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EDITORIAL COMMENT

Angioplasty for Chronic Thromboembolic Pulmonary Hypertension

10 Years to Sharpen a Sword

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease characterized by persistent obstruction of pulmonary arteries with organized thrombi and secondary pulmonary microvasculopathy.[1] If left untreated, the prognosis is very poor, with a 5-year survival rate of only 10% in patients with a mean pulmonary artery pressure >50 mm Hg.[2] In 1962, Moser et al[3] reported the first case with CTEPH successfully treated with pulmonary endarterectomy (PEA).[3] Since then, PEA has gained widespread acceptance globally and has emerged as the standard treatment for CTEPH because of its substantial improvement in survival outcome.[4] Despite advances in surgical techniques, approximately 40% of patients with CTEPH are deemed ineligible for surgery because of inaccessible vascular obstruction or prohibitive comorbidities.[5] Balloon pulmonary angioplasty (BPA), an endovascular procedure to mechanically dilate the stenosis and obstruction of pulmonary arteries, is an important alternative for patients with inoperable CTEPH. In 2008, our group initiated BPA at Shanghai Pulmonary Hospital (Shanghai, China) and successfully treated patients with CTEPH (**Figure 1A**). Regrettably, we did not conduct a prospective study to confirm its efficacy and safety in this patient population. In 2012, landmark studies from Japan reported their refined BPA strategy and promising results for patients with inoperable CTEPH.[6,7] In 2016, we organized a group of Chinese interventional cardiologists specializing in pulmonary hypertension to visit Kyorin University School of Medicine (Tokyo, Japan) at the invitation of Prof Toru Satoh, a pioneer in BPA technique, to learn and introduce this innovative technique and strategy into China (**Figure 1B**). Over the last decade, a growing body of evidence derived from noncomparative studies, predominantly assessing hemodynamic parameters and exercise capacity pre- and post-procedure, has indicated that BPA appears to represent an effective therapeutic modality for individuals afflicted with inoperable CTEPH.[8-10] Results from 2 randomized controlled trials comparing the efficacy of BPA with riociguat, the first medical therapy approved for inoperable CTEPH, indicated that BPA might offer greater functional and hemodynamic improvements than medical therapies.[11,12] Despite growing evidence in favor of BPA, whether it confers long-term survival benefit comparable to PEA in CTEPH remains unclear but expectant.

In this issue of *JACC: Asia*, Masaki et al[13] reported results from the CTEPH AC registry (a multicenter, prospective, observational registry of patients with CTEPH in Japan) to investigate the long-term outcomes of CTEPH patients treated with BPA and PEA. In this study, 369 treatment-naive and 691 on-treatment patients, classified according to the presence of prior reperfusion therapy, were enrolled. The proportions of patients treated with the BPA and the PEA were 84.8% and 15.2% in treatment-naive patients, and 81.3% and 18.7% in on-treatment patients, respectively. The primary outcome was defined as the incidence of morbidity and mortality events. Their results indicated that BPA strategy had as acceptable morbidity and mortality as PEA strategy in both treatment-naive (5-year incidence of 10.2% vs 16.1%) and on-treatment patients (5-year incidence of 9.7% vs 6.9%). The 5-year all-cause mortality rates of patients with CTEPH decreased to <5% with both BPA

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FIGURE 1 Landmark Events of BPA in China

(A) Typical images of BPA for a patient with CTEPH at Shanghai Pulmonary Hospital，Tongji University (Shanghai, China) in 2008. Pulmonary angiography showed Chronic total occlusion lesions of pulmonary arteries of right middle and lower lobes before BPA procedure (left), recanalized pulmonary artery of right lower lobe immediately post-procedure (middle), and at six months post-procedure (right).
(B) Organized by Prof. Toru Satoh, Chinese CTEPH expert group visited Kyorin University School of Medicine (Tokyo, Japan) at the Spring Festival 2016, and exchanged expertise in BPA techniques with Prof. Toru Satoh and his colleagues. Front row, from the left: Zai-Xin Yu (余再新), Xiangya Hospital, Central South University; Takumi Inami (伊波 巧), Bing-Xiang Wu (吴炳祥), The Second Affiliated Hospital of Harbin Medical University; Toru Satoh (佐藤 徹), Zhi-Cheng Jing (荆志成), Guangdong Provencal People's Hospital, Guangdong Academy of Medical Sciences; Haruhisa Ishiguro (石黒晴久); Second row, from the left: Fu-Hua Peng (彭富华), FuWai Hospital,Chinese Academy of Medical Sciences; Xin Jiang (蒋鑫), Guangdong Provencal People's Hospital, Guangdong Academy of Medical Sciences; Gang-Cheng Zhang (张刚成), Zhongnan Hospital of Wuhan University; Zhen-Wen Yang (杨振文), Tianjin Medical University General Hospital; Kai-Jun Cui (崔凯军), West China hospital, Sichuan University; Sheng Liu (刘盛), FuWai Hospital,Chinese Academy of Medical Sciences; Yoshio Nishina (仁科善雄).
BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension.

and PEA strategies. Using data from a nationwide registry, this study firstly defined the incidence of morbidity and mortality events as the primary outcome, showing promising outcomes for patients with CTEPH in the modern era with similar long-term outcomes between inoperable patients treated with BPA and operable patients treated with PEA. Remarkably, because of the study design of different treatment strategies underlying different populations, no direct comparison of outcomes could be achieved between the 2 treatment strategies.

The proportions of patients treated with BPA in this study exceeded 80%, far more than that from Europe and the United States.[14] As the investigators discussed, this difference can be partly explained by distinctive characteristics of CTEPH patients in Japan, including with an older age, female predominance, and lower prevalence of prior venous thromboembolism, which might contribute to more patients with distal type of lesions in Japan. Another reason that cannot be ignored is that more patients with proximal lesions can be treated with BPA in Japan because of their rich experience in BPA. A recently published study by Nishihara et al[15] from Okayama Medical Center in Japan compared efficacy and safety of BPA in CTEPH patients with surgically accessible and inaccessible lesions. Their results indicated that, although improvements were less pronounced in

CTEPH patients with proximal lesions compared to those without such lesions, BPA significantly improved hemodynamic and functional parameters to comparable levels in both groups, with no difference in the frequency of complications and cumulative survival rates. These data may support the notion that BPA represents an important alternative for CTEPH patients with proximal lesions who are deemed inoperable due to factors such as comorbidities, advanced age, frailty, or patient preference, et cetera. In addition, the PEA procedure is challenging and technically demanding, contributing to a limited number of PEA expert centers (conducting >50 PEA procedures per year) in most countries. This disparity between the number of PEA procedures performed and the actual demand highlights the pressing need for additional research comparing the efficacy and safety of BPA vs PEA for proximal lesions in CTEPH to add more evidence for BPA in proximal lesions of CTEPH.

Pulmonary arterial hypertension medications targeting microvasculopathy in CTEPH have also come a long way in recent years. Riociguat has been reported to improve hemodynamic parameters and exercise capacity and is the first medical therapy approved for inoperable CTEPH.[16] Subcutaneous treprostinil has been reported as a safe intervention that enhances exercise capacity in patients with severe inoperable CTEPH. It has received marketing authorization for individuals classified as WHO functional class III or IV in Europe.[17] Furthermore, the effectiveness of other medications used for pulmonary arterial hypertension (such as endothelin receptor antagonists and phosphodiesterase type-5 inhibitors) in individuals with CTEPH is still in debate. Nevertheless, these medications are routinely prescribed by physicians in real-world clinical settings to alleviate symptoms.[18,19] In this study, pulmonary arterial hypertension medications were used in more than one-half of the patients, nearly equal in both BPA and PEA strategies.[13] It is difficult to rule out the impact of pulmonary arterial hypertension medications on long-term outcomes of patients with CTEPH in both treatment strategies. Survival benefit from PEA in operable CTEPH is clear as reported in previous studies,[4] but evidence of that from BPA in inoperable CTEPH is scarce. So, further studies comparing long-term survival improvement between pulmonary arterial hypertension medications and medications plus BPA for patients with inoperable CTEPH are needed to accurately assess the survival benefit of BPA procedure for patients with inoperable CTEPH.

The hemodynamic criteria for CTEPH used in this prospective registry was a mean pulmonary arterial pressure ≥25 mm Hg, which has been updated to more than 20 mm Hg in recent 2022 European Society of Cardiology/European Respiratory Society guidelines for the diagnosis and treatment of pulmonary hypertension.[1] The decrease of cutoff value on hemodynamic criteria for pulmonary hypertension urges more focus on what has previously been called "borderline" pulmonary hypertension. Similarly, the current guideline proposes the term of chronic thromboembolic pulmonary disease (CTEPD) to unify symptomatic patients with pulmonary organized thrombus obstructions, with (ie, CTEPH) and without pulmonary hypertension. This conceptual change aims primarily to highlight the subset of CTEPH patients without pulmonary hypertension but who exhibit exercise limitations and reduced quality of life and may have been overlooked previously. A calculation extrapolated that one CTEPH patient ever diagnosed indicated ~20 times more CTEPD patients with previous history of acute pulmonary embolism.[20] Both the decrease of cutoff value on hemodynamic criteria and the conceptual of CTEPD enhance the awareness of early diagnosis and thus early treatment for this severe disease. Some case series previously indicated that CTEPD with "borderline" pulmonary hypertension or without pulmonary hypertension could benefit from both PEA[21] and BPA,[22] resulting in symptom relief, improved exercise capacity, and enhanced quality of life. However, because of the unknown natural history of CTEPD without pulmonary hypertension, there remains insufficient knowledge on risk-benefit analysis to support routine recommendation of PEA, a traumatic surgery, for these patients. In that case, BPA might be a preferred initial choice and warrants more studies in the future.

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