Pulmonary Artery Diameter Predicts Lung Injury After Balloon Pulmonary Angioplasty in Patients With Chronic Thromboembolic Pulmonary Hypertension

Koichi Sugimoto,1,2 MD, Kazuhiko Nakazato,1 MD, Nobuo Sakamoto,1 MD, Takayoshi Yamaki,1 MD, Hiroyuki Kunii,1 MD, Akiomi Yoshihisa,1 MD, Hitoshi Suzuki,1 MD, Shu-ichi Saitoh,1 MD, and Yasuchika Takeishi,1,2 MD

Summary

Balloon pulmonary angioplasty (BPA) has been an attractive strategy for chronic thromboembolic pulmonary hypertension (CTEPH), even though it occasionally causes lung injury. However, predictive factors of lung injury after BPA have not been established. Pulmonary artery (PA) dilatation is often observed in patients with pulmonary hypertension. We investigated the association between PA diameter and complications after BPA.

The subjects were 19 CTEPH patients who underwent BPA. Patients were divided into two groups: patients with lung injury including asymptomatic lung infiltration on computed tomography (CT) images or mild hemoptysis (group L, n = 9) and no complications (group N, n = 10). PA diameter was measured on CT and corrected by the body surface area (PA diameter index).

There were no significant differences in hemodynamic indices or the number of treated vessels between the two groups. Right, left, and main PA diameter indices were higher in group L than in group N. Among the clinical variables, the right, left, and main PA diameter indices were significant predictors for lung injury caused by BPA (right PA: OR 1.819, 95%CI 1.056-3.135, P < 0.05; left PA: OR 1.857, 95%CI 1.091-3.159, P < 0.05; main PA: OR 1.399, 95%CI 1.001-1.956, P < 0.05).

The PA diameter index can be used to effectively predict the risk of lung injury after BPA. (Int Heart J 2017; 58: 584-588)

Key words: Complication, Predictor

Chronic thromboembolic pulmonary hypertension (CTEPH) is a relatively rare and fatal disease that leads to right heart failure due to chronic obstruction of the pulmonary artery by organized thrombus. An elevated mean pulmonary arterial pressure (mPAP) (> 30 mmHg) is reported to have a poor prognosis.1,2 Recently, the CHEST-1 study demonstrated the improvement of exercise tolerance by administration of riociguat, a soluble guanylate cyclase stimulator,3 but there was insufficient reduction of mPAP. Although pulmonary endarterectomy (PEA) is a first choice for treatment of CTEPH,4 not all patients are suitable candidates due to distal localization of the lesions or to the high risk associated with surgery. Balloon pulmonary angioplasty (BPA) results in a dramatic reduction of pulmonary artery pressure and can be performed in inoperable patients.5 Indeed, there have recently been more reports showing the effectiveness of BPA.6,7 However, pulmonary edema or hemorrhage occurs at a relatively high frequency. Possible causes of lung injury are thought to be mechanical injury by a guide wire or balloon and reperfusion injury by cytokine release.8,9 Inami, et al have proposed that the pulmonary edema predictive scoring index (PEPSI), which is calculated from the grade of pulmonary blood flow change and pulmonary vascular resistance (PVR), is a useful predictor for reperfusion pulmonary edema after BPA.10 However, since PEPSI is an invasive predictor, a non-invasive and pre-procedure predictor needs to be identified.

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Pulmonary artery dilatation is often recognized in patients with severe pulmonary hypertension. Iyel, et al reported that the pulmonary artery to aorta ratio shows a significant correlation with pulmonary artery pressure in severe chronic obstructive pulmonary disease patients.11 Schötzl, et al reported that pulmonary artery diameter corrected by body surface area is the only independent predictor for prognosis after PEA.12 Additionally, pulmonary artery dilatation correlates with the risk of unexpected death in CTEPH.13 However, the importance of the pulmonary artery diameter during and after BPA procedures is still unclear. We, therefore, examined the usefulness of pulmonary artery diameter in predicting lung injury after BPA.
Study subjects: The subjects were 19 CTEPH patients diagnosed by a lung perfusion scan, right heart catheterization, and selective pulmonary arteriography who underwent BPA (2 males, 17 females, age 61.0 ± 10.8 years) from July 2011 to February 2016 at Fukushima Medical University. The patients had symptoms in World Health Organization Functional Class (WHO-FC) II or greater. All of the patients underwent chest computed tomography (CT) to measure the pulmonary diameter index at pre-procedure and to evaluate complications due to BPA at post-procedure regardless of symptoms such as hemoptysis. Typical imaging findings of asymptomatic lung injury are shown in Figure 1. The patients were divided into two groups: group L (with lung injury, consisting of 2 cases of severe lung injury that required oral intubation and 4 cases of hemoptysis and 3 cases of asymptomatic lung infiltration recognized by chest X-ray or CT, n = 9) and group N (no lung injury after BPA, n = 10). Written informed consent was obtained from all study subjects. The study protocol was approved by the Ethics Committee of Fukushima Medical University in compliance with the Declaration of Helsinki.

Measurement of pulmonary artery diameter: The pulmonary artery diameter was measured by 3 examiners by CT at the main pulmonary artery (Figure 2) as described in a previous study. We also measured the right and left pulmonary artery diameters (Figure 2). CT examinations were performed using a 64-slice CT scanner (Aquilion 64, Toshiba Medical Systems Co., Ltd., Tochigi, Japan). Pulmonary artery diameter was corrected by body surface area (pulmonary diameter index). Right heart catheterization data and the PA diameter index were measured during initial hospitalization.

BPA procedures: All BPA procedures were carried out under proper anticoagulation therapy (approximately 2.0 prothrombin time international ratio of warfarin, 200 to 250 seconds of activated clotting time during BPA procedures) (Table I). We used a plastic jacket wire to penetrate through the obstructive lesions, and then replaced it with a conventional guide wire using a micro catheter to avoid peripheral perforation before observation by intravascular ultrasound (IVUS, Eagle Eye Platinum; Volcano, San Diego, CA, USA) and balloon expansion. The optimal balloon size was determined after measuring the vessel diameter by IVUS (60% to 80% of the reference diameter). The endpoints of ballooning were an improvement of blood flow on IVUS with color Doppler or pulmonary venous return confirmed by angiography. In every session, vessels from a maximum of two branches selected from only one side of the lungs were treated. After BPA, all patients under-
went overnight non-invasive positive pressure ventilation for respiratory management regardless of the presence or absence of complications. Patients were hospitalized and underwent BPA several times to finally achieve mPAP < 30 mmHg. The interval of each session was 2 to 4 weeks retrospectively.

Statistical analysis: Continuous variables are presented as the mean ± SD or median (interquartile). Categorical variables are expressed as numbers and percentages. The chi-square test was used for comparisons of categorical variables. Data of the two groups were compared using the independent Student’s t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. Logistic regression analysis was performed to assess the contribution of the major risk factor to complications after BPA. A value of $P < 0.05$ was considered significant for all comparisons. These analyses were performed using a statistical software package (SPSS ver. 21.0, IBM, Armonk, NY, USA).

**RESULTS**

Figure 3 shows the efficacy of BPA on cardiac index, mPAP, and PVR in all the patients. The median number of sessions was 3.0 (interquartile range, 2.0 - 4.0) and the median number of treated vessels was 7.0 (inter quartile range, 4.0 - 10.0) (Table I). BPA markedly reduced the levels of mPAP (47.6 ± 13.0 to 31.2 ± 11.3 mmHg, $P < 0.01$) and PVR (11.4 ± 8.2 to 6.0 ± 4.7 WU, $P < 0.05$). In two cases, BPA could not be repeated until the hemodynamic indices were sufficiently improved because of severe pulmonary edema.

Table I shows comparisons of the clinical characteristics between the N and L groups. There were no significant differ-
Table II. Logistic Analysis of Possible Predictors for Complications After BPA

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate</th>
<th>$P$</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% Confidence interval)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.010 (0.927 - 1.100)</td>
<td>0.824</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.889 (0.047 - 16.661)</td>
<td>0.937</td>
</tr>
<tr>
<td>WHO-FC</td>
<td>1.000 (0.140 - 7.118)</td>
<td>1.000</td>
</tr>
<tr>
<td>BNP</td>
<td>1.001 (0.998 - 1.003)</td>
<td>0.634</td>
</tr>
<tr>
<td>CI</td>
<td>0.824 (0.239 - 2.321)</td>
<td>0.714</td>
</tr>
<tr>
<td>mRAP</td>
<td>1.038 (0.849 - 1.268)</td>
<td>0.718</td>
</tr>
<tr>
<td>mPAP</td>
<td>0.996 (0.928 - 1.069)</td>
<td>0.907</td>
</tr>
<tr>
<td>PVR</td>
<td>1.041 (0.923 - 1.175)</td>
<td>0.509</td>
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<tr>
<td>Main PA diameter index</td>
<td>1.399 (1.001 - 1.956)</td>
<td>0.049</td>
</tr>
<tr>
<td>Right PA diameter index</td>
<td>1.573 (1.048 - 2.359)</td>
<td>0.029</td>
</tr>
<tr>
<td>Left PA diameter index</td>
<td>1.857 (1.091 - 3.159)</td>
<td>0.022</td>
</tr>
<tr>
<td>Use of vasodilators</td>
<td>0.889 (0.047 - 16.661)</td>
<td>0.937</td>
</tr>
<tr>
<td>Number of BPA sessions</td>
<td>0.626 (0.315 - 1.242)</td>
<td>0.180</td>
</tr>
<tr>
<td>Number of treated vessels</td>
<td>0.798 (0.593 - 1.075)</td>
<td>0.137</td>
</tr>
</tbody>
</table>

WHO-FC indicates World Health Organization functional class; BNP, B type natriuretic peptide; CI, cardiac index; mRAP, mean right atrial pressure; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PA, pulmonary artery; and BPA, balloon pulmonary angioplasty.

Discussion

Lung injury due to BPA occurs in about 60% of cases, of which 3-17% require respiratory management with a ventilator. Although the mechanism of lung injury has been considered to be reperfusion injury by cytokine release or pressure overload, recent reports have demonstrated that mechanical damage by the guide wire or balloon is also one of the causes. However, in the present study, lung injury did not depend on the increasing frequency of BPA sessions or treated vessels, technique of the operator, balloon size, pressure of the balloon inflation, or guide wires. Although lung injury does not occur in all BPA sessions in patients with pulmonary artery dilatation, we believe that pulmonary artery dilatation is, at least in part, related to lung injury after BPA. This finding suggests that not only the procedures of BPA, but also patient factors such as vulnerability of the peripheral vascular wall contribute to the development of complications after BPA. Based on the examination of lung tissue obtained by biopsy, Yamaki, et al have reported that pulmonary hemorrhage after PEA occurs easily in cases with formation of collaterals around the occluded vessels or medial wall thinning by blood flow disruption. However, a method for evaluating the vulnerability of the pulmonary peripheral vascular wall by non-invasive imaging has not been reported. The PA diameter of the central portion we measured in this study may reflect lesion progression in peripheral blood vessels.

Feinstein, et al have shown that mPAP > 35 mmHg is a risk factor for lung injury, and Inami, et al have shown that PEPSI is useful for the prediction of lung injury, but both require invasive techniques. Prediction of lung injury by measurement of the pulmonary artery diameter index has a major advantage in its simplicity, non-invasiveness, and pre-procedure evaluation.

Study limitations: There are some potential limitations. First, this study is an observational study at a single institution so the number of subjects was relatively small and there are potential biases and confounders that may be responsible for our findings. Although we carried out the assessments using logistic regression analysis, we could not rule out residual confounding from unknown or unmeasured variables, and the effects of differences in backgrounds might not have been completely adjusted. Hence, the data may not be applicable to all operators or institutions, and further investigation with a larger population is required.

Conclusion: Considering the risk of complications preoperatively is important in order to perform BPA safely. Measurement of the pulmonary artery diameter on CT may be useful in the prediction of lung injury after BPA.

Disclosures

Conflict of interest: Koichi Sugimoto belongs to endowed departments supported by Acterion Pharmaceuticals Japan. This company is not associated with the present study.
REFERENCES


SUPPLEMENTAL FILE
Supplemental Table
Please see supplemental file; https://www.jstage.jst.co.jp/article/ihj/58/4/58_16-365/_article/supplement