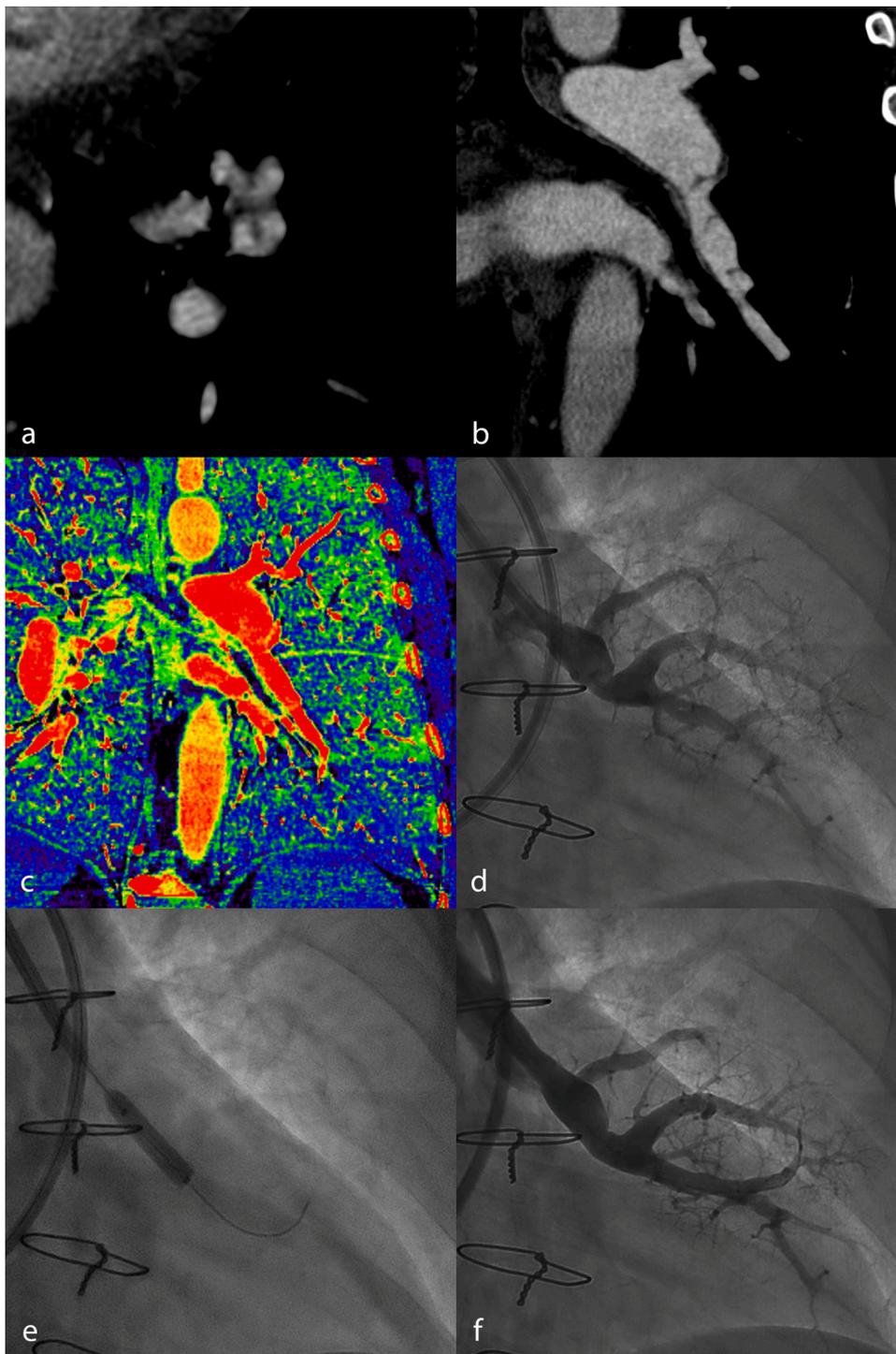
Fig. 2. Dual-energy CT pulmonary angiography shows several webs in the left lower lobe's anterior and lateral segmental arteries on axial (**a**) and coronal reformatted (**b**) images. Coronal reformatted iodine density map reveals impaired perfusion in the left lower lobe (**c**). Selective transcatheter pulmonary angiography shows incomplete opacification of the anterior segmental artery due to webs (**d**). Following treatment with balloon pulmonary angioplasty (**e**), a final angiogram shows the absence of stenosis (**f**).

limitations, BPA should not be considered in total unilateral occlusion or large central clots [48].

6. Target groups, indications, contraindications

Eligibility assessment is a challenging and multifactorial task requiring a multidisciplinary team of CTEPH experts whose members may vary depending on local practice. Core members may include PH pulmonologists, diagnostic cardiologists and radiologists, interventional radiologists/cardiologists. Including cardiothoracic surgeons is an attractive means of providing a balanced and thorough multidisciplinary discussion of tailored treatment. Depending on patients' ability

to receive general anesthesia, input from anesthesiologists can influence treatment decisions. Whenever a BPA program is started, a concomitant PEA track should be available and discussed in the multidisciplinary team since PEA remains the method of choice for eligible patients with CTEPH. Furthermore, due to the absence of systematic post-PE screening programs, PH management teams should closely collaborate with pulmonary embolism response teams since most CTEPH patients are identified through acute PE referrals. Although consensus regarding PEA and BPA's merits gradually develops, there may still be considerable variability in practice across institutions and nations. Patients who have the highest benefit from BPA are those with an unfavorable risk/benefit ratio for PEA, more distal location of obstructive thrombotic lesions, and
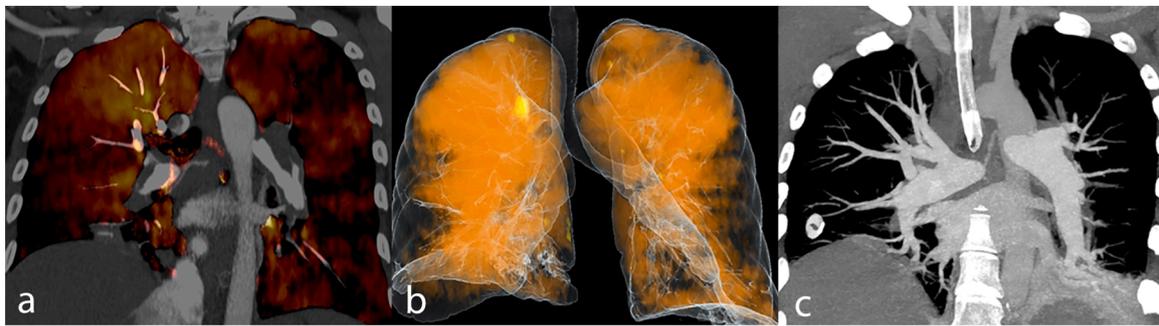
Fig. 3. Dual-energy CT pulmonary angiography displayed as an iodine density overlay (**a**), and total pulmonary blood volume image (**b**). Extensive bilateral eccentric mural thrombosis of the central pulmonary arterial branches (**a**) with corresponding decreased lung perfusion areas (**a** and **b**) are seen. Post endarterectomy CT pulmonary angiography reveals patency of the branches (**c**); accompanying reperfusion edema of the left lower lobe is also noted.

persistent or recurrent PH after previous endarterectomy. Advanced age itself is not considered a contraindication for a BPA procedure; a small-sample study of aged CTEPH patients (median age of 81) demonstrated safe and efficacious outcomes [56]; evidently, elderly patients might carry a larger risk of periprocedural complications and mortality. As expected, Patients with poorer baseline hemodynamic status may have a higher complication risk.

7. Technical considerations of pulmonary angioplasty

Pulmonary angioplasty procedural approaches may vary between different centers. The usually practiced technique is as follows: typically, the procedure begins with a general or selective angiogram to determine the extent and distribution of thromboembolic lesions. In our practice, selective angiograms are guided by CTPA to save time and contrast media. A pre-shaped 6-French guiding catheter is introduced through a long 6, 7, or 8-French sheath inserted through the femoral or jugular vein, advanced to reach the pulmonary trunk, and guided to the right or left main pulmonary artery. In the next step, a 0.014 or 0.018-inch guidewire is used to cross the target lesion, and a balloon catheter of appropriate size is selected to dilate the vessel. Careful verification of proper guidewire placement is mandatory before balloon inflation. For initial treatments, undersized balloons are used, whereas larger balloons can be employed in subsequent sessions according to the reference vessel diameters provided by angiography. Generally, multipurpose type catheters are suitable for the right lung's segmental arteries, whereas Amplatz type catheters are appropriate for segmental arteries of the left lung. The lobe exhibiting the least perfusion, as identified by lung perfusion scintigraphy, is commonly treated first. During the procedure, intravenous heparin is administered to target an activated clotting time of 200 s, and oxygen is supplemented to keep the saturation level above 95 %. If the lesions being treated are located in the lower lobes, the patient is asked to hold his breath or inhale deeply to stretch the pulmonary arteries and help the guidewire reaching its target. Unlike PEA, BPA does not require general anesthesia. The best therapeutic result is obtained through multiple sessions of angioplasty 3–7 days apart. Usually, 4–6 different BPA procedures per patient are necessary to achieve complete treatment. Initial experiences advocated limiting BPA to one major vessel (e.g., lobar or segmental) per session or two small vessels (e.g., subsegmental). We still apply these rules for the first session and in patients with a high baseline pressure (>40 mmHg). Because extensive reperfusion is expected to enhance BPA's therapeutic effect, most interventionists recommend treating the most remarkable webs in the lower lobes first. Like many procedures, the fluoroscopy duration limit is 60 min per session. Periprocedural predictive factors of successful reperfusion, including venous return, are still debated and under evaluation. Furthermore, factors associated with post-reperfusion edema and the role of systemic supply are unknown.

8. Evidence for pulmonary angioplasty

Table 2 demonstrates the largest (including 50 patients or more) studies so far. The most extensive case series reported to now is a seven-center Japanese registry by Ogawa et al. of 1408 procedures for 308 patients. Follow-up data from 196 patients revealed a significant reduction in mPAP from 43 to 24 mmHg after the final BPA session and 22 mmHg at follow-up evaluation, accompanied by a significant decline in the necessity for concomitant oxygen and medical treatment. The overall complication rate was 36 %, and the three-year survival rate was 94.5 % [57]. Aoki et al. also evaluated the long-term effect and outcome of pulmonary angioplasty in 84 inoperable CTEPH patients [58]. Results showed that BPA decreased the mPAP to almost normal levels (from 38 to 25 mmHg) and led to significantly improved PVR, BNP levels, and accordingly 6MWD. Most notably, the plasma BNP levels, hemodynamics amelioration and exercise capacity persisted during the long-term follow-up period (43 ± 27 months). For 77 patients who completed BPA treatment, the 5-year survival rate reached to 98.4 % [58].

A study assessed the outcome of inoperable CTEPH patients treated with BPA and those managed with PEA, and the results indicated similar safety and efficacy in both groups [59]. Of note, the mortality rates were 3.4 % and 8.3 % in BPA and PEA patients, respectively.

Another same-year study by Inami et al. compared the outcomes of medical and invasive (BPA or PEA) approaches as CTEPH patients therapy. While the interventional (BPA or PEA) group had a significantly worse baseline hemodynamic status, they had significantly higher 5-year survival rates than the medically-treated group (98 % versus 64 %, respectively; $p < 0.0001$). Although in the interventional group the effect on total pulmonary resistance (TPR), 6MWD, and plasma BNP levels were similar for PEA and BPA, the surgical procedure resulted in a greater mPAP reduction [60]. Recently, Sumimoto et al. observed substantial RV reverse remodeling following BPA treatment in 45 CTEPH patients assessed with speckle-tracking echocardiography, as well as hemodynamic improvement [61], further supporting the use of BPA. Of note, the improvement of subjective symptoms and pulmonary hemodynamics after BPA is not immediate, and a certain amount of time is needed before the maximal therapeutic effect is seen [21]. Recently, a study evaluated the Electrocardiographic (ECG) parameters associated with RV hypertrophy in 60 CTEPH patients before and after BPA procedures, which showed decreased mPAP and an improvement in ECG findings related to RV hypertrophy. By comparing ECGs and mPAP measurements, the authors found that amplitude decrease of the S and R waves (lead V6) and P wave (lead II) before and after BPA strongly correlated with mPAP decline. Also, at 6-month follow-up, a decrease in the R wave amplitude (V1 lead) and S wave (V5 lead) implied a better functional status [62].

Despite a substantial body of literature related to contemporary BPA practice, the available data is still limited, based on non-randomized
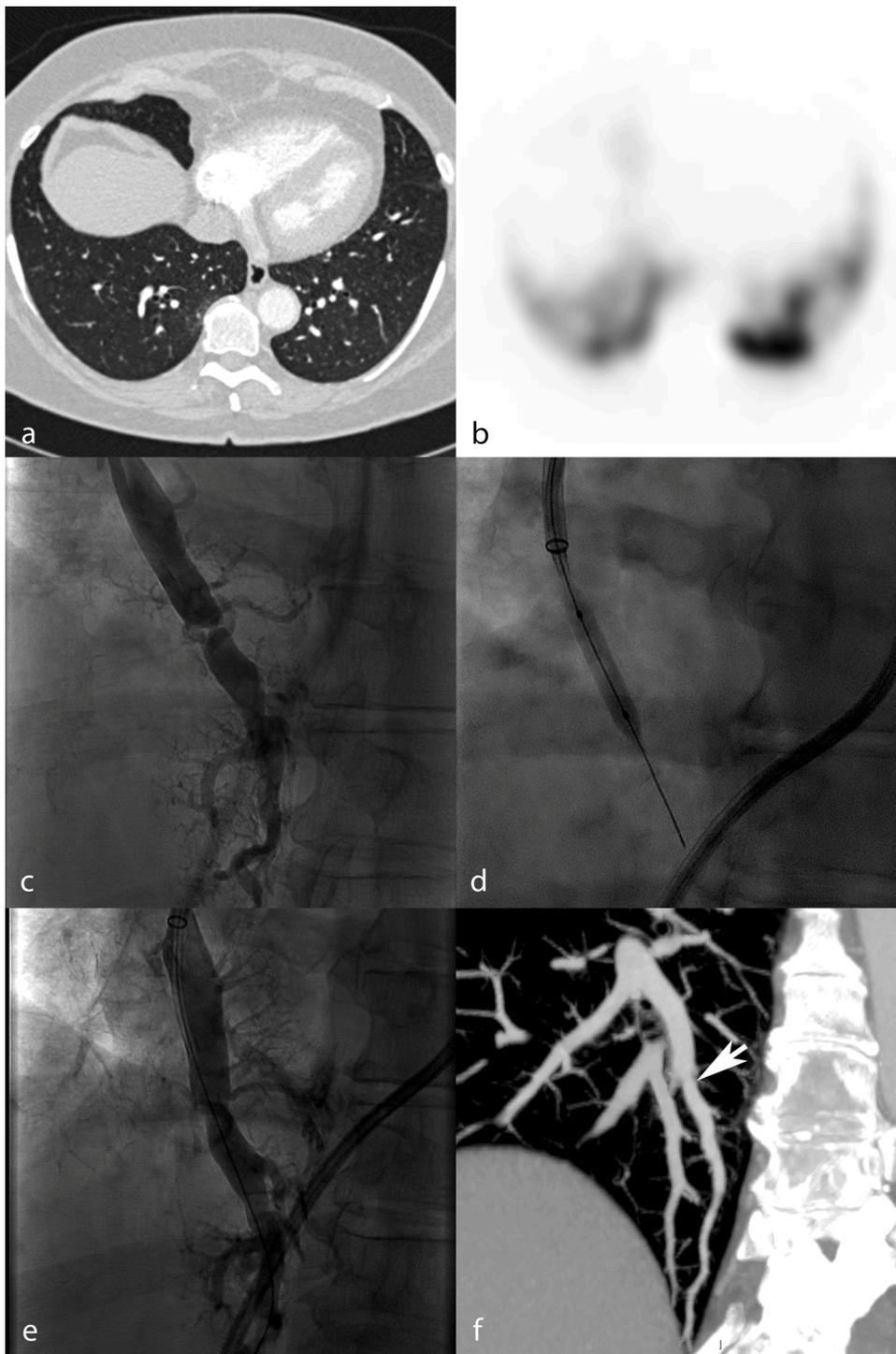
Fig. 4. Chest CT in the lung window (a) and corresponding lung scintigraphy (b) showing bilateral perfusion defects sparing the left posterior basal segment in a patient with a history of acute pulmonary embolism one year prior, and documented precapillary pulmonary hypertension. One of multiple stenoses (c) at transcatheter angiography consistent with CTEPH. Balloon pulmonary angioplasty of the right posterior basal artery (d) and post-angioplasty angiogram shows substantial stenosis reduction. Follow-up CT pulmonary angiography in oblique maximum intensity projection (MIP) reformat persistent stenosis relief in the right posterior basal artery (white arrow) 2 years later.

series. No randomized-controlled trials comparing PEA with BPA currently exist, and consequently, BPA is mostly applied in patients deemed non-eligible for surgery or having recurrent PH after PEA. Ont the other hand, current research attempts to fill gaps in the literature related to BPA vs. medical therapy. First and foremost, the Riociguat Versus Balloon Pulmonary Angioplasty results in Non-operable Chronic ThromboEmbolic Pulmonary Hypertension (RACE) trial are eagerly awaited. In this trial, patients were randomized to receive either BPA or Riociguat, with a 26-week follow-up. According to preliminary data presented at the European Respiratory Society (ERS) 2019 conference [63], PVR was reduced by almost 60 % in the BPA arm versus 32 % in the Riociguat arm (p < 0.0001). While BPA appears to be more efficient than

Riociguat, these results open the door to further research, including the investigation of combined therapy. This promising hybrid therapy could act as a "bridge" therapy before BPA to improve patients' hemodynamic condition and potentially diminish post-procedural complication risks or be used after BPA in patients whose hemodynamic response is not satisfactory. While the combination has been successfully described [64], other reports of worsening of clinical and hemodynamic status [65] mandate the issue to be systematically evaluated.

Secondly, the multicentre randomized controlled trial of balloon pulmonary angioplasty and Riociguat (MR BPA) trial [66] also randomized inoperable CTEPH patients to receive either BPA or Riociguat, with a 12-month follow-up. It will hopefully shed more light on the
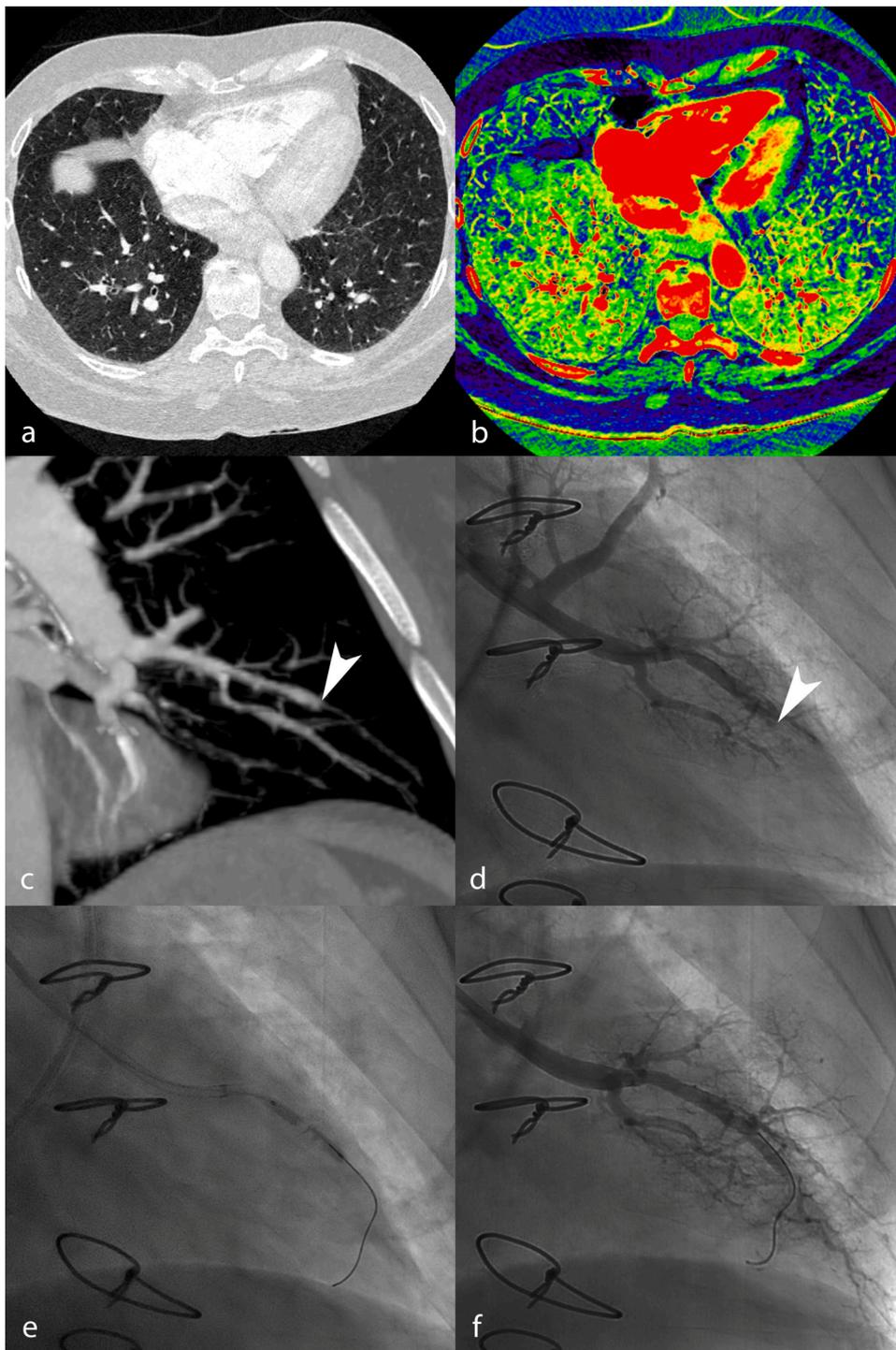
Fig. 5. Dual-energy CT pulmonary angiography in the lung window **(a)** shows virtually indiscernible mosaic attenuation, much better depicted on the iodine density map **(b)** where perfusion defects in the right middle lobe, lingula, and left inferior lateral segments are seen. A coronal maximum intensity projection (MIP) in the standard window **(c)** shows a subsegmental occlusion (white arrowhead), confirmed upon transcatheter angiography **(d)**. Balloon pulmonary angioplasty **(e)** and subsequent selective angiography with restored parenchymal perfusion **(f)**. Note that ideally, the wire guide **(e)** should cross the lesion and be straight in the vessel under treatment, which was not the case in this example where the occlusion was too long to be crossed all at once. This is why the angioplasty was performed with suboptimal wire positioning.

appropriateness of endovascular treatment for CTEPH.

9. Combined BPA-PEA, rescue BPA, and BPA application in non-hypertensive chronic thromboembolism conditions

Wiedenroth et al. proposed combined BPA-PEA as a novel option for highly selected high-risk CTEPH patients with inoperable contralateral pulmonary artery obstructions. Candidates underwent BPA treatment on the inoperable lung in the middle of the rewarming phase of the cardiopulmonary bypass [67].

There have been suggestions for "Rescue BPA" in a few case reports in terms of stabilization before PEA in patients with promptly worsening

heart failure [68,69].

Chronic thromboembolic disease (CTED) contrasts from CTEPH by the absence of PH at rest. Curiously, a small study assessed BPA as a potential treatment for these patients, during which 35 BPA interventions were performed in 10 consecutive CTED patients. Follow-up 6 months after the last intervention showed improvement in the PVR, pulmonary arterial compliance, functional class and 6MWD [70].

10. Safety and complications of BPA

Possible BPA procedure complications consist of pulmonary artery injury, which may directly or indirectly result in pulmonary edema

Table 1

Comparison of treatment strategies for chronic thromboembolic pulmonary hypertension (CTEPH).

Life-long anticoagulation is required regardless of other therapies			
	Medical therapy	BPA	PEA
Indication	Inoperable patients	Technically inoperable	Recommended first-line treatment All operable patients with CTEPH
	Residual obstruction	Unfavorable risk to benefit ratio	
		Patients who failed to benefit from PEA	
Evidence	Small RCTs	Observational data and small RCT	Retrospective studies and prospective registries
Hemodynamic effect (PVR difference [dynes $\times$ s $\times$ cm^{-5}])	30 % reduction [226] [13]	60 % reduction [>500] [21–,22, 23,63]	65 % reduction [>500] [85]
Clinical effect (6MWD increase) [m]	40	50 to 70	>100
Long-term outcome	Unknown; sustained effect over 2 years	Limited data: 85–98% 5-year survival	Limited data; 75–90% 5-year survival

6MWD: 6-minute walking distance, BPA: Balloon Pulmonary Angioplasty, PEA: Pulmonary Endarterectomy, PVR: Pulmonary Vascular Resistance, RCT: Randomized Controlled Trial.

(reperfusion lung edema), hemorrhage, pleural effusion, and pseudoaneurysm formation. Peri or post-procedure coughing or hemoptysis would be alarming signs. Radiation and contrast exposure to the operator and patient is another continuing concern with BPA.

Inami et al. assorted Pulmonary Artery Injury (PAI) into wire perforation, high-pressure perfusion injury, pulmonary artery rupture, and pulmonary artery dissection [71]. The most frequent procedural arterial injury is wire perforation, which can be hampered by avoiding too deep insertion of guidewires into lesions without distal visibility and stabilizing the guiding catheter. These complications can be asymptomatic or cause signs and symptoms such as coughing, hemoptysis, tachycardia, and increased PAP. High-pressure perfusion injury is mainly seen in patients with severe baseline pulmonary hypertension (mPAP > 50 mmHg), and is induced by sudden exposure of distal pulmonary branches and tissue to the high proximal PAP following balloon dilation. Applying the proposed pressure-wire technique can assist in deterring this complication. The high-pressure injury may also follow forceful and/or rapid injection of contrast material preventable by gentle injection. Arterial rupture commonly occurs due to the use of inappropriately-selected balloons or overdilation of the stenotic point. Inami et al. also introduced a Pulmonary Edema Predictive Scoring Index (PEPSI) based on the total change in pulmonary flow grade and baseline pulmonary vascular resistance to predict the risk of reperfusion pulmonary edema [72]. Also, they evaluated the outcome for a combination of PEPSI and pressure-wire technique in a study [73]. Kurzyna et al. demonstrated that targeting bands, webs, and rings while avoiding total occlusions using smaller balloons and guidewires with soft tips significantly reduces the complication rate (hemoptysis and reperfusion injury) [74].

Once pulmonary artery injury occurred, timely and appropriate management is key. The recommended methods are vaso-occlusion using a metallic coil or bio-absorbable gelatin, stent-graft delivery, and prolonged balloon sealing [75]. In case of bleeding and high clotting time, slow protamine infusion may be initiated. As mentioned above, type A and B lesions have the lowest, while type E lesions have the highest complication rate.

11. Local effects of pulmonary angioplasty

Angiographically, treated stenoses may remain apparent immediately after BPA because the re-expansion of vessel diameter can evolve [76]. Pre-procedure and immediate post-procedure PVR, as well as NT-proBNP, are long-term predictors of procedure prognosis [77,78]. Of interest, a study showed hemodynamic improvement and PVR reduction

Table 2

Overview of available evidence related to balloon pulmonary angioplasty-largest studies including 50 or more patients.

First Author, Year, [Ref]	No. of patients	No. of procedures	Baseline mPAP (mmHg)	Post BPA mPAP (mmHg)	Baseline PVR (WU)	Post BPA PVR (WU)	6MWD Improvement (m)	Long Term Survival	Acute Mortality Rate
Mizoguchi, 2012 [22]	68	255	45.4 ± 9.6	24 ± 6.4	11.8 ± 4.6	4.1 ± 1.9	296 to 368	97% at 2.2 ± 1.4 yrs.	1 RHF
Inami, 2014 [60]	68	213	42.9	25	12.5	5.8	349 ± 130–424 ± 111	98.5% at 2 yrs.	1.47 %
Inami, 2014 [73]	103	350	41	21	8.7	2.7	360 to 420	NR	0.97 %
Shimura, 2015 [86]	110	423	43	26	8.1	4.2	NR	100 % at 1.97 yrs.	0
Kawakami, 2016 [49]	97	500	45.1 ± 10.8	23.3 ± 6.4	12 ± 5.7	3.9 ± 1.9	276.3 ± 123.2 359.3 ± 91.9	NR	4%
Ogo, 2016 [91]	80	385	42 ± 11	25 ± 6	11 ± 5.3	5.1 ± 2.3	372 ± 124–470 ± 99	NR	0
Olsson, 2017 [70]	56	266	40 ± 12	33 ± 11	7.4 ± 3.6	5.5 ± 3.5	358 ± 108–391 ± 108	NR	1.8 %
Kurzyna, 2017 [74]	56	157	50.7 ± 10.8	35.6 ± 9.3	10.3 ± 3.7	5.9 ± 2.8	306 ± 153–397 ± 123	94.6 % at 1 and 2 yrs.	5.4 %
Ogawa, 2017 [57]	308	1408	43.2 ± 11	24.3 ± 6.4	10.7 ± 5.6	4.5 ± 2.8	318.1 ± 122.1–401.3 ± 104.8	96.8% at 1–2 yrs. 94.5% at 3 yrs.	2.6 %
Aoki, 2017 [58]	77	424* (no of pts:84)	38 ± 10	25 ± 6	7.3 ± 3.2	3.8 ± 1.0	380 ± 138–486 ± 112	98.4 % at 5 yrs.	0
Kimura, 2017 [87]	67	405	39.3 ± 11.0	20.0 ± 4.2	9.7 ± 6.8	3.4 ± 1.5	322 ± 109–446 ± 104	NR	0
Moriyama, 2018 [88]	53	~318	37.2 ± 11.2	19.4 ± 4.4	~7.0 ± 5.5	~3.0 ± 1.5	351.4 ± 94.2–432.2 ± 90.8	NR	0
Brenot, 2019 [89]	184	1006	43.9 ± 9.5	31.6 ± 9.0	7.5 ± 2.8	4.1 ± 2.2	396 ± 120–441 ± 104	95.1% at 3yrs	3.8 %

on the untreated contralateral side in a series of unilateral BPA sessions [79].

The histological mechanisms by which BPA improves hemodynamics are still being studied; few case reports available from pathological specimens suggest arterial lumen dilation by forcing the organized thrombus to one side, whether accompanied by vessel wall dissection and partial detachment of lumen thrombus [80], or by incision and compression of thrombi without dissection [81]. The former phenomenon stresses the importance of applying smaller balloons in initial sessions to lower the risk of wall injury and complications. Another study analyzed the occlusive lesions using gray-scale and virtual histology (VH) intravascular ultrasound (IVUS) pre-and post-BPA, which revealed an increment in lumen area without expanding the total vessel area. The IVUS-VH technique has the power for in vivo characterization of tissue composition and derived color-coded images suggest variable susceptibility of the organized thrombus to imposed mechanical compression. Therefore, it helps evaluate lesion vulnerability to the applied compression and potentially predict the expected BPA effect [82].

Maruoka et al. investigated the applicability of three-dimensional fractal analysis using 99mTc-MAA SPECT pulmonary perfusion scintigraphy as a non-invasive tool for assessment of BPA results in CTEPH patients. The increased uptake volume in both lungs and lesser heterogeneity on SPECT images were associated with the lower mPAP in CTEPH patients. In post-BPA SPECT, they found fractal analysis to be discriminative between BPA success and failure with 75 % sensitivity, 79 % specificity, 78 % accuracy, and an area under the receiver operating characteristic curve of 0.85 [83].

With the evolution of BPA and its growing application, novel techniques and devices are being innovated to predict BPA outcomes before and after the procedure, diminish complication rates and eventually amend results. In this regard, Miyazaki et al. invented a radiation protection sheet supported by an acrylic table to minimize radiation exposure of the operator and medical staff during BPA procedures [84].

12. Conclusion

On the road to establishing a standard therapy option, the BPA technique should be unified worldwide. Expert CTEPH centers with all treatment options available on-site should be designated, and proper training programs be designed. The most suitable therapeutic option for each patient should be determined by multidisciplinary discussion to reduce the complication rates and maximize patient benefits. While PEA remains the preferred therapy, BPA, with its promising results, brings bright horizons ahead.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

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