

Point-by-point responses to reviewers' comments

Dear Editors and the reviewers:

Thanks a lot for reviewing our manuscript and giving us an opportunity to revise our paper. We have carefully taken reviewers' comments into consideration when preparing our revision. The constructive advice of the editors and reviewers has substantially improved our paper.

Our detailed responses to the comments are as follows:

Science Editor: 1 Scientific quality: The manuscript describes a review of the balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. The topic is within the scope of the WJCC. (1) Classification: Grade C; (2) Summary of the Peer-Review Report: This is a review of a wide range of studies related to BPA. However, it cites a wide range of literature, the reviewer afraid that it may be difficult for readers to read because they are not sure which information is important. The questions raised by the reviewers should be answered; and (3) Format: There are 2 tables and 6 figures. A total of 160 references are cited, including 59 references published in the last 3 years. There are 4 self-citations. 2 Language evaluation: Classification: Grade B. The language has been edited a native English speaker. 3 Academic norms and rules: The Copyright License Agreement should be signed by all authors. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by National Precision Medical Research Program of China. The topic has not previously been published in the WJCC. 5 Issues raised: (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); and (2) The authors did not provide original pictures. Please provide the original figure

documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. 6 Re-Review: Required. 7 Recommendation: Conditional acceptance.

Authors: We would like to thank the editors for carefully evaluating our paper. Our responses to reviewers can be found in the following texts. Approved grant application form has been uploaded. Original pictures embedded in PowerPoint have been provided. The audio core tip is also attached.

Reviewer #1: General Comments This is a review of a wide range of studies related to BPA. While it cites a wide range of literature, the reviewer afraid that it may be difficult for readers to read because they are not sure which information is important. For example, the paragraphs on inflammatory markers, cardiac function and myocardial injury seem unnecessary.

Authors: Although BPA is an interventional technique described early in 1988 for CTEPH, only nearly 300 articles have been published so far, most of which got published online in the last 8 years, meaning that great progress and booming development have taken place. The purpose of our paper is to provide a comprehensive state-of-the-art review of BPA for CTEPH from different aspects, i.e. pathophysiology of CTEPH, BPA history and development, therapeutic principles, indications and contraindications, interventional procedures, imaging modalities, efficacy and prognosis, complications and managements, bridging and hybrid therapies, ongoing clinical trials and future prospects, thus inevitably citing a wide range of literature. We do understand the reviewer' s concerns, that is why we use structured writing, and we believe that a clear lay-out of this manuscript will enable and facilitate easy understanding by interested

readers. At present, most of BPA studies focus on the effect evaluation from different aspects, such as hemodynamics and exercise capacity (most widely), right ventricular function (by different imaging techniques), cardiopulmonary function (assessed by cardiopulmonary exercise test and pulmonary function test), yet these effects have not been extensively summarized, therefore, we spared large space for this point. Inflammatory markers and myocardial injury have rarely been explored, although there are limited published articles, these two parts are essential aspects of the important section 'EFFICACY AND PROGNOSIS EVALUATION' , we strongly believe that the readers will benefit from this kind of essential discussion on BPA effects.

Reviewer #1: Major Comments COMPLICATIONS AND MANAGERMENTS It is not common to perform BPA using PEPSI because of its complexity. The most important findings which reported from Inami T' s researches are the report that RPO did not occur when the distal pressure of the target lesion was <33 mmHg (ref. 1). Based on this study, it has been recommended to limit incomplete dilation with an undersized balloon in the case of a proximal mPAP > 40 (35 mm Hg in some facilities). 1) Pressure-wire-guided percutaneous transluminal pulmonary angioplasty: a breakthrough in catheter-interventional therapy for chronic thromboembolic pulmonary hypertension. Inami T, Kataoka M, Shimura N, Ishiguro H, Yanagisawa R, Fukuda K, Yoshino H, Satoh T. JACC Cardiovasc Interv. 2014 Nov;7(11):1297-306.

Authors: We agree with the reviewer that it is not common to perform BPA using PEPSI today. The effective role of PEPSI with or without pressure-wire guidance to reduce reperfusion pulmonary edema (RPE) was demonstrated based on two important articles (Inami T, Kataoka M, Shimura N, et al. Pulmonary edema predictive scoring index (PEPSI), a new index to predict risk of reperfusion pulmonary edema and

improvement of hemodynamics in percutaneous transluminal pulmonary angioplasty. *JACC Cardiovasc Interv.* 2013;6(7):725–736. doi:10.1016/j.jcin.2013.03.009; Inami T, Kataoka M, Shimura N, et al. Pressure-wire-guided percutaneous transluminal pulmonary angioplasty: a breakthrough in catheter-interventional therapy for chronic thromboembolic pulmonary hypertension. *JACC Cardiovasc Interv.* 2014;7(11):1297–1306. doi:10.1016/j.jcin.2014.06.010). As we discussed in ‘COMPLICATIONS AND MANagements’, RPE was once considered as a major and fatal complication after BPA in the early stage, PEPSI was a useful tool to minimize the risk of RPE after BPA at that time. However, this kind of strategy is too stringent and impractical for specialized centers and experienced hands where vessel lesions from 4-10 sites are typically treated within one BPA session. In addition, as the reviewer mentioned, PEPSI with pressure-wire guidance to achieve distal mPAP <35 mmHg is too complex and requires extra time and money due to the use of pressure-wire. Thanks to the reviewer, we added this point in our discussion.

Reviewer #1: BPA PRINCIPLE Unlike PEA, BPA only depresses fibrous tissue, not eliminates it. Reports of different amounts of fibrous tissue in bands, webs, and occlusive lesions are true, but most important thing for the readers, the efficacy of BPA is limited when the amount of fibrous tissue is high.

Authors: The reviewer usefully reiterate several important points discussed in our paper. We agree with the reviewer that PEA removed the accessible organized thrombus within one procedure, yet intravascular organized thrombi were not eliminated by BPA. BPA functions through dissection and compression of fibrous tissues as well as vessel stretching. We thank the reviewer for his/her recognition of our word expression on different amounts of fibrous tissue in bands, webs, and occlusive lesions. As was discussed in our manuscript, ‘*The mechanism of*

lumen enlargement at the site of subtotal occlusion was similar to that of web lesion, but the organized thrombus was only mildly compressed owing to large amount of fibrous tissues' , thus limited efficacy may be observed through compressing organized thrombus which contains high amount of fibrous tissue, we emphasize what the reviewer think is important by adding *'indicating limited efficacy might be achieved in lesions rich in fibrous tissue' .*

Reviewer #1: INDICATIONS AND CONTRAINDICATIONS Although the authors describe that old age is not a relative contraindication for PEA, BPA generally has more tolerant indications for old age and co-morbidities than PEA. Diabetes or hypertension does not contraindication to BPA. Furthermore, it is misleading to state that active infection is a contraindication to BPA, as BPA was performed in patient with CTEPH who suffer acute pneumonia. BPA is also not contraindicated in severe hepatic and renal dysfunction. Although COPD is not contraindicated, the most important precaution regarding BPA in patients with pulmonary disease is that if BPA is performed in the area of ventilatory disorders, It can cause hypoxemia.

Authors: We agree with the reviewer that elder age is actually not a contraindication for PEA or BPA, as demonstrated by similar effects and survival between young and old patients, and we modify our word expressions in the manuscript to illustrate this point more clearly, and write as *'In-hospital mortality and overall survival rates after PEA were comparable in patients aged ≥ 70 years and < 70 years[72]. Similarly, hemodynamic improvements, length of ICU and hospital stay, BPA-associated complications, and all-cause mortality were all comparable between younger and elderly patients receiving BPA[58, 73, 74], suggesting elder age is actually*

not a contraindication for PEA or BPA' . We agree with the viewpoints stated by the reviewers, and we **NEVER** point to diabetes, hypertension, active infection, and severe hepatic and renal dysfunction as contraindications to BPA, as we discuss in our paper, these conditions are **relative contraindications** for BPA procedures, BPA can certainly be performed in these situations, but careful consideration and caution must be taken when the above conditions exist. We believe there must be some misunderstandings here.

Reviewer #1: LESION SELECTION AND INTERVENTIONAL PROCEDURE Although the author uses the wording of "FFR" , it is not appropriate wording because the flow reservoir is not measured. The wording of "Ratio of distal: proximal pressures across the target lesion (Pd / Pa)" is sometimes used. Because BPA does not use a stent, it is difficult to achieve adequate dilatation, and the evaluation of dilatation is not important in OCT and IVUS immediately after dilatation. Because spontaneous vessel dilatation occurs (ref. 1), it difficult to predict the vessel status of the chronic phase due to on an acute phase luminal evaluation. Acute vascular lumen opening as a therapeutic goal should not be recommended because it increases the risk of vascular rupture and RPO. 1) Negative acute hemodynamic response to balloon pulmonary angioplasty does not predicate the long-term outcome in patients with chronic thromboembolic pulmonary hypertension. Hosokawa K, Abe K, Oi K, Mukai Y, Hirooka Y, Sunagawa K. Int J Cardiol. 2015 The femoral vein approach is feasible and practiced even with the inferior vena cava filter.

Authors: Thanks for the reviewer' s good advice, we delete the inappropriate expression 'FFR' and replace it with 'the distal to proximal pressure ratio across the targeted lesion' .

Actually, we do not recommend routine use of OCT or IVUS in our center, and we have to admit that using OCT or IVUS to merely evaluate instant effects immediately after balloon dilatation is unnecessary, however, the roles of OCT or IVUS in selecting optimal balloon size and judging whether the guiding wire is in the true vessel lumen or not should not be neglected, OCT or IVUS is usually utilized under these conditions. Here in our manuscript, we just summarize and list several items or ways that we can use to roundly judge when to terminate balloon dilatation, and we are not intended to recommend using OCT or IVUS to evaluate instant pulmonary blood flow. We do understand that spontaneous vessel dilatation occurs after BPA, as was previously discussed in our paper, 'It is worth noting that a single vessel should not be dilated too aggressively to avoid any complications, the effect of dilatation may not be immediately apparent, and the targeted vessel will be spontaneously dilated as blood flows (Figure 6)[80, 81]' . We also agree with the reviewer that RHC and BPA can be performed through the femoral vein approach even with the inferior vena cava (IVC) filter. Some successful examples of transcatheter interventions across an inferior vena cava filter have been reported (PMID: 11285601; 12822152; 23468455), but femoral approach with IVC filter may be confronted with complications such as filter migration or dislodgment as well as guidewire or catheter entrapment (PMID: 12822152), in this regard, femoral approach with IVC filter is not commonly recommended unless we have to, in our center' s experience, we never attempt femoral approach in patients with IVC filter.

Reviewer #1: Regarding Current therapeutic goal of BPA procedure is to achieve normalization of hemodynamics (mPAP<25 mmHg) and oxygen saturation >95% without using

any vasodilators or oxygen supplementation [85–87]. Symptoms on exertion may persist even when $mPAP < 25$. It is unclear whether riociguat is effective or not, and there is no concrete evidence on therapeutic goal. The author has to describe that the therapeutic goal of BPA is controversial.

Authors: To achieve normalization of hemodynamics ($mPAP < 25$ mmHg) and oxygen saturation $> 95\%$ without using any vasodilators or oxygen supplementation is the current therapeutic goal of BPA procedure in National Hospital Organization Okayama Medical Center, Japan, which is the largest BPA center (with more than 2000 procedures) in the world (PMID: 28596430, 28193682, 29669971), that is quite consistent with our therapeutic notion of BPA procedures. We agree that symptoms on exertion may persist even when $mPAP < 25$ among CTEPH patients, but those patients usually have $< 95\%$ oxygen saturation without oxygen supplementation. As suggested by the reviewer, we acknowledge the controversial role of the therapeutic goal of BPA in our manuscript, and write as ‘Although controversies exist, current therapeutic goal of BPA procedure is to achieve normalization of hemodynamics ($mPAP < 25$ mmHg) and oxygen saturation $> 95\%$ without using any vasodilators or oxygen supplementation, at least in our center and Okayama Medical Center, the world largest BPA center[85–87]’ . Thanks for the reviewer’s good advice.

Reviewer #1: PROMISING IMAGING MODALITIES IVUS, which has a lower resolution than OCT, is difficult to assess for thin organised thrombi in the vessel. IVUS is used primarily to measure vessel diameter to determine balloon size.

Authors: Thanks for the reviewer’s comments, we revise related contents and write as

'IVUS is an endovascular imaging technique that uses a miniaturized ultrasound probe to generate sound waves and produce real-time intravascular images, and due to relatively lower resolution compared with OCT, IVUS has limited ability to assess thin organized thrombi, and is mainly applied to determine vessel diameter so as to select the appropriate balloon' .

Other revisions:

1. We revised the references to meet the formatting rules according to the 'Submission Guidelines' .
2. We updated the data of Figure 1 till Apr 26, 2020.
3. We revised the formats of Figure Legends according to 'Format for Manuscript Submission: Review' .
4. Some grammatical errors in Table 1 were corrected.

All changes in the manuscript are indicated in the text by using track changes.

Thanks once again for reviewing our paper.

Yours sincerely

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