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High perfusion pressure as a predictor of reperfusion pulmonary injury after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background: Clinical efficacy of balloon pulmonary angioplasty (BPA) to the patients with non-operable chronic thromboembolic pulmonary hypertension (CTEPH) for improving pulmonary hemodynamics and exercise tolerance has been reported in these several years. However, reperfusion pulmonary injury (RPI) remains to be a major complication of BPA to overcome. This study elucidated the local predictor of RPI.
Methods: Twenty-eight consecutive patients with non-operable CTEPH underwent BPA for lesions in the segmental or sub-segmental vessels. Pre- and post-BPA pulmonary arterial pressures at proximal (Pp) and distal (Pd) to the stenosis were measured by a 0.014-in. pressure wire. Positive or negative RPI was evaluated by chest computed tomography in each re-perfused segment separately 4 h after BPA.
Results: Pressure measurements pre- and post-BPA were obtained from 110 lesions, where Pd and pressure ratio (Pd/Pp) increased after BPA in all lesions. Among them, RPI was observed in 49 lesions (44.5%). In the RPI-positive lesions, post-BPA Pd and post-BPA Pd/Pp were higher compared with the RPI-negative lesions. Multivariate logistic analysis revealed that the post-BPA Pd was independently associated with RPI incidence. Receiver operating characteristic curve analysis demonstrated the best cut-off value of 19.5 mm Hg for post-BPA Pd to predict RPI.
Conclusions: High reperfusion pressure after BPA could be a predictor of RPI. Monitoring local pressure during BPA procedure may have a potential to reduce the incidence of RPI.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by the obstruction of the pulmonary arteries with organized thrombus and intraluminal fibrous tissue, which leads to elevated pulmonary vascular resistance (PVR), severe pulmonary hypertension, and right heart failure [1–5]. In addition, if appropriate medical intervention is not provided, the prognosis of patients with CTEPH is extremely poor, with a reported only 10% five-year survival rate in patients with a mean pulmonary arterial pressure (PAP) of >50 mm Hg [6]. In this context, pulmonary endarterectomy (PEA) is a gold standard of treatment that can dramatically reduce PAP and improve the prognosis of patients with CTEPH [7–9]. However, PEA for CTEPH with peripherally located organized thrombi has been reported to be less effective for the improvement in pulmonary hemodynamics and a higher perioperative mortality rate compared with that for CTEPH with proximal thrombi [10,11]. Thus, it has been reported that up to 40% of patients with CTEPH were considered non-operable, due to peripherally located organized thrombus or other comorbidities [7]. Therefore, a safer and more effective treatment for non-operable CTEPH is urgently needed.

The first report of balloon pulmonary angioplasty (BPA) for a patient with CTEPH was published in 1988 [12]. In 2001, Feinstein et al. reported marked improvements in the pulmonary hemodynamics and exercise tolerance in the series of BPA to 18 patients with CTEPH [13]. Recent several studies reported the refined BPA procedure and agitated the interest of many interventionists due to its clinical efficacy [14–18]. In addition, we have reported that BPA could achieve comparable reduction in mean PAP with PEA [15]. At the same time, reperfusion

Abbreviations: BPA, balloon pulmonary angioplasty; CI, cardiac index; CO, cardiac output; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; IVUS, intravascular ultrasound; MLD, minimal lumen diameter; NIPPV, non-invasive positive pressure ventilation; PAG, pulmonary angiography; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PEA, pulmonary endarterectomy; Pd, mean pulmonary arterial pressure distal to the stenosis; Pp, mean pulmonary arterial pressure proximal to the stenosis; PVR, pulmonary vascular resistance; ROC, receiver-operating characteristic; RPI, reperfusion pulmonary injury; 95% CI, 95% confidence interval.

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pulmonary injury (RPI), a major complication of BPA is yet to be resolved. Previous reports have shown that RPI after BPA occurred in 53–64% of cases [13–16]. RPI includes hemosputum, worsening of hypoxemia, or increased density of chest computed tomography (CT) in the dilated segment regardless of symptoms [14]. RPI is thought to be caused by pulmonary edema and/or pulmonary bleeding. Because of the difficulty to differentiate between these etiologies by only chest X-ray or CT, it is called reperfusion pulmonary "injury". Although it has been hypothesized that exposure to high reperfusion pressure after balloon dilation may lead to RPI [14], no published reports have monitored the local pressure around the stenosis before and after BPA. In the present study, we analyzed the effect of BPA on the local pressure hemodynamics, and investigated whether the local pressure might be a predictor of RPI.

2. Methods

2.1. Patient enrollment

Between October 2012 and April 2015, 48 patients were diagnosed as CTEPH at Kobe University Hospital in Japan. The diagnosis of CTEPH was established according to the published clinical guidelines [19]. All patients had a more than 25 mm Hg of mean PAP and less than 15 mm Hg of pulmonary capillary wedge pressure (PCWP), and were definitively diagnosed as CTEPH after identification of multiple stenosis and obstruction of the bilateral pulmonary arteries via pulmonary angiography (PAG). The distribution of the thromboembolic lesions and intimal thickening of the pulmonary artery was evaluated using contrast-enhanced chest CT and PAG, and the results were reviewed by experienced cardiologists, cardiovascular surgeons, and radiologists. The assessment of operability was conducted by cardiologists and cardiovascular surgeons according to the criteria for PEA [20], which consider the distribution of stenosis, obstruction, and intimal thickening, age, and comorbidities. Based on these assessments, 19 patients were judged to be operable and underwent PEA, while 29 patients were judged to be non-operable and therefore suitable for BPA. Only data from BPA were included in this analysis.

The design of the present study was approved by the Ethics Committee of Kobe University, and conformed to the tenets of the Declaration of Helsinki. All enrolled patients provided their informed written consent.

2.2. Hemodynamic and exercise tolerance analysis

We performed right heart catheterization and measured the PAP, right atrial pressure, and PCWP using a flow-directed thermodilution catheter immediately before the first BPA procedure in each patient. PVR and cardiac output (CO) were calculated using the Fick method. In addition, 6-min walk distance and the World Health Organization functional class were obtained 1 or 2 days before the first BPA procedure.

2.3. Balloon pulmonary angioplasty and pulmonary arterial pressure analysis

In each BPA session, we placed a 9-Fr sheath (XEMEX Introducer Set, Zeon Medical, Tokyo, Japan) into the vein (typically into the femoral vein or the internal jugular), and then brought a 70 cm or 90 cm 6-Fr Britetip sheath introducer (BRITE TIP® Interventional Sheath Introducer; Cordis/Johnson & Johnson, Bridgewater, NJ, USA) to the main pulmonary artery via the 9-Fr sheath, using a Radifocus 0.035-in. guide wire (Terumo, Tokyo, Japan) and a 5-Fr pigtail catheter (Goodtec catheter, Goodman, Aichi, Japan). When the sheath was inserted, an initial dose of heparin (2000–5000 U) was administered, and 1000 U of heparin was administered every hour to maintain 200–300 s of intra-operative activated clotting time. We then selected a segmental or subsegmental pulmonary artery using a 6-Fr guide catheter (Autobahn; Multipurpose, or Judkins right 4.0; NIPRO Corporation, Osaka, Japan) via the long sheath, and performed angiography to identify any stenoses or occlusions. A 0.014-in. guide wire (Cruise; Asahi Intecc, Aichi, Japan or Chevalier 14 Floppy, FMD, Saitama, Japan) was passed through the target lesions under the support of a microcatheter (Prominent Raptor, Tokai Medical Products, Aichi, Japan). Using intravascular ultrasound (IVUS) (Eagle Eye® Platinum; Volcano Corp, Rancho Cordova, CA, USA), we measured the vessel diameter at the site of the thrombi [14], and the lesions were dilated to an appropriate size using balloon catheters (2.0–9.0 mm, depending on the diameter of the vessel). To prevent pulmonary arterial injury, the maximum balloon size was slightly smaller than the actual vessel diameter, and did not exceed 90% of the actual vessel diameter [14]. The procedures were repeated on other segments after one week interval during the same admission until the mean PAP had normalized. RPI symptom comprises hemosputum, desaturation, intratracheal intubation, hemodynamic compromise which needs percutaneous cardiopulmonary support and periprocedural mortality. Procedure time for one BPA session was limited up to 2 h for safety assurance. If necessary, we administrated oxygen or non-invasive positive pressure ventilation (NIPPV) to the patient.

2.4. Angiographic analysis

Pulmonary angiographic data before and immediately after BPA were analyzed using edge-detection techniques (QCA-CMS5.1, Medis Imaging Systems, Leiden, The Netherlands). The quantitative angiographic parameters included: (1) the minimal lumen diameter (MLD), (2) the reference vessel diameter, which was measured at an apparently normal area proximal to the target stenosis, (3) the vessel expansion ratio, which was defined as the MLD after balloon expansion divided by the MLD before the wire passed through the lesion, and (4) the balloon-vessel ratio, which was defined as the balloon diameter divided by reference vessel diameter before the BPA.

2.5. Pulmonary arterial pressure assessment

The local PAP was measured at proximal and distal to the stenosis. Exclusion criteria for pressure assessment included severe bending lesions, uncrossable lesions, lesions without pressure gradient, and lesions with short peripheral margin. After we passed a 0.014-in. guide wire through the target lesion, the guide wire was changed to a pressure wire (Aeris, Saint Jude Medical Systems, Uppsala, Sweden). After dilation of the stenosis by balloon catheter, we performed additional assessments of the mean proximal and distal PAPs. Pp was defined as the mean PAP proximal to the stenosis measured at the tip of guiding catheter and Pd as the mean PAP distal to the stenosis measured using the pressure wire sensor. The pressure ratio was calculated as Pd divided by Pp, and the absolute increase in Pd as the post-BPA Pd was subtracted by the pre-BPA Pd.

2.6. Computed tomography analysis

4 h after each BPA session, we took chest CT to evaluate incidence and location of RPI. RPI was defined when there was any increase in density (regardless of the size) observed on CT image in the corresponding pulmonary segment of the dilated pulmonary artery (Fig. 1). All CT images were analyzed by two independent observers who were blinded to all clinical information. When the two observers' decisions were inconsistent, a third observer analyzed the images for making the final decision.

2.7. Statistics analysis

All data were presented as mean ± standard deviation or odds ratios and 95% confidence intervals (95% CI), unless otherwise stated. Analyses were performed using SPSS statistical software (v. 17.0, SPSS, Chicago,