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AHA SCIENTIFIC STATEMENT

Status and Future Directions for Balloon Pulmonary Angioplasty in Chronic Thromboembolic Pulmonary Disease With and Without Pulmonary Hypertension: A Scientific Statement From the American Heart Association

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ABSTRACT: Balloon pulmonary angioplasty continues to gain traction as a treatment option for patients with chronic thromboembolic pulmonary disease with and without pulmonary hypertension. Recent European Society of Cardiology guidelines on pulmonary hypertension now give balloon pulmonary angioplasty a Class 1 recommendation for inoperable and residual chronic thromboembolic pulmonary hypertension. Not surprisingly, chronic thromboembolic pulmonary hypertension centers are rapidly initiating balloon pulmonary angioplasty programs. However, we need a comprehensive, expert consensus document outlining critical concepts, including identifying necessary personnel and expertise, criteria for patient selection, and a standardized approach to preprocedural planning and establishing criteria for evaluating procedural efficacy and safety. Given this lack of standards, the balloon pulmonary angioplasty skill set is learned through peer-to-peer contact and training. This document is a state-of-the-art, comprehensive statement from key thought leaders to address this gap in the current clinical practice of balloon pulmonary angioplasty. We summarize the current status of the procedure and provide a consensus opinion on the role of balloon pulmonary angioplasty in the overall care of patients with chronic thromboembolic pulmonary disease with and without pulmonary hypertension. We also identify knowledge gaps, provide guidance for new centers interested in initiating balloon pulmonary angioplasty programs, and highlight future directions and research needs for this emerging therapy.

Key Words: AHA Scientific Statements ■ angioplasty, balloon ■ endarterectomy ■ hypertension, pulmonary ■ pulmonary embolism ■ thromboembolism

Chronic thromboembolic pulmonary disease (CTEPD) with pulmonary hypertension (PH), also known as CTEPH, is the most feared long-term complication after an acute pulmonary embolism (PE).[1] The incidence of CTEPD with PH is estimated at 2% to 3% of all acute PEs.[1–5] This disease process is characterized by persistent intraluminal pulmonary vascular obstruction resulting from incomplete clot resolution and fibrotic transformation of residual clots in the pulmonary vasculature.[1] Patients often report lifestyle-limiting exercise intolerance and may progress to right-sided heart failure and death. Historically, pulmonary endarterectomy (PEA), also referred to as pulmonary thromboendarterectomy in the literature, an open surgical procedure performed with deep hypothermic circulatory arrest during which a surgeon manually removes these chronic thrombi, is potentially curative and thus has been the cornerstone of treatment.[6,7] PEA remains

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the treatment of choice for technically operable patients who are good surgical candidates evaluated at expert CTEPH centers. However, it is offered to only a subset of such patients because of various patient, anatomic, and institutional factors.[8,9] More recently, percutaneous revascularization of pulmonary vascular obstructions with balloon pulmonary angioplasty (BPA) has emerged as a potential treatment option for individuals who are unsuitable candidates for PEA or have residual obstruction after PEA.[10–13]

Although BPA has the potential to positively affect many patients, proper promulgation of this therapy accounting for the risk-benefit profile of the procedure for individual patients has yet to be formally addressed by any group of experts. Adoption of BPA to date has been driven primarily by personal peer-to-peer contact and training. There is a need for a consensus document that details necessary personnel/expertise, patient selection, preprocedural workup, and procedural performance for safe and effective BPA.

This consensus document represents a state-of-the-art opinion from key thought leaders aimed at addressing the gaps in the current clinical practice of BPA. More specifically, we summarize the current status and consensus opinion for BPA in the care of patients with CTEPD with and without PH. We also discuss potential knowledge gaps and research needs for this emerging therapy.

ANATOMICAL CONSIDERATIONS

The main pulmonary artery divides into the right main pulmonary artery and left main pulmonary artery. At the right lung hilum, the pulmonary artery divides into a superior trunk (also called the truncus anterior) and an inferior trunk (called the interlobar artery because it runs in the interlobar fissure parallel to the bronchus intermedius). The left main pulmonary artery is shorter than the pulmonary artery and is a direct posterior continuation of the main pulmonary trunk. It has a variable branching pattern and does not divide like its counterpart on the right and merely runs in the interlobar fissure on the left side.[14,15]

Each lung is divided into 10 segmental zones, with the main segmental origin coming from either the superior or inferior trunk on the right side and the left main pulmonary artery interlobar trunk on the left side. Segmental anatomy is similar in both lungs with a few caveats:

1. The left upper lobe A1 (apical) and A2 (posterior) segments are often supplied as a common segmental artery (left A1+2) and arise directly off the left main pulmonary artery.
2. Left A4 and A5, although anatomically similar to the right lung, supply the lingula as opposed to a true middle lobe; these are categorized as superior and inferior segments as opposed to medial and lateral segments on the right.
3. Left A7 segment is diminutive, given the presence of a cardiac silhouette, and is often supplied as a subsegmental branch off the left A8 segment.

Figure 1 describes the anatomical features and includes suggested nomenclature for individual lung segments. Nonselective invasive pulmonary angiogram (NS-iPA) performance and interpretation in CTEPH are subject to interobserver variability about anatomical disease level assessment. For operability assessment, disease level is routinely assessed with NS-iPA or computed tomography pulmonary angiogram (CTPA), depending on local center preference and experience. CTPA has excellent diagnostic accuracy for main, lobar, and segmental disease locations but lower accuracy for subsegmental disease.[16] NS-iPA is therefore needed to complete an operability assessment when CTPA and ventilation-perfusion scans are inconclusive. When NS-iPA is an inconclusive initial modality for disease-level assessment, a complementary CTPA assessment may identify nonobstructive clot adherent to the wall in the proximal lobar branches. Other options in this setting include selective invasive pulmonary angiography (S-iPA) and intravascular ultrasound assessment or optical coherence tomography. Figure 2 summarizes the anatomical disease level classification suggested by this group for routine clinical practice. In the BPA era, NS-iPA is also used as a reference, providing a road map for selective segmental trunk cannulation.[17]

Best Practices for NS-iPA Performance

This section summarizes our suggested best practices for NS-iPA performance and interpretation. With the use of digital subtraction, 2 angiograms are performed for each lung during deep inspiratory breath holds in orthogonal projections.[17,18] Orthogonal imaging is achieved through the following:

1. Frontal and lateral projections (left anterior oblique 0, cranial 0, and left anterior oblique 70–90 [or right anterior oblique 70–90], cranial 0) or
2. Ipsilateral oblique (right anterior oblique 20–45, left anterior oblique 20–45 angulation for right and left lung, respectively) and contralateral oblique projections (left anterior oblique 40–60 and right anterior oblique 40–60 angulation for right and left lung imaging, respectively).

Frontal and lateral projections minimize perfusion zone overlap. However, in the case of steep lateral angulation, the radiation dose is higher for both the patient and operator, rendering these projections less desirable as a road map for BPA. In contrast, although vessel and perfusion zone overlap is greater with ipsilateral and contralateral oblique projections (Figure 1), they are associated with a lower radiation dose and less scatter, rendering them more desirable as reference road maps during BPA. Optimal views for necessary angiographic information

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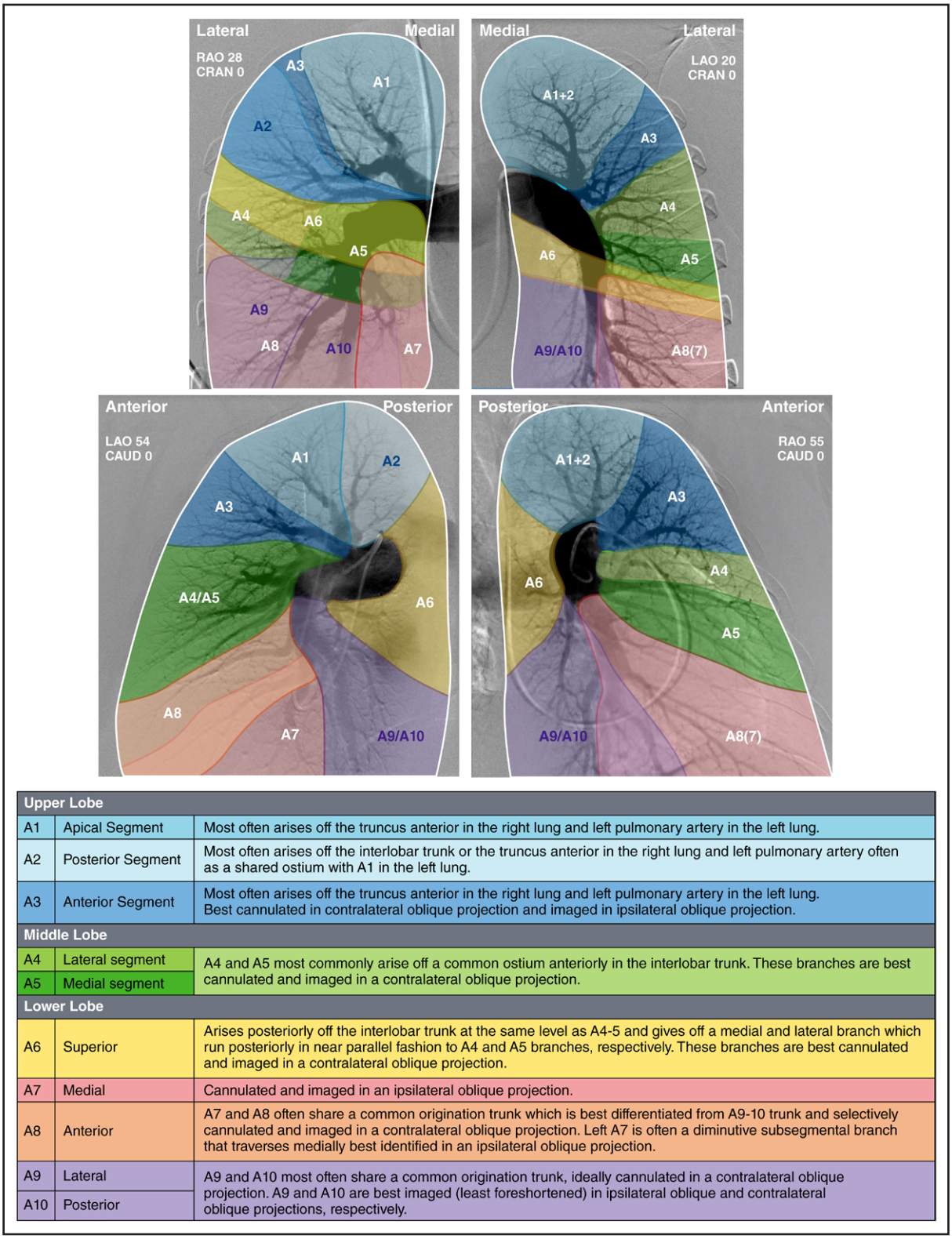


Upper Lobe		
A1	Apical Segment	Most often arises off the truncus anterior in the right lung and left pulmonary artery in the left lung.
A2	Posterior Segment	Most often arises off the interlobar trunk or the truncus anterior in the right lung and left pulmonary artery often as a shared ostium with A1 in the left lung.
A3	Anterior Segment	Most often arises off the truncus anterior in the right lung and left pulmonary artery in the left lung. Best cannulated in contralateral oblique projection and imaged in ipsilateral oblique projection.
Middle Lobe		
A4	Lateral segment	A4 and A5 most commonly arise off a common ostium anteriorly in the interlobar trunk. These branches are best cannulated and imaged in a contralateral oblique projection.
A5	Medial segment	
Lower Lobe		
A6	Superior	Arises posteriorly off the interlobar trunk at the same level as A4-5 and gives off a medial and lateral branch which run posteriorly in near parallel fashion to A4 and A5 branches, respectively. These branches are best cannulated and imaged in a contralateral oblique projection.
A7	Medial	Cannulated and imaged in an ipsilateral oblique projection.
A8	Anterior	A7 and A8 often share a common origination trunk which is best differentiated from A9-10 trunk and selectively cannulated and imaged in a contralateral oblique projection. Left A7 is often a diminutive subsegmental branch that traverses medially best identified in an ipsilateral oblique projection.
A9	Lateral	A9 and A10 most often share a common origination trunk, ideally cannulated in a contralateral oblique projection. A9 and A10 are best imaged (least foreshortened) in ipsilateral oblique and contralateral oblique projections, respectively.
A10	Posterior	

Figure 1. Lung perfusion zones, key anatomical features, and suggested nomenclature for individual lung segments.
CAUD indicates caudal; CRAN, cranial; LAO, left anterior oblique; LPA, left pulmonary artery; and RAO, right anterior oblique.

will vary according to the patient's anatomical configuration. This factor, in addition to local expertise and practice patterns, should govern which approach is used at each individual center. Using biplane angiography for NS-iPA and S-iPA, if available, can also reduce total contrast dose while simultaneously reducing radiation dose.

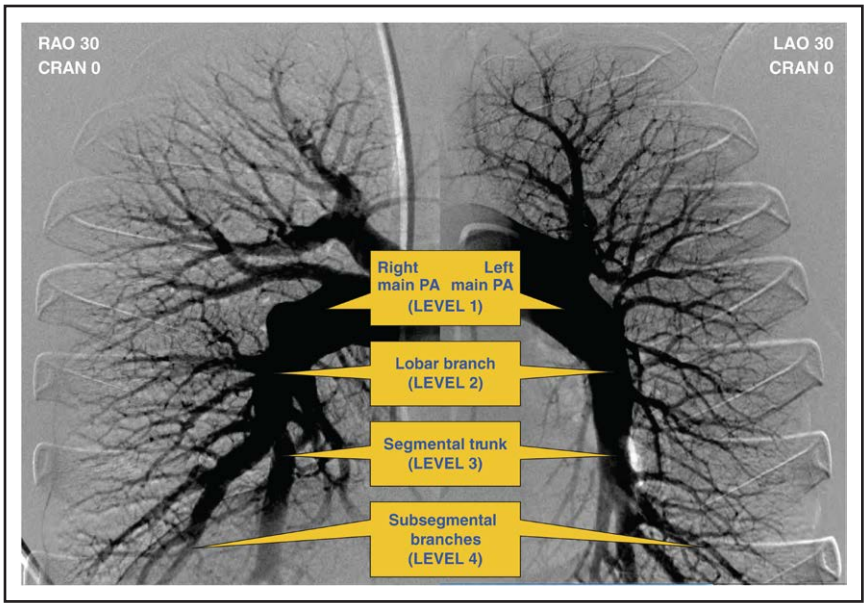


Figure 2. Anatomical disease level classification on NS-iPA for routine clinical practice.
CRAN indicates cranial; LAO, left anterior oblique; NS-iPA, nonselective invasive pulmonary angiogram; PA, pulmonary artery; and RAO, right anterior oblique.

Best Practices for NS-iPA Performance Interpretation

We propose a systematic perfusion zone methodology for NS-iPA interpretation (Figure 1). In principle, anteroposterior and ipsilateral oblique projections help differentiate between medial and lateral structures, whereas lateral and contralateral oblique projections help differentiate between anterior and posterior structures. Each perfusion zone corresponds to an individual pulmonary segment (Figure 1) and is assessed for the degree of hypoperfusion and disease characterization in the pulmonary artery branches supplying the zone.[17]

PATIENT SELECTION

Although patient selection for BPA is an evolving field, we provide practical suggestions for this process that are based on our current understanding of disease phenotypes and procedural techniques. The belief that the process should be a multidisciplinary, team-based approach is at the core of our suggested approach to assessing and managing CTEPD with and without PH (Figures 3 and 4). Multidisciplinary teams should include experts in diagnostic image interpretation, PEA, BPA, and CTEPH medical management. This is necessary to confirm the diagnosis (exclude CTEPH mimics such as fibrosing mediastinitis, pulmonary arterial tumor, vasculitis, and acute PE)[19] and to guide the next steps in the management of such patients. Table 1 summarizes our opinion on the necessary components of an expert CTEPH center and an expert PH center.

The composition of a multidisciplinary CTEPH team may vary, depending on local availability of resources, but should have core expertise in the following:

1. The diagnosis and medical management of pulmonary vascular disease (pulmonary medicine or cardiovascular medicine)[20];
2. Radiological expertise in cross-sectional cardiothoracic imaging and nuclear medicine[21];
3. Surgical expertise in PEA[22];
4. Interventional expertise in NS-iPA and BPA[18,23]; and
5. Nursing expertise in the management of pulmonary vasodilator therapies.

Failure to include any one core area of expertise at the decision-making step may lead to care recommendations reflecting local availability rather than the most optimal therapeutic strategy for an individual patient with CTEPH. Once the diagnosis of CTEPH is confirmed, several key considerations influence the next steps. The anatomical disease level is the first factor to consider in the selection of treatment options. Figure 2 highlights disease levels (1–4) as noted on NS-iPA. Disease in levels 1 through 3 is generally considered surgically accessible and is best managed with PEA if otherwise feasible. Although expert surgeons have demonstrated excellent outcomes even in patients with level 4 disease in the pre-BPA era, we believe isolated level 4 disease is best managed with BPA because effective PEA for such distal disease is performed only at select centers.[24] Key factors that play a role in the decision between PEA and BPA include the presence of surgically accessible disease and the sufficient correlation among patient symptoms, obstructive disease burden, cardiopulmonary hemodynamic abnormalities, and the absence of other patient-related contraindications to surgery (eg, advanced age, frailty, or extensive comorbidities).[24,25]

Recently published European Society of Cardiology/European Respiratory Society guidelines for diagnosing and treating PH now give BPA a Class I

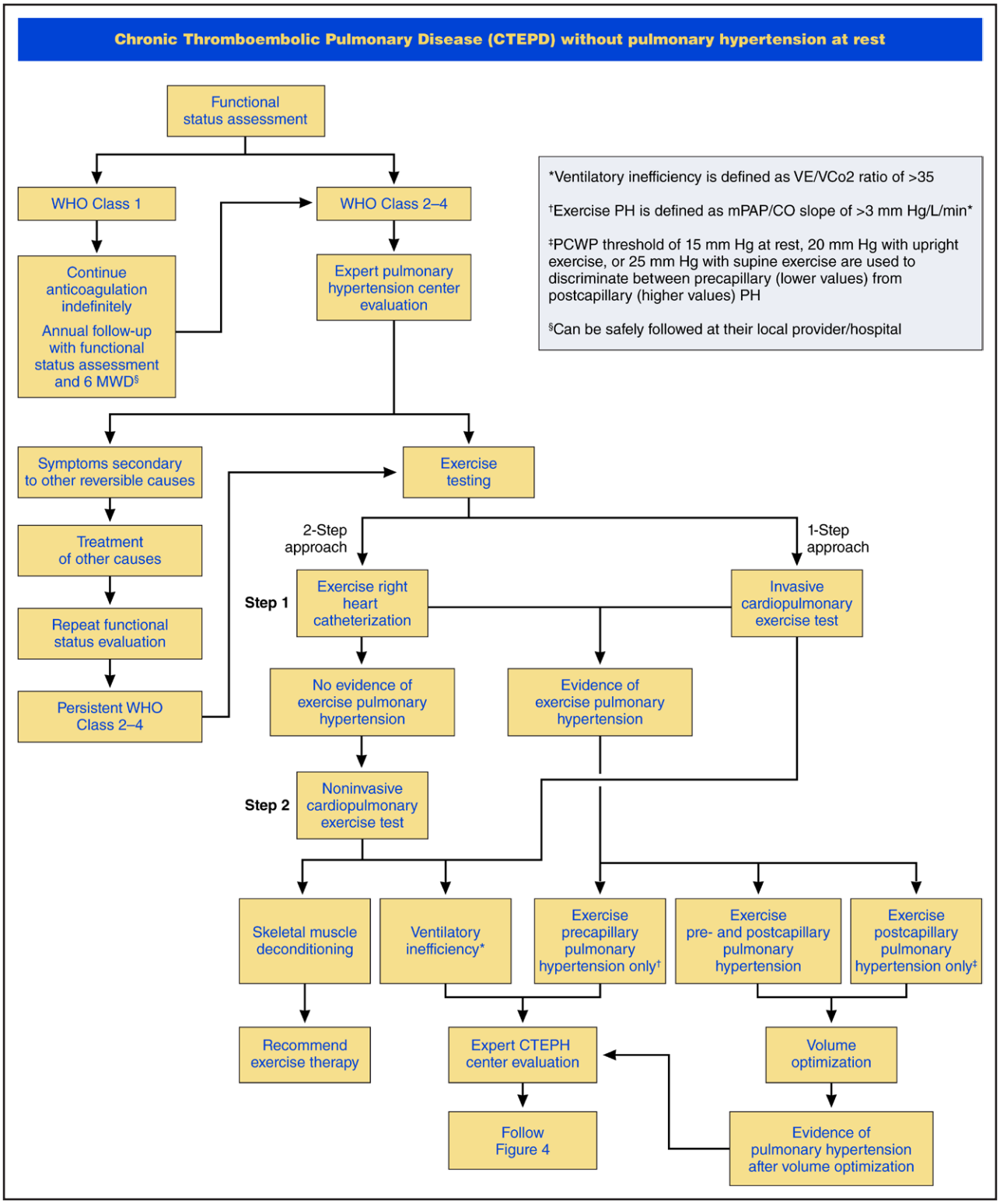


Figure 3. Recommended management algorithm for CTEPD without pulmonary hypertension at rest.
CO indicates cardiac output; CTEPD, chronic thromboembolic pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary artery pressure; PCW, pulmonary capillary wedge pressure; 6MWD, 6-minute walk distance; VCo2, carbon dioxide output; VE, alveolar ventilation; and WHO, World Health Organization.

indication for treating distal level 4 CTEPH.[6] This recommendation was based in part on the results of the RACE trial (Riociguat Versus Balloon Pulmonary Angioplasty in Non-Operable Chronic Thromboembolic Pulmonary Hypertension) and MR BPA trial (Multicenter Randomized Controlled Trial of Balloon Pulmonary Angioplasty

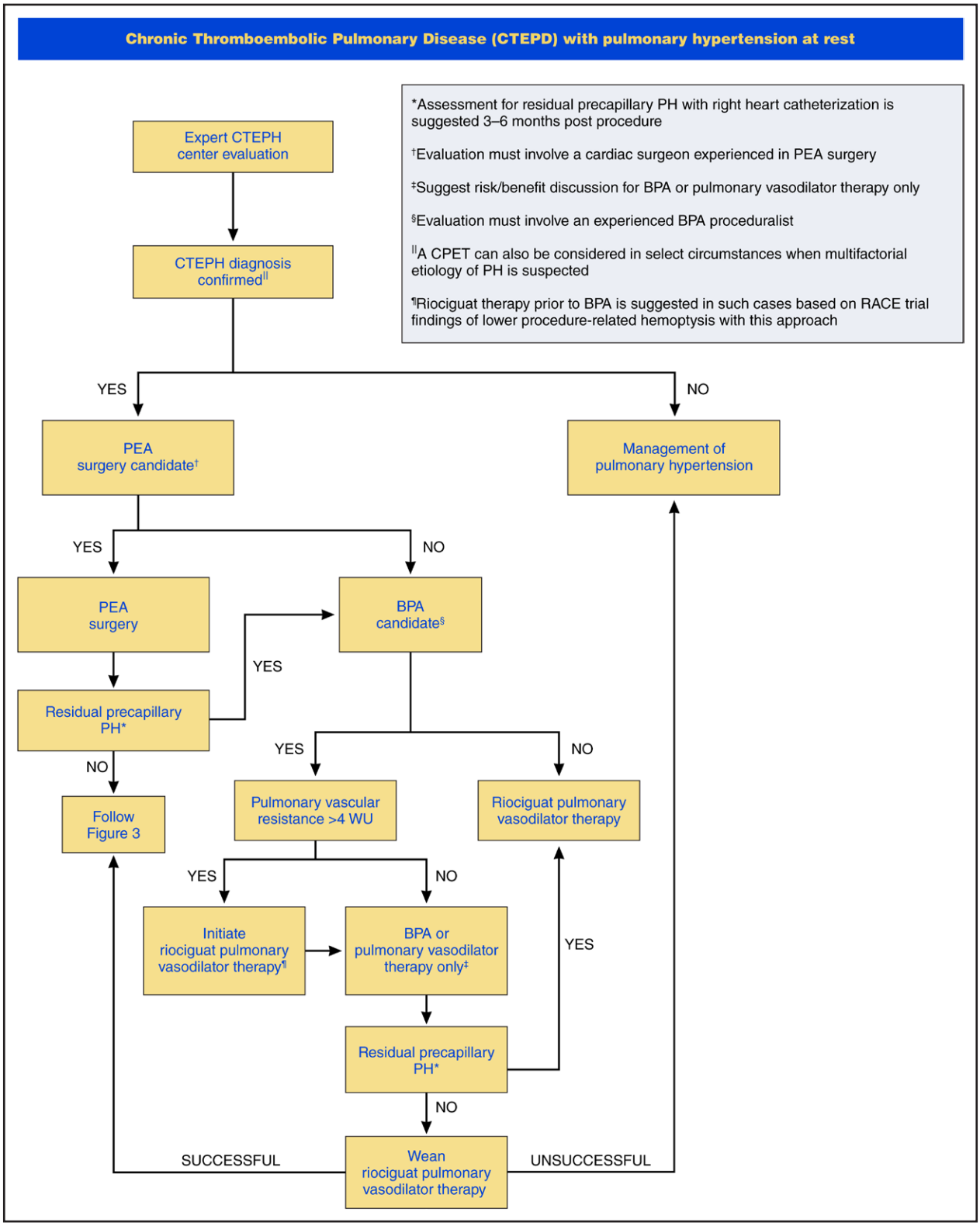


Figure 4. Recommended management algorithm for CTEPD with pulmonary hypertension at rest.
BPA indicates balloon pulmonary angioplasty; CPET, cardiopulmonary exercise test; CTEPD, chronic thromboembolic pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; RACE, Riociguat Versus Balloon Pulmonary Angioplasty in Non-Operable Chronic Thromboembolic Pulmonary Hypertension; and WU, Wood units.

and Riociguat in Patients With Chronic Thromboembolic Pulmonary Hypertension), which showed a more pronounced reduction in pulmonary vascular resistance in patients who underwent BPA as first-line treatment of inoperable CTEPH and pulmonary vascular resistance >4 Wood units compared with those receiving medical

Table 1. Suggested Competencies of an Expert CTEPH Center and an Expert PH Center

CTEPH care delivery competencies	Expert CTEPH center	Expert PH center	Referring centers/ physicians
Initial screening for CTEPD with ventilation-perfusion imaging	✓	✓	✓
Echocardiographic surveillance for PH	✓	✓	✓
Left- and right-sided heart catheterization, including exercise right-sided heart catheterization	✓	✓	✓
Initial management and stabilization for acute and chronic cor pulmonale, not including ECMO or pulmonary embolectomy (catheter or surgery)	✓	✓	✓
Systemic thrombolysis for high risk acute PE	✓	✓	✓
Counseling occupational and healthy living choices, including physical activity, rehabilitation, and anticoagulation management	✓	✓	✓
Venous health management	✓	✓	✓
Experienced PH physicians with expertise in all facets of PH medical management	✓	✓	
Advanced echocardiographic imaging expertise for right ventricular assessment	✓	✓	
Cross-sectional imaging expertise in diagnosis of pulmonary thromboembolic disease	✓	✓	
Catheter- and surgery-based acute pulmonary embolectomy or thrombolysis	✓	✓	
Expertise in performance and interpretation of both noninvasive and invasive CPET	✓	✓	
Comprehensive inpatient PE service and post-PE follow-up clinic	✓		
Nuclear medicine expertise in CTEPD diagnosis	✓		
Experienced diagnostic radiologist with expertise in CTEPH imaging interpretation	✓		
Invasive pulmonary angiogram performance and expertise in CTEPD diagnosis interpretation	✓		
Experienced PEA surgeon*	✓		
Experienced BPA interventionalist*	✓		
Onsite ECMO support availability	✓		
Lung transplantation	✓		

BPA indicates balloon pulmonary angioplasty; CPET, cardiopulmonary exercise testing; CTEPD, chronic thromboembolic pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; ECMO, extracorporeal membrane oxygenation; PE, pulmonary embolism; PEA, pulmonary endarterectomy; and PH, pulmonary hypertension.

*European Respiratory Society/European Society of Cardiology guidelines recommend an annual volume of 30 patients undergoing BPA or >100 BPA procedures and >50 PEA surgeries for expert center designation.[6]

treatment with riociguat.[26,27] The RACE trial results also support the initiation of riociguat as pretreatment before BPA in such patients.[26] Table 2 summarizes published BPA experiences at various CTEPH centers worldwide.

Although BPA can be performed in patients who cannot tolerate or afford riociguat pretreatment, this should be done only after shared decision-making about the risks and benefits of such an approach.[27] The same is true for patients who are otherwise candidates for PEA but decline surgery because of personal preference.[74] BPA is often considered in patients with residual CTEPH after PEA. Although both BPA and medical management with riociguat have been given a Class 1 recommendation in this situation, this recommendation for BPA is supported only by observational case series data in the case of BPA.[6,75] Early reports also suggest increased hemoptysis and vessel injury rates with BPA in post-PEA patients compared with those undergoing BPA in de novo distal CTEPH.[76] Shared decision-making and a risk-benefit assessment for each individual patient at an expert CTEPH center are recommended in such cases.

BPA is also considered in patients with chronic thromboembolic disease without PH at rest.[70] Such patients can have symptoms attributable to various conditions, including exercise PH, ventilatory inefficiency resulting from pulmonary vascular obstruction, skeletal muscle deconditioning, left-sided heart disease, uncorrected congenital heart disease, and parenchymal lung disease.[77] Figure 3 details our suggested approach in such patients. Exercise testing (exercise right-sided heart catheterization and invasive cardiopulmonary exercise testing) may help with the phenotyping of these patients with 1 or more of these causes of dyspnea in CTEPD without resting PH.[78,79] PEA surgery and BPA have been shown to improve patients' symptoms, hemodynamics, and ventilatory inefficiency.[49,80–82] Still, the use of these approaches needs to be better studied in such populations at this time.

Another group of particular interest when considering BPA includes individuals with mild symptoms and mild CTEPH, mainly because the new European definition of precapillary PH includes a mean pulmonary artery pressure >20 mm Hg and pulmonary vascular resistance >2 Wood units.[6] It is likely that such patients will present to centers in larger numbers as minimally invasive approaches like BPA gain traction. As a general rule, asymptomatic patients with mild CTEPH likely do not require intervention, but this group suggests

Table 2. Summary of Key Original Articles on BPA Since 2001, Including Case Series (≥5 patients) and Clinical Trials

Location	First author	Year	BPA sessions, n	Patients, n	Follow-up, mo	WHO class	6MWD	BNP	QoL	Hemodynamics	ECHO	CTPA	MRI	CPET	Complications
Boston, MA	Feinstein[28]	1994–1999	47	18	36	✓	✓			✓					✓
Oslo, Norway	Broch[29]	2003–2014	NR	32	35	✓		✓		✓	✓				
Prague, Czech Republic	Jansa[30]	2003–2019	160	64	3	✓	✓	✓	✓	✓					✓
Okayama, Japan	Mizoguchi[12]	2004–2011	255	68	26	✓	✓	✓		✓					✓
Multicenter, Japan	Ogawa[31]	2004–2013	1408	308	14	✓	✓	✓		✓					✓
Tokyo, Japan	Inami[32]	2009–2013	213	68	3	✓	✓	✓		✓					✓
	Inami[33]	2009–2013	350	103	14		✓	✓		✓					✓
	Moriyama[34]	2011–2016	318	53	NR	✓	✓	✓		✓	✓				
	Tsugu[35]	2012–2014	NR	25	NR					✓	✓				
	Tsukada[36]	2012–2016	525	82	6	✓	✓	✓		✓		✓			
	Nishiyama[37]	2017	360	60	6	✓	✓			✓	✓				
Tohuko, Japan	Aoki[38]	2009–2016	424	84	42	✓	✓	✓		✓		✓			✓
	Akizuki[39]	2012–2014	62	13	3		✓			✓				✓	
Osaka, Japan	Ogo[40]	2011–2015	385	80	12	✓	✓	✓		✓					✓
Kobe, Japan	Taniguchi[41]	2011–2019	324	81	2.7	✓	✓	✓		✓					
Suita, Japan	Fukui[42]	2012–2013	64	20	4	✓	✓	✓		✓			✓		
Nagasaki, Japan	Yamagata[43]	2013–2016	31	11	1	✓	✓	✓		✓					✓
Madrid, Spain	Velázquez[44]	2013–2017	156	46	15.3	✓	✓	✓		✓					✓
Multicenter, Germany	Olsson[45]	2013–2016	266	56	13.8	✓	✓	✓		✓	✓				✓
Kyushu, Japan	Yamasaki[46]	2013–2017	102	29	16.8	✓	✓	✓		✓	✓		✓		
Hanover, Germany	Maschke[47]	2013–2017	266	67	1										✓
	Schoenfeld[48]	2014–2016	NR	29	2	✓	✓	✓					✓		
Bad Nauheim, Germany	Wiedenroth[49]	2014–2018	358	64	6	✓	✓	✓	✓	✓					✓
Leuven, Belgium	Godinas[50]	2014–2018	91	18	1	✓	✓	✓		✓	✓				✓
Paris, France	Brenot[51]	2014–2017	1006	184	6.1	✓	✓			✓					✓
Warsaw, Poland	Roik[52]	2014–2015	27	9	5	✓	✓	✓		✓					✓
Rochester, MN	Anand[53]	2014–2018	75	31	NR	✓	✓			✓	✓				✓
Vienna, Austria	Gerges[54]	2014–2019	712	120	36	✓	✓	✓		✓					✓
Taiwan	Chen[55]	2014–2020	59	13	21	✓	✓	✓		✓	✓				✓
Amsterdam, the Netherlands	Van Thor[56]	2015–2019	172	38	6	✓	✓	✓		✓					✓
Seoul, Korea	Kwon[57]	2015–2017	52	15	6	✓	✓			✓	✓				✓
Krakow, Poland	Magoń[58]	2015–2017	103	17	6	✓	✓	✓		✓					
United Kingdom	Hoole[59]	2015–2018	95	30	3	✓	✓	✓	✓	✓	✓			✓	✓
Beijing, China	Zhang[60]	2016–2019	137	46	0						✓				
Chile	Sepúlveda[61]	2016–2019	81	22	17.3	✓	✓	✓		✓					✓
Otwock, Poland	Kurzyna[62]	2017	157	56	24	✓	✓	✓		✓					✓
Israel	Segel[63]	2017	47	5	5–11	✓	✓			✓					✓
Paris, France	Jais[26]	2016–2019	400	52	12	✓	✓	✓		✓					✓
Multicenter, Japan	Kawakami[64]	2016–2019	150	32	12	✓	✓	✓		✓					✓
Almada, Portugal	Calé[65]	2017–2019	57	11	6	✓	✓	✓		✓					✓
Beijing, China	Jin[66]	2018–2019	40	25	0	✓	✓	✓		✓	✓			✓	✓
Istanbul, Turkey	Kanar[67]	2019	52	20	3	✓	✓	✓		✓	✓				
Grenoble, France	Piliero[68]	2013–2020	646	156	6	✓	✓	✓		✓					✓
Guangzhou, China	Hong[69]	2019–2021	210	92	0			✓		✓					✓
San Diego, CA	Mahmud[70]	2021	164	39	NR	✓	✓			✓					✓
Ann Arbor, MI	Rich[71]	2023	78	17	NR	✓	✓			✓					✓
Philadelphia, PA	Bashir[72]	2023			NR	✓	✓			✓					✓
Seattle, WA	Carlozzi[73]	2018–2021	135	25	NR	✓	✓			✓					✓

BNP indicates brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CPET, cardiopulmonary exercise testing; CTPA, computed tomography pulmonary angiogram; Echo, echocardiogram; MRI, magnetic resonance imaging; NR, not reported; QoL, quality of life; 6MWD, 6-minute walk distance; and WHO, World Health Organization.

individualized shared decision-making for each patient in this circumstance. Although PEA or BPA may lead to meaningful improvement for symptomatic patients even with mild PH, pulmonary vasodilator therapy and close clinical follow-up may also lead to an equally acceptable outcome in such patients.[83] Further studies involving this population are needed.

Although many patients in the previously described populations are considered for BPA, only some such patients should proceed to BPA. Careful consideration for BPA candidacy involves assessing patient factors likely to predict outcomes. Cautious consideration of factors, including the clot burden, lesion classification, how amenable the lesions are to BPA, and hemodynamic derangement, is paramount for appropriate patient selection and thus successful BPA outcome.[24] Lesion classification and its role in BPA planning are discussed in more detail in the section on BPA technical performance.

Other considerations when considering the use of BPA are comorbidities, including chronic kidney disease,[84] the ability to tolerate the interruption of anticoagulation necessary for each BPA session, and the patency of the deep venous system that allows percutaneous access to the pulmonary arterial system. BPA is safe and effective in patients with CTEPH with CKD, and judicious use of intravenous contrast (typically by limiting contrast dose to ≤3 times baseline glomerular filtration rate) is suggested for such patients on the basis of our local practice.[71]

PROCEDURAL PERFORMANCE

An overview of a typical BPA procedure and our suggestions are illustrated in Figure 5. Successful cannulation of segmental origins is essential, and mastery of various anatomical variations is vital. Guide extension catheters are particularly useful for deep coaxial engagement, allowing reduced contrast dose on S-iPA.[17,23] Lesion assessment based on careful S-iPA is vital for lesion characterization, and lesion severity may be fully appreciated only with an examination in orthogonal views because of the asymmetry of the stenosis.[17] Figure 6 illustrates common lesion subtypes in a typical BPA procedure.

When vessels appear angiographically patent by S-iPA but the corresponding venous return is an abnormal, adjunctive assessment with resting pressure gradient measurement is helpful in the identification of obstructive intravascular webbing. Such lesions are dilated with the ratio of proximal pressure (Pa) to distal pressure (Pd) as a guide until either brisk venous return or a Pd:Pa ratio >0.80 is achieved.[33] This threshold remains an empirical suggestion without well-powered validation studies.

Although brisk venous return restoration is desired after every vessel treatment, it is only sometimes achieved.[53] Failure to restore brisk venous return is due to insufficient dilatation or distal pulmonary arteriopathy. Adjunctive tools such as intravascular pressure gradient assessment or intravascular imaging to accurately size the dilatation balloon can be helpful. If brisk venous return is not established despite dilatation with a 1:1 sizing balloon or a Pd:Pa ratio >0.8 is achieved across the pulmonary arterial branch, the absence of brisk venous return is considered secondary to underlying pulmonary arteriopathy. This situation may be best managed with pulmonary vasodilator therapy. Another critical consideration is the role of sequential dilatation with larger balloons in subsequent sessions. Chronically occluded diminutive-appearing subsegmental pulmonary arteries often accommodate only a small balloon on initial revascularization; these vessels may remodel and grow to facilitate dilatation with a larger balloon during subsequent treatment sessions.[85]

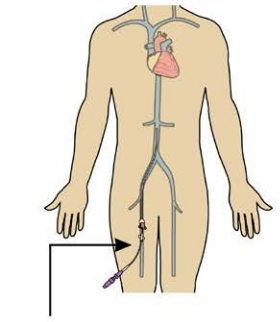
BPA Procedure–Related Complications

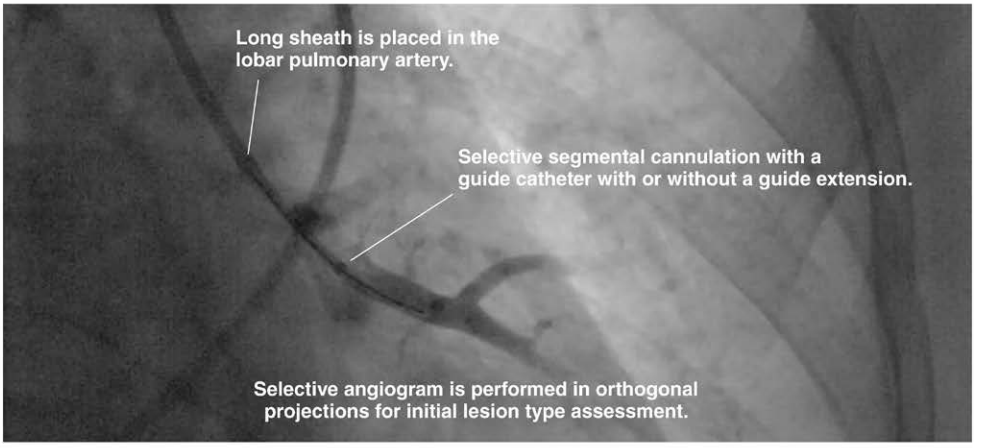
Although BPA has demonstrated efficacy since its inception >4 decades ago, initial reports of complications identified up to a 6% mortality rate and ≈17% mechanical ventilation rate in the setting of BPA[28]; these rates halted the initial rapid adoption of BPA. Subsequently, Mizoguchi et al[12] reported improved safety after procedural refinement, reinvigorating interest in BPA on a global scale. Since then, the BPA procedure has undergone additional refinements, and several centers have reported excellent safety and efficacy data (Table 2).

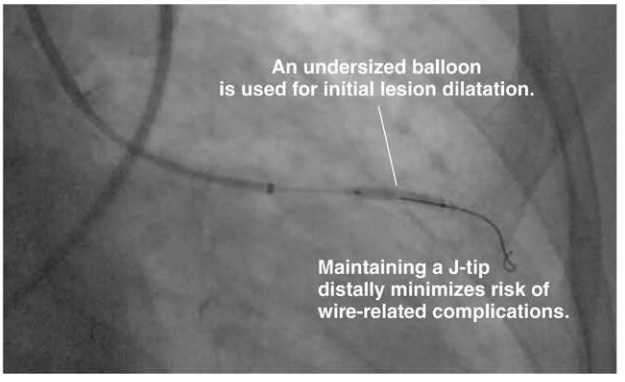
A recent report pooled safety outcomes with BPA from 26 original articles from 4 continents and 18 countries. The analysis included 1675 patients with CTEPH undergoing a total of 7603 BPA procedures. It observed a decreasing incidence of procedure-related complications with BPA over time. More specifically, from the first period (2013–2017) to the second period (2018–2022), the cumulative incidence of hemoptysis and vascular injury decreased from 14.1% (474/3351) to 7.7% (233/3029); lung injury decreased from 11.3% (377/3351) to 1.4% (57/3943); invasive mechanical ventilation rate dropped from 0.7% (23/3195) to 0.1% (4/3101); and mortality rate decreased from 2.0% (13/636) to 0.8% (8/1032; $P<0.01$ for all comparisons).[10] We believe that the reduced complication rates are attributable mainly to refinement in technique and patient selection, increasing adjunctive pulmonary vasodilator therapy use, and evolving anticoagulation practices in eligible patients.

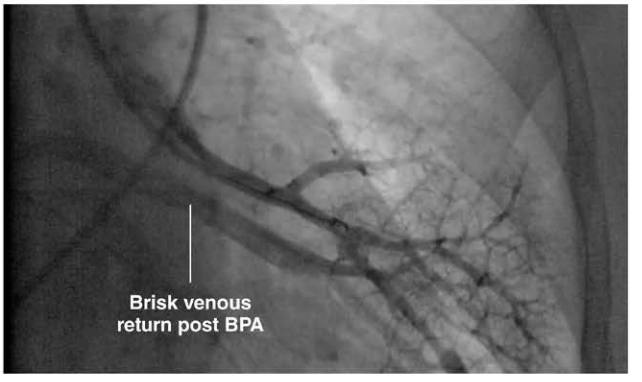
The most common BPA procedure–related complications include lung injury (described as reperfusion pulmonary edema in earlier reports) and hemoptysis. In most severe cases, both complications can rapidly progress to acute respiratory and circulatory failure requiring advanced airway management, noninvasive positive pressure ventilation to invasive mechanical ventilation,

Identify target pulmonary zones (segments) by evidence of hypoperfusion on V/Q scan and NS-iPA; as well as otherwise healthy lung parenchyma on cross sectional imaging.
Femoral vein access is preferred. Baseline right heart catheterization is performed before every BPA session. Intravenous heparin with ACT goal of 200-250 sec is suggested for periprocedural anticoagulation. We suggest limiting radiation dose to ≤2 Gy and contrast dose to <3x GFR per procedure.
Baseline NS-iPA is used as a reference for selective cannulation using pre-shaped guide catheters.
S-iPA is performed without digital subtraction to further stratify them into standard and high risk zones based on individual pulmonary arterial lesion subtypes. Keeping sedation light allows for patient participation in inspiratory holds.
Standard risk pulmonary zones are revascularized first followed by higher risk zones in subsequent sessions.
Scoring balloons can be used for recalcitrant lesions, cutting balloons should not be used given high risk of vessel injury.
Primary goal of the lesion dilation is to improve perfusion rather than to reduce the angiographic stenosis, especially during initial BPA sessions with high resting pulmonary arterial pressure.
Over time, vessel remodeling with flow restoration and final treatment can ensure minimal residual stenosis and optimal perfusion.









Suggested guide catheters for selective cannulation

Segmental Branch	Catheter Suggestion	Segmental Branch	Catheter Suggestion
Right A1	JR†4 or AL§3	Left A1	JR†4 or AL§1
Right A2	JR†4	Left A2	JR†4 or AL§1
Right A3	JR†4	Left A3	JR†4 or AL§1
RightA4-5	JR†4 or AL§1	Left A4-5	JL‡3.5/4 or Champ 2.5
Right A6	JR†4	Left A6	JR†4
Right A7-8	JR†4	Left A7-8	MPA*-2 or JR†4
Right A9-10	MPA*-2	Left A9-10	MPA*-2 or JR†4

Figure 5. Procedural approach and key considerations of a typical BPA procedure.
ACT indicates activated clotting time; BPA, balloon pulmonary angioplasty; GFR, glomerular filtration rate; NS-iPA, nonselective invasive pulmonary angiogram; S-iPA, selective invasive pulmonary angiogram; and V/Q, ventilation-perfusion scan. *Multipurpose A. †Judkins Right. ‡Judkins Left. §Amplatz Left. Adapted with permission from Patel et al.[17]

and extracorporeal membrane oxygenation support. It is reassuring that most patients with lung injury and hemoptysis do not end up needing such extreme measures.[64,86] Most patients with lung injury often require supplemental oxygen only for 2 to 4 hours after the procedure with or without noninvasive positive pressure ventilation. Patients with worse baseline cardiopulmonary hemodynamics and those receiving revascularization in

the higher-risk lesions subsets are more likely to develop lung injury.[26,64]

Kawakami et al[64] recently proposed a thromboembolic disease lesion classification: (1) ring lesions, (2) web lesions, (3) subtotal occlusions, (4) total occlusions, and (5) diffusely tortuous vessels distal to the subsegmental branches. Although each individual thromboembolic lesion type may be present in most patients, vascular complications occurred in >40% of the tortuous lesion 5 subtype. BPA should therefore be avoided in diffusely tortuous vessels distal to the subsegmental branches to minimize procedural complications. Vascular complication rates were also higher with subtotal and total occlusion lesions (higher risk) than the ring and web-like lesions (standard risk). Figure 6 illustrates lesion subtypes 1 through 4 before and after BPA. The risk of lung injury development is minimized by preprocedural medical and volume optimization and careful lesion risk stratification during the BPA procedure.[71]

Hemoptysis during BPA may be a sign of vascular injury (the most feared and direct procedure-associated complication).[86] Clinical severity can range from scant self-resolving hemoptysis with no apparent angiographic vascular injury to large-volume hemoptysis and pulmonary hemorrhage. More severe forms of hemoptysis are often associated with angiographic evidence of vessel perforation, which requires prompt balloon tamponade. Wire choice and distal wire tip management are also critical for minimizing hemoptysis risk during BPA, given significant respiratory motion leading to elongation and shortening of these branches (most pronounced in lower lobe segments), which can easily lead to wire-mediated vessel perforation. As a general rule, we suggest using nonhydrophilic soft-tip (tip load <1 g) 0.014-in coronary guide wires as the first choice, along with always maintaining a J-shaped distal tip in these cases for that reason (Figure 5). Experienced operators may use other wires, but extreme caution must be exercised when heavy tip loads or hydrophilic wires are used. Hemoptysis is usually limited to a scant and self-resolving event with or without anticoagulation reversal.

In addition, every center and operator must always have contingency plans for more severe hemoptysis. Proximal balloon occlusion as a first step affords time to allow the operator to consider a more permanent solution. More severe hemoptysis and respiratory instability resulting from balloon oversizing and vessel rupture are managed with prompt selective intubation into the unaffected lung. This could be occlusive vascular coils or gelatin foam injection at the target segmental artery. We suggest doing BPA in 1 lung at a time during each BPA session.

Treatment Goal and Postprocedural Care

Anticoagulation with intravenous heparin is initiated as soon as feasible after hemostasis is successfully achieved at the access site, and postprocedural care at most centers involves inpatient monitoring with telemetry for 24 to 48 hours. Although this group recommends brief anticoagulation interruption before BPA and intravenous heparin during BPA, many BPA centers do perform BPA without interruption of anticoagulation. A recent report suggested excellent outcomes with outpatient postprocedural monitoring for 12 to 23 hours, although this should be performed at select centers with considerable BPA experience.[71]

The goal of optimal BPA is the dilation of all treatable lesions. It has been reported that the improvement in patient hemodynamics correlates with the number of treated segments, and thus, the goal of complete revascularization in patients with CTEPH is ideal. However, this is impossible with only a single procedure. Therefore, the BPA treatment is completed over several sessions, with each procedure limited by contrast volume, total radiation time, or total procedure time. Generally, 4 to 8 BPA procedures are necessary to complete the BPA treatment for any individual patient. Follow-up assessment after completion of the BPA session varies from center to center. Generally, right-sided heart catheterization is performed 3 to 6 months after BPA completion to evaluate the need for additional BPA or adjunctive PH medical therapy. Some centers also routinely perform ventilation-perfusion imaging or NS-iPA at 3 to 6 months after BPA.

Long-term noninvasive and clinical follow-up should be continued and is sufficient without the need for invasive hemodynamic or angiographic evaluation unless symptoms become progressive or noninvasive evaluation suggests the recurrence of PH. If cardiopulmonary exercise testing was used in the patient selection process before BPA, repeat testing to assess interval changes in key parameters is also suggested 3 to 6 months after the final session.

GUIDANCE FOR CENTERS INITIATING NEW BPA PROGRAMS

BPA is one of many necessary tools within a successful expert CTEPH program. This group therefore suggests initiating BPA programs only within experienced CTEPH centers offering PEA as part of the treatment armamentarium for CTEPH. BPA should be performed only in a multidisciplinary, expert CTEPH program (Table 1). Even at experienced CTEPH centers, establishing a BPA program should progress stepwise, with early sessions targeting lower-risk lesions in patients with few comorbidities.[62] Careful and conservative patient and lesion selection will likely result in optimal patient outcomes and overall programmatic success with BPA. More complex lesions in higher-risk patients should be performed only after the operator and center gain experience. Peer guidance and support from experienced centers and

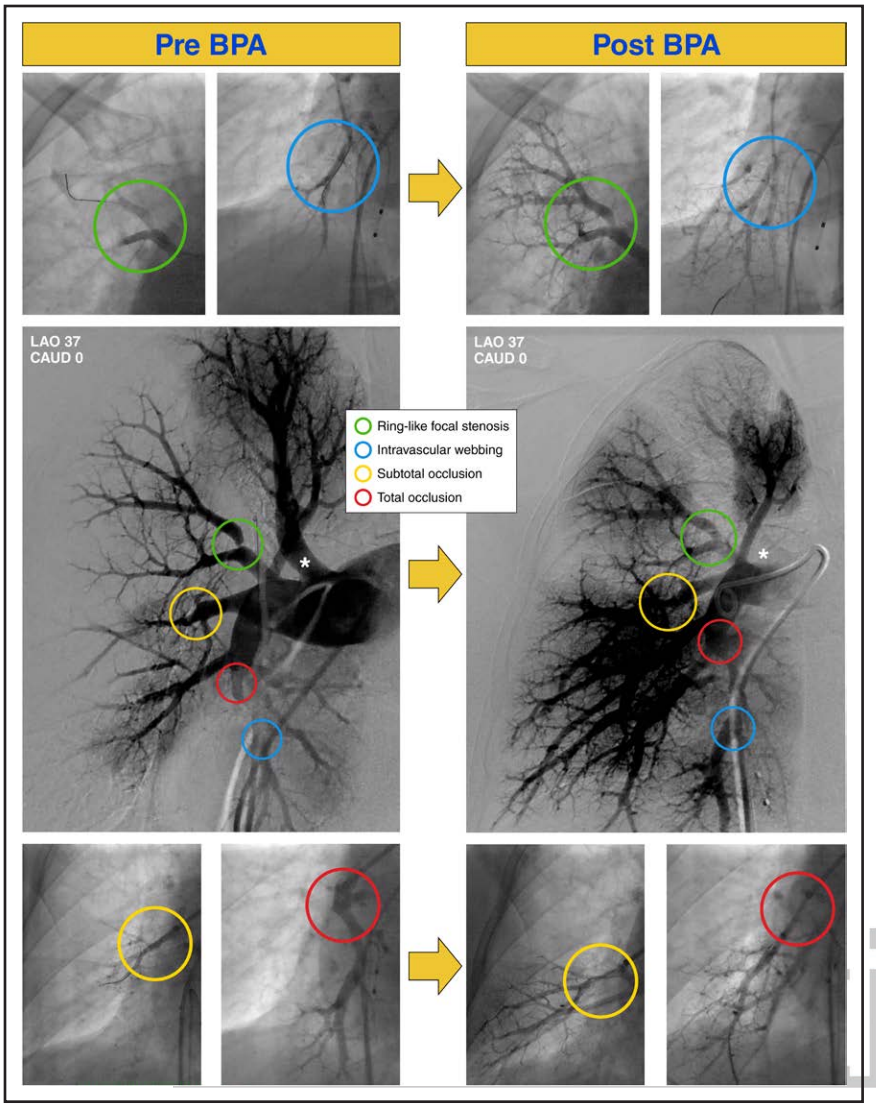


Figure 6. Individual lesion subtypes illustrated before and after BPA on nonselective and selective pulmonary angiography.
Left, Nonselective and selective angiograms before balloon pulmonary angioplasty (BPA). **Right**, Corresponding angiograms for the same patient after BPA. CAUD indicates caudal; and LAO, left anterior oblique. *Pre-BPA and post-BPA nonselective invasive pulmonary angiogram images in the **middle** are in the same projection (LAO 37 CAU 0). The pigtail catheter was positioned more distally in the interlobar trunk in the post-BPA image; hence, the truncus arteriosus was not opacified by contrast injection.

operators are invaluable in making the learning curve less steep for new programs.

EVIDENCE DEVELOPMENT FOR THE FUTURE

BPA is now a Class 1 recommendation for inoperable and residual CTEPH.[6] Despite significant advances, BPA remains a procedure in evolution, and several knowledge gaps must be addressed. The lack of data uniformity with predefined parameters of BPA procedural success and treatment complications is a significant limitation in the current published literature on BPA. The parameters of procedural success and definitions of complications must be standardized. This quality measure will enable the appropriate collation of registry data and comparative analyses across populations, centers, and countries.[87] Table 3 lists some critical knowledge gaps; here, we highlight them further by each core subtopic.

Imaging Considerations

Although the basic pulmonary segmental anatomy is well described, granular details about variations in subsegmental branch anatomy need to be elucidated. Establishing consensus anatomical definitions for subsegmental branch vessel anatomy will allow consistency across institutions and operators, facilitate core laboratory evaluation, and result in successful high-quality evidence collection. A ventilation-perfusion scan is recommended for CTEPD screening, whereas a CTPA is a preferred diagnostic test for acute PE. Ideally, a singular imaging modality could be used for diagnosing both acute and chronic thromboembolic disease. Dual-energy computed tomography imaging has shown promise, but its role is limited, given issues with artifacts and the lack of protocols allowing reproducible imaging.[17] Safe and effective BPA guided by cone-beam CTPA has also been reported and may be helpful in pre-BPA target lesion assessment.[40]

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Table 3. Summary Suggestions for Future Evidence Development

Anatomical and imaging considerations
Standardization of subsegmental branch vessel nomenclature
Definitions for individual lesion characterization
Objective, well-validated criteria to quantify pulmonary hypoperfusion
Future imaging modalities that will allow reliable assessment of lung parenchyma and acute and chronic thromboembolic pulmonary disease in a singular study
Imaging tools that will allow objective lung perfusion quantification and assessment of interval change in perfusion in between and after sequential BPA sessions
Patient selection
Randomized comparative data for BPA vs medical therapy in surgically inaccessible disease and mild or no cardiopulmonary hemodynamic impairment at rest
Randomized comparative data for BPA vs PEA in patients with predominantly level 3 disease
Role of BPA in special patient populations with advanced CKD, underlying lung parenchymal disease, multifactorial PH, or residual CTEPH after PE
Procedural performance
BPA-specific endovascular interventional equipment
Role of intravascular testing (imaging and physiology) and validation of thresholds for lesion severity and adequate dilatation
Development of fusion (CT and fluoroscopy) imaging protocols that will allow more efficient navigation within pulmonary arterial branches during BPA
Postprocedural follow-up
Indications and protocols for optimal pulmonary vasodilator wean in patients after BPA
Utility and indications for follow-up perfusion imaging after BPA
Data on long-term pulmonary arterial branch patency after BPA

BPA indicates balloon pulmonary angioplasty; CKD, chronic kidney disease; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary embolism; PEA, pulmonary endarterectomy; and PH, pulmonary hypertension.

Patient Selection Considerations

Two multicenter randomized trials (MR BPA and RACE) of BPA versus medical therapy with riociguat in distal inoperable disease have been published.[26,27] Although BPA was noted to be a safe and effective therapy in both studies, future research will confirm these findings on long-term follow-up and in other patient populations such as post-PEA patients. We also need guidance on weaning pulmonary vasodilator medications after effective BPA. Additional trials, including a phase 2b trial (NCT04780932), are ongoing or planned to offer safe and efficacious treatment strategies for patients with inoperable CTEPH presenting with severe hemodynamic compromise.[88]

Another vital area requiring elucidation involves PEA decision-making in the BPA era. This group realizes that it is largely subjective, and it is likely that the local availability of BPA will ultimately affect those who are considered marginal operative candidates. Decision-making likely represents a spectrum that includes patients for whom nearly all clinicians would favor PEA and those for whom almost all would favor BPA.[24] For example, clinicians typically prefer PEA for patients with few medical comorbidities, proximal disease, and PH in proportion to their observed disease. On the other hand, clinicians might be more likely to recommend BPA for patients with high surgical risk from multiple comorbidities, distal disease, and a less robust correlation between observed disease and severity of PH. Patients in the middle of this spectrum, where experts might disagree about anatomical or physiological surgical risk (such as those with mid to distal segmental disease), are more challenging. These areas of disagreement represent another important focus for further research.

Procedural Performance Considerations

Future innovation needs to focus on BPA-specific endovascular interventional equipment development (catheters and sheaths that are directional and stable). Although we empirically suggest a Pd:Pa ratio >0.80 as a marker of adequate balloon dilatation, this and other such thresholds must be validated in well-powered future studies. Another possibility is for angiographic assessment of pressure gradients that allows more uniform assessment of when a vessel is sufficiently revascularized.

Postprocedural Follow-Up Considerations

Prospective randomized studies are warranted both in combination with optimal medical therapy and versus surgical revascularization in the presence of mid and distal segmental disease. Patient selection depends heavily on the surgical and BPA experience at each center. However, as greater understanding is built globally at CTEPH centers, a more standardized approach to patient selection for BPA or PEA will emerge. Standardized end points for BPA procedures must be defined to compare outcomes and data across centers and regions. Restenosis after BPA seems infrequent, but the long-term patency of revascularized pulmonary artery branches after BPA remains largely unknown.[89] Standardized protocols for careful follow-up after BPA and studies with longitudinal follow-up are needed to address this knowledge gap. Rehabilitation may improve exercise capacity after BPA, although the data supporting this approach are also limited.

CONCLUSIONS

PEA, when possible, remains the treatment of choice, and all patients need to be evaluated at expert CTEPH centers, as defined here, that are able to offer both PEA and BPA. BPA is undergoing a natural evolution, becoming safer and more efficacious with increasing adoption and refinement

over the years. Continued refinement of procedural technique and patient and lesion selection will continue to advance the field. With meticulous planning and gradual escalation of balloon sizing and the number of lesions treated per session, BPA can achieve effective pulmonary artery revascularization with an acceptable safety profile.

Although BPA is gaining recognition as an option for treating patients with CTEPH, availability is becoming one of the most significant limiting factors. The next frontier in BPA therapy involves the continued dissemination of knowledge of technical experts to allow ease of access, similar to the advent of other interventional procedures. Working with peers and colleagues to disseminate BPA safely and reliably will flatten the learning curve for new operators interested in acquiring the skills to treat such patients percutaneously.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Disclosures

Writing Group Disclosures

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Scott H. Visovatti	The Ohio State University Wexner Medical Center	None	None	None	None	None	United Therapeutics*	None

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*Modest.

†Significant.

Reviewer Disclosures

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*Modest.

†Significant.

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