The Evolving Role of Balloon Pulmonary Angioplasty in the Management of Chronic Thromboembolic Pulmonary Hypertension

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Patients with chronic thromboembolic pulmonary hypertension (CTEPH), characterized by pulmonary artery obstruction with unresolved embolism, have poor prognosis. Although pulmonary endarterectomy is the treatment of choice in the management of CTEPH, some patients are not operable. Balloon pulmonary angioplasty (BPA) is a catheter-based interventional treatment for patients with CTEPH. BPA has been considered a high-risk procedure, although the beneficial effects were promising. BPA has been modified and refined over the last 10 years. Recent evidence about modern BPA has consistently demonstrated the beneficial clinical effects with acceptable risks. BPA is now recommended in nonoperable CTEPH patients in addition to targeted medical therapy, although several questions such as long-term prognosis remain unanswered. BPA is still evolving for its application in the CTEPH treatment strategy. Further investigations are still necessary to define the role of BPA.

HISTORY AND EVOLUTION OF BALLOON PULMONARY ANGIOPLASTY

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease characterized by pulmonary artery occlusion or stenosis by embolism. CTEPH is a life-threatening disease associated with high pulmonary artery pressure that leads to right heart failure and death, if left untreated.[1] While the preferred, evidence-based treatment for CTEPH is pulmonary endarterectomy (PEA),[2] more than one-third of patients with CTEPH do not qualify for this procedure, according to the international CTEPH registry.[3] Instead, a targeted medical therapy can be employed and has been shown to be effective in treating nonoperable CTEPH,[4,5] although it is not curative.

Balloon pulmonary angioplasty (BPA) is a catheter-based interventional treatment that uses a balloon catheter (commonly 2 to 4 mm in diameter) to open an obstructed pulmonary artery (Figure 1). The first case in which

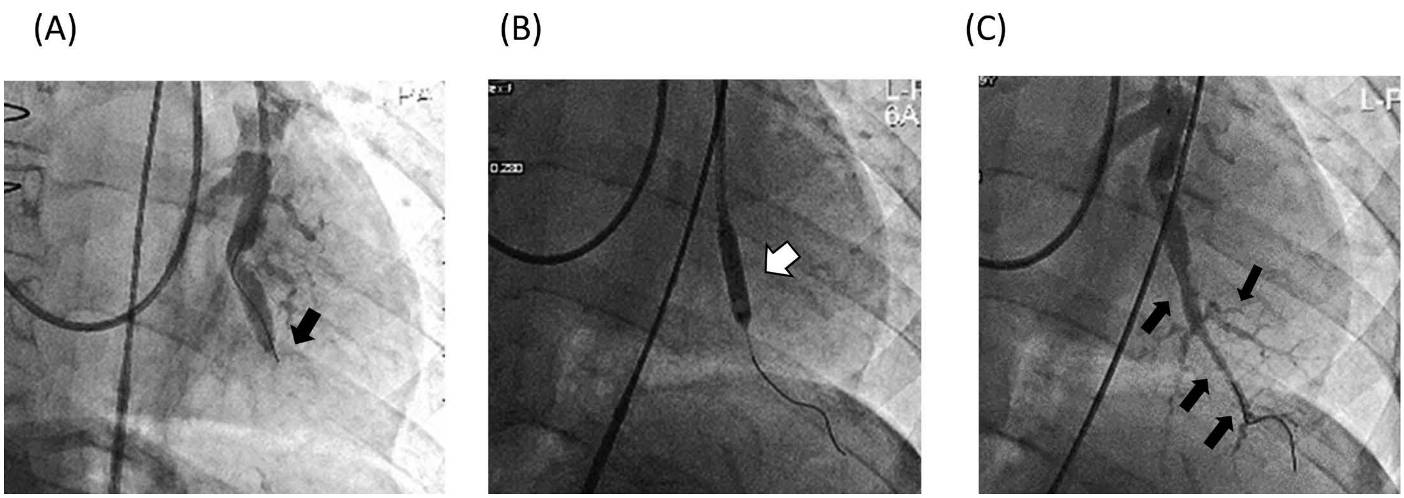

Figure 1: Angiography images of balloon pulmonary angioplasty. (**A**) Selective pulmonary angiography just before balloon angioplasty. Arrow: stenosis. (**B**) Ballooning for pulmonary artery stenosis. (**C**) Selective pulmonary angiography just after balloon angioplasty. Arrow: improved distal pulmonary artery flow.

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Table 1. Hemodynamic Results of Balloon Pulmonary Angioplasty[11,a]

Study	n	PVR (dyn/s/cm^{-5}) before BPA	PVR (dyn/s/cm^{-5}) After BPA	BPA effects on PVR
Sugimura et al.[8]	12	627 ± 236	310 ± 73	–54%
Mizoguchi et al.[10]	68	942 ± 367	327 ± 151	–65%
Andreassen et al.[12]	20	704 ± 320	472 ± 288	–33%
Fukui et al.[13]	20	889 ± 365	490 ± 201	–45%
Taniguchi et al.[15]	29	763 ± 308	284 ± 128	–63%
Ogo et al.[17]	80	880 ± 424	376 ± 160	–57%
Ogawa et al.[18]	308	853.7 ± 450.7	288.1 ± 194.5	–66%
Olsson et al.[19]	56	591 ± 286	440 ± 279	–26%
Brenot et al.[20]	154	604 ± 226	329 ± 177	–43%

Abbreviations: BPA, balloon pulmonary angioplasty; PVR, pulmonary vascular resistance.

[a]Data are presented as mean ± standard deviation unless otherwise noted.

BPA was used in the management of CTEPH was reported in 1988.[6] In 2001, Feinstein et al. described a series of 18 cases of CTEPH that were treated with BPA with positive hemodynamic effects, but a high incidence of complications.[7] Since then, Japanese pulmonary hypertension physicians and interventionists have modified and refined BPA procedures.[8–11] This review summarizes the evolving role of BPA in the management of CTEPH.

CLINICAL BENEFITS OF BPA IN CTEPH

Reports on the use of BPA over the last 10 years have consistently demonstrated favorable hemodynamic effects (Table 1). Early reports from Japan showed beneficial effects in nonoperable CTEPH, such as lowering of pulmonary vascular resistance (PVR) by 33% to 65% and improvement in World Health Organization functional class and 6-minute walking distance (6MWD).[8,10,12–15] Furthermore, exercise capacity and ventilatory efficiency, as measured by cardiopulmonary exercise tests, were reported to have improved.[16] Right ventricular (RV) remodeling has been reported to be reversed with BPA, improving RV volume, RV systolic function, interventricular septal bowing, and RV dyssynchrony.[13] A number of recent BPA reports from Japan also support the beneficial effects in CTEPH (Table 1),[17,18] though the reproducibility of these results in non-Japanese populations has been questioned. Recent BPA data from Germany[19] and France[20] also showed the applicability and reproducibility of BPA in their patient populations (Table 1).

There still remains a lack of long-term follow-up in patients having undergone BPA, although mid-term survival appears excellent in BPA groups.[21] Moreover, the prognosis of the patients who undergo BPA without targeted medical therapy is not clear.[21]

COMPLICATIONS OF BPA

BPA still carries a risk of potentially fatal complications. Clinically apparent lung injuries in early reports were frequent, occurring in approximately 60% of cases, and 17% of patients required mechanical ventilation.[10] High pulmonary arterial pressure,[7] the first BPA session, and severe hemodynamic parameters such as low cardiac output and high serum brain natriuretic peptide levels[9] have been reported to be the risk factors for lung injury after BPA. However, recently, the understanding of the mechanism for lung injury has been clarified. Lung injury caused by reperfusion edema is now considered a relatively rare complication of BPA.[11] Current consensus is that lung injury after BPA is mainly mechanical vascular injury caused by the distal tip of the wire or balloon overinflation (Figure 2).[22] Pulmonary perforation is identified in 0% to 7% of cases.[9,10,12,13] The pulmonary vascular perforation or rupture can

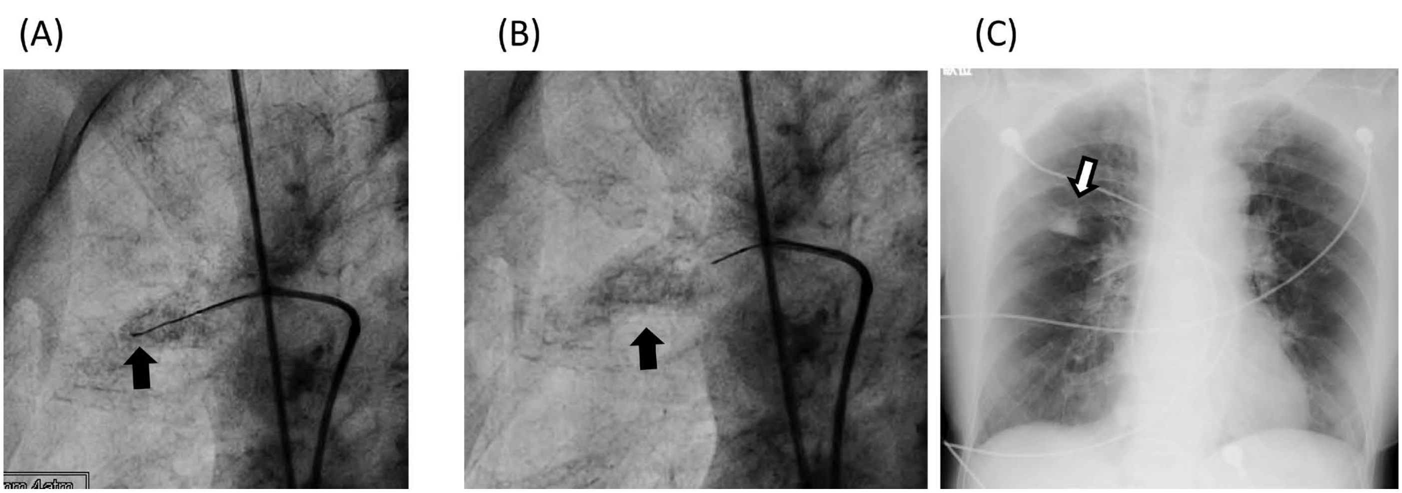

Figure 2: Lung injury caused by wire perforation during balloon pulmonary angioplasty. (**A**) Intervention wire. Arrow: wire and consolidation around the tip of wire. (**B**) After pullback of wire. Arrow: consolidation. (**C**) Chest x-ray image after balloon pulmonary angioplasty. Arrow: consolidation.

result in severe lung hemorrhage and even death. Periprocedural mortality has been reported to be up to 10%.[9,13,14] The incidence of BPA complications is decreasing, and the procedure is becoming safer due to a better understanding of the mechanisms, refined technical approach, and the improved management of complications.[22] Using a soft wire and a small-sized balloon is important to avoid serious lung injury. Employing a stepwise strategy to open some target vessels using balloons smaller than the size of the surrounding vessel during early sessions, particularly in cases with adverse hemodynamic parameters followed by the opening of larger vessels in subsequent sessions, has become standard.

CURRENT ISSUES AND LIMITATIONS OF BPA

Current BPA complication rates are obtained from large BPA expert centers. BPA is highly reliant on operator techniques and experiences. French data demonstrated better hemodynamic improvement and fewer complications with more recent procedures, suggesting that a learning curve exists for BPA.[20] Whether BPA procedures carried out in nonexpert centers increase the complication rates remains unclear. The restenosis or recurrence rates and long-term prognosis more than 5 years after BPA also remain undetermined. Comparison of the clinical effects between PEA and BPA for more distal forms of CTEPH also remains to be determined. One retrospective study suggested that the prognoses of patients who underwent BPA were comparable to those who underwent PEA.[14] However, these results should be carefully interpreted because BPA was only performed in nonoperable CTEPH patients. Analyses of long-term patency and impact on subsequent prognosis are awaited for BPA. One of the limitations of current BPA studies is the inclusion of patients treated with targeted medical treatment. Therefore, the efficacy of BPA and impact on survival may be confounded by medical treatment. Furthermore, BPA treatment goals, the role of preexistent targeted medical therapy, residual pulmonary hypertension after BPA, radiation exposure, and cost effectiveness[23] are issues that require further clarification.

FUTURE PERSPECTIVES

Patients with chronic vascular occlusions but normal pulmonary hemodynamics at rest, otherwise described as chronic thromboembolic disease (CTED), also require attention. BPA may be beneficial for CTED, as PEA has previously showed beneficial effects in CTED patients.[24] Comparisons between BPA and targeted medical therapy raise important clinical questions and the results of the RACE trial (NCT02634203) may be helpful in this regard.

BPA can also be applied in combination with PEA. A case series of hybrid treatment with BPA and PEA has been reported from Germany.[25] PEA for proximal lesions in one lung and BPA for distal lesions in the other lung is certainly a unique approach. BPA for residual pulmonary hypertension after PEA has been shown to be beneficial in terms of hemodynamics, but clinical benefits remain uncertain.[26] The role of pretreatment with BPA followed by PEA may also be an interesting approach to reduce PEA risk. Further investigation is needed to respond to each of these important yet unanswered questions.

CONCLUSIONS

CTEPH is a life-threatening disease with pulmonary hypertension that is characterized by obstruction in the pulmonary arteries. BPA, a catheter-based interventional treatment for CTEPH, was previously a less effective treatment with significantly higher rates of complications. Improvements in the BPA procedure continue to result in higher efficacy and lower complication rates. BPA is currently not a substitute for PEA but is one of the treatment choices for nonoperable CTEPH. Therefore, application of BPA should be thoroughly discussed by multidisciplinary CTEPH teams which include PEA surgeons. Further investigations into the unanswered questions regarding BPA, such as long-term prognosis, are required to further define its clinical role.

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