Catheter-Based Therapy for Inoperable Chronic Thromboembolic Pulmonary Hypertension

Jane A. Leopold, MD

Interventional cardiologists have been innovators in treating all forms of vascular and valvular heart disease in the systemic circulation; however, the pulmonary circulation has not received the same degree of interest from our community. Recent advances in the diagnosis and management of pulmonary vascular diseases and multidisciplinary collaboration among pulmonologists, cardiologists, and surgeons have brought the interventional treatment of pulmonary vascular disease to the forefront. One area of particular interest is the interventional management of chronic thromboembolic pulmonary hypertension (CTEPH) in inoperable patients. CTEPH is a form of pulmonary hypertension that is characterized by a mean pulmonary artery pressure (mPAP) ≥25 mm Hg, a pulmonary artery occlusion pressure of <15 mm Hg, and the presence of partially or completely occlusive thrombi in the main, lobar, segmental, or subsegmental pulmonary arteries that are present after at least 3 months of effective anticoagulation.[1] The incidence of CTEPH is estimated to be 1.6 to 7.9 cases per million, and ≈0.6% to 4.8% of individuals may develop CTEPH within 2 years of an acute pulmonary embolism.[2,3] The true incidence of CTEPH is likely underestimated owing to the nonspecific nature of the associated symptoms. Patients typically present with exercise intolerance, fatigue, and exertional dyspnea and may also have chest discomfort, peripheral edema, light-headedness, or syncope.[2,3]

At present, surgical pulmonary endarterectomy is the only established and curative therapy for CTEPH; all patients with CTEPH should be evaluated at expert centers to determine candidacy for surgery. Surgery decreases mortality with an estimated survival at 1, 2, and 3 years of 93%, 91%, and 89% in operated patients compared with 88%, 79%, and 70% in nonoperated patients.[4] Despite the survival advantage offered by surgery, recent findings from international registries have revealed that ≤37% of patients with CTEPH are deemed inoperable owing to distal pulmonary vascular disease, poor right ventricular function, or other comorbidities, whereas another 15% who do undergo surgical endarterectomy are left with residual pulmonary hypertension requiring further intervention.[4–6] Taken together, ≈40% to 50% of patients with CTEPH require a nonsurgical therapeutic alternative, leading to a resurgence of interest in balloon pulmonary angioplasty (BPA) as a therapeutic intervention.[6]

BPA to treat CTEPH was first described in 1988[7]; however, it was not until 2001 when outcomes from a single-center series were reported that BPA was thought to be a potentially effective alternative to surgical endarterectomy. In this early experience, 18 patients (mean age: 51.8 years) underwent an average of 2.6 separate BPA sessions with an average of 6 balloon dilations per session. Balloon dilation decreased mPAP (42±12 versus 33±10 mm Hg; P=0.002) and significantly improved New York Heart Association functional class and 6-minute walk distance. Reperfusion pulmonary edema occurred in 11 of 18 patients, either at the time of catheterization or within 48 hours of the procedure, and 1 patient died from right ventricular failure. Nonetheless, at repeat catheterization 1 to 40 months after the index procedure, all dilated vessels were patent, and 16 of the 18 patients were alive at a median follow-up of 34.2 months.[8]

During the past 5 years, the experience with BPA has increased substantially. In selected nonoperable patients, case series describe improvements in mPAP, pulmonary vascular resistance, functional class and exercise capacity, heart failure markers, and right ventricular function. These studies collectively confirmed earlier success with BPA and did so with lower procedural complication rates.[9–15] The procedure has been used successfully to treat patients who have undergone surgical pulmonary endarterectomy, yet have residual pulmonary hypertension. In a study of 9 patients who were treated with BPA, an average of 4.1 years (2.9–7.1) after pulmonary endarterectomy, there was a reduction in mPAP (43 [30–52] versus 26 [21–29] mm Hg), decreased indices of heart failure, and improved functional class.[16] BPA has also been performed as part of a hybrid procedure for rare cases, where there is operable disease in one lung, but not the other. In this scenario, patients undergo BPA after surgical endarterectomy during the rewarming phase of deep hypothermic circulatory arrest. In 3 patients who underwent this hybrid procedure, mPAP and pulmonary vascular resistance were improved significantly, and all patients were discharged by 2 weeks and were alive at 6 to 10 months with improved exercise capacity.[17]

The BPA procedure has undergone iterative modifications during the past decade to improve safety and efficacy by focusing on patient selection, lesion evaluation, and technical aspects of procedural performance.[13,18–20] Although the 2015 European Society of Cardiology/European Respiratory Society guidelines currently list the indication for BPA as Class IIb; Level of Evidence C, there is a growing body of evidence to support the use of BPA in appropriately selected

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From the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Correspondence to Jane A. Leopold, MD, Brigham and Women's Hospital, 77 Ave Louis Pasteur, NRB0630K, Boston, MA 02115. E-mail jleopold@partners.org

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candidates.[21] Patients who are deemed inoperable may be considered for BPA. They should have hemodynamic evidence of pulmonary hypertension with a mPAP ≥25 mm Hg and a pulmonary vascular resistance >3 Wood Units. Patients should also be World Health Organization or New York Heart Association functional class 2 or higher on optimal medical therapy. Procedures should be performed at expert referral centers with advanced hemodynamic support and extracorporeal membrane oxygenation capability.

Anatomic location and lesion type are also criteria used to determine appropriateness for BPA with each affected pulmonary artery evaluated individually. Selective pulmonary angiography is performed to define lesion location and type with the majority of BPA procedures performed in lesions in the segmental and accessible subsegmental pulmonary arteries. The lesions are classified according to their angiographic appearance as complete obstructions, abrupt narrowing, ring-like stenosis, pouching defects, or webs.[14,22] The procedural success rate for BPA varies with the type of lesion being treated. For ring-like stenoses, abrupt narrowing, and web-like lesions, the success rate is almost 100%. The success rate decreases to ≈90% for subtotal obstructions and <50% to 63.6% for pouching defects, total occlusions, or tortuous vessels.[14,22] If there is a large amount of proximal organized thrombus, BPA is deferred because of the inability to retrieve liberated thrombus.

The main limitation of angiography is that in some lesions, it does not provide an accurate assessment of the lumen diameter. This has led to the use of intravascular ultrasound or optimal coherence tomography (OCT) imaging to improve lesion visualization, although the latter comes at the cost of increased contrast use. Comparative studies have found that OCT provides superior resolution when compared with pulmonary angiography or intravascular ultrasound and is better suited to identify lesion morphologies.[20] Intravascular imaging with OCT has shown that lesions categorized as webs, bands, abrupt narrowings, or complete occlusions by pulmonary angiography may have lesion morphologies that are far more complicated. OCT has identified septated lesions comprised of thick or thin walls and in some cases ≥5 lumens in pulmonary artery lesions. These OCT-defined patterns were present in all of the angiographic classification subsets, suggesting diverse heterogeneity in lesions and possibly explaining the differential success rates for angiographically defined lesions to BPA.[12] The other advantage of image guidance for BPA is that it can be used to prevent aggressive overdilation and, thereby, decrease the risk of vessel rupture. Thus, intravascular imaging should be used as an adjunct to the BPA procedure for defining lesion anatomy and intraprocedural decision-making.

Pressure wires have also been used to guide BPA, determine lesion success, and limit reperfusion pulmonary edema. Since pressure wires were introduced, the procedural end point changed from angiographic flow (grades 0–3, similar to the TIMI [Thrombolysis in Myocardial Infarction] Study flow grade for the coronary circulation) to a ratio of the distal to proximal pressure of >0.8. This should not be confused with the cut-off of 0.8 used in fractional flow reserve testing in the coronary circulation, where this ratio is measured at maximal hyperemia; in the pulmonary circulation, it is measured at baseline. A review of the angiographic pulmonary flow grade score and the pressure ratio of 493 target vessels found a strong correlation (R=0.90; P=0.0001) between these measures with pressure ratios of 0.20, 0.30, 0.60, and 0.90 corresponding to angiographic pulmonary flow grades 0, 1, 2, and 3, respectively.[9,11] The second, and perhaps more important, advantage of using a pressure wire during the procedure is that previous studies identified a distal pressure of ≥35 mm Hg as the point, where the risk of reperfusion pulmonary edema increases substantially.[9,11] This has led to the use of a distal pressure of 35 mm Hg as a metric to terminate the BPA procedure.[9,11]

In the current era, BPA is performed over the course of 3 to 5 sessions with ≈ 4 to 10 vessels treated per session. The sessions are spaced out during a period of weeks to limit complications, contrast dose, and fluoroscopy time. In brief, the procedure is done via the right internal jugular (preferred) or femoral vein. Patients receive light conscious sedation, and heparin is given to achieve an activated clotting time of ≈200 s. A long introducer sheath is advanced to the left or right pulmonary artery. A 6F guide catheter (multipurpose, Amplatz, or Judkins Right) is inserted through the sheath into the pulmonary arteries for selective pulmonary angiography. Pulmonary artery lesions are identified, and vessel and lesion diameter are assessed using quantitative coronary angiography tools and data from previous computed tomography angiography. Selected lesions are crossed using 0.014″ wires with the patient doing deep inspiration as needed to stretch the pulmonary vessels and facilitate wire passage. Intravascular imaging is used to interrogate the lesions and pressure wire measurements to guide the procedure. The vessel is then dilated with undersized balloons of increasing diameter (1.5–10.0 mm) with a goal of restoring normal blood flow but not necessarily eliminating the lesion completely. Lesions in the inferior segments are often prioritized for treatment because they are easier to access, and the lower lobes have a more extensive vascular network than the other lobes.[13,22]

Despite modifications to the BPA procedure, there are a number of complications, including death, reperfusion pulmonary edema, and vessel injury that can occur. Death associated with the procedure is 0.34% in appropriately selected patients, which is a decline from the initial report of 5.6%. The rate of significant reperfusion pulmonary edema has also declined over time with careful monitoring of distal pulmonary artery pressures. Before monitoring, moderate–severe or extremely severe reperfusion pulmonary edema on chest x-ray occurred in 6.4% of patients. With pressure wire monitoring, this has declined to <1%.[9,11] Other vessel-related injuries include pulmonary artery dissection, guidewire perforation, or frank rupture and have been found to occur in ≈10.2% of treatment sessions with 7.8% of sessions requiring additional intervention, such as a covered stent or coil embolization.[10] The complication rate has been linked to the type of lesion treated. For abrupt narrowing, web-like or ring-like lesions, the complication rate is 2% to 3%, although it increases to ≈16% for subtotal occlusions.[13]

The interventional management of CTEPH remains a young field with many unanswered questions, and interventional cardiologists are well positioned to advance clinical care

in this area through partnership with a multidisciplinary team of CTEPH specialists. The current BPA procedure borrows heavily from techniques used to treat coronary artery disease but has yet to trial cutting balloons, scored balloons, or stenting with bare-metal stents, drug-eluting stents, or bioresorbable scaffolds as mechanisms to improve clinical outcomes and limit complications. Similarly, the use of embolic protection devices could increase the number of treatable vessels to include those that are currently deferred because of the presence of proximal thrombus. It is time for the interventional community to expand our horizons, recognize the pulmonary circulation, and become leaders in conducting future clinical trials of pulmonary vascular interventions for CTEPH.

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