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ORIGINAL RESEARCH

Treatment of Vascular Injury During Balloon Pulmonary Angioplasty in Patients With Chronic Thromboembolic Pulmonary Hypertension

Kentaro Ejiri, MD, PhD,[a,b] Aiko Ogawa, MD, PhD,[c] Hiroto Shimokawahara, MD, PhD,[a] Hiromi Matsubara, MD, PhD[a,c]

ABSTRACT

BACKGROUND Treatment strategy for vascular injury during balloon pulmonary angioplasty (BPA) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) was uncertain.

OBJECTIVES This study aimed to identify an optimal therapeutic strategy for vascular injury during BPA in patients with CTEPH.

METHODS This study reviewed 207 patients with CTEPH and 956 BPA procedures between November 1, 2012 and November 30, 2015. Patients who were diagnosed with vascular injury during BPA, which was defined as angiographic signs or sudden respiratory and hemodynamic defects were included in this study. The study investigated the safety and efficacy of the hierarchically systematic treatment strategy including gelatin sponge embolization (GSE).

RESULTS More than one-half of the 79 patients and 133 procedures with vascular injury were improved by general treatment with reversal of heparin and high-flow oxygen administration. The investigators performed conventional treatment of proximal vessel occlusion using a guiding or balloon catheter in 47 procedures (35%) in which the culprit vessels could be detected under patients' stable conditions. In 32 procedures (24%) without detected culprit lesions or improvement by conventional treatment, GSE could significantly improve patient condition. The treatment strategy obtained successful bailout in 98% of procedures with vascular injury. No patients who underwent GSE died within 30 days after the treatment. There was no significant difference in cumulative mortality rate (median follow-up: 6.6 years) between groups with or without GSE (15.6% vs 8.2%; adjusted HR: 1.47; 95% CI: 0.25-8.69; $P = 0.67$).

CONCLUSIONS Treatment strategy including GSE would be promising for vascular injury during BPA in patients with CTEPH. (JACC: Asia 2022;2:831-842) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by stenosis or obstruction of the pulmonary arteries caused by chronically organized thrombi with fibrotic changes.[1] Although the curative treatment for CTEPH is pulmonary thromboendarterectomy,[2] a certain proportion of patients are not suitable for pulmonary thromboendarterectomy because of the presence of

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ABBREVIATIONS AND ACRONYMS

BPA = balloon pulmonary angioplasty

CTEPH = chronic thromboembolic pulmonary hypertension

FiO_2 = fraction of inspired oxygen

GSE = gelatin sponge embolization

PAP = pulmonary arterial pressure

PVR = pulmonary vascular resistance

SpO_2 = oxygen saturation

surgically inaccessible distal subsegmental disease, being elderly, or having comorbidities limiting the option of surgery.[3] Pulmonary hypertension-specific drugs are mildly effective for patients with inoperable CTEPH,[1,4] but in patients with mechanical obstruction in the segmental and subsegmental branches, alternative percutaneous approaches are actively being pursued.

Balloon pulmonary angioplasty (BPA) is a percutaneous treatment option that uses a balloon catheter to dilate pulmonary arterial stenoses.[5] A refined and optimized BPA procedure has emerged as an alternative therapeutic option for patients with CTEPH who are inoperable.[6,7] These patients require multiple BPA procedures, resulting in a risk of clinically serious complications after BPA, such as lung injury. In patients with CTEPH who are treated with BPA, we previously reported that vascular injury caused by procedural complications during BPA is the main cause of lung injury after BPA.[8] The incidence of lung injury detected by high-resolution computed tomography scan with clinical symptoms was 22%, and the incidence of lung injury requiring invasive ventilator support was 13%.[8] Immediate treatment of vascular injury during BPA might prevent lung injury as a serious complication after BPA. However, the optimal treatment options for vascular injury during BPA remain unresolved. In this study, we aimed to identify the optimal therapeutic strategy for clinically apparent vascular injury during BPA in patients with CTEPH.

METHODS

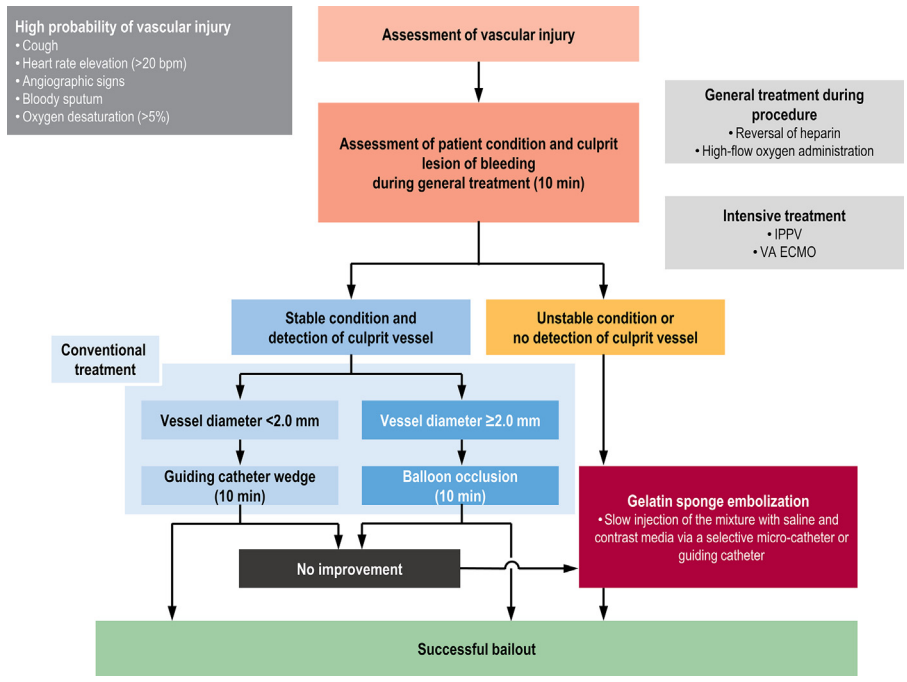
STUDY DESIGN AND PARTICIPANTS. This was a single-center, retrospective, observational study. The study population consisted of consecutive patients with CTEPH undergoing BPA procedures at the National Hospital Organization Okayama Medical Center between November 2012 and November 2015. Patients with CTEPH who had apparent vascular injury during BPA were included in this study. This study did not include patients after 2015 to assess long-term safety of our treatment strategy for vascular injury during BPA. Additionally, there were few patients who met inclusion criteria of this study after 2015 because the advanced learning curves for complications during BPA could lead lower incidence of vascular injury. To avoid the bias of the effect of previous BPA before the study period on assessing the safety and efficacy of our treatment strategy for vascular injury, we excluded patients in whom invasive ventilation was implemented before and during the procedures. A diagnosis of CTEPH was based on detailed medical history, physical examination, chest radiography, computed tomography scan, transthoracic echocardiography, lung ventilation-perfusion scintigraphy, and right heart catheterization. All patients were tested for other causes of pulmonary hypertension, including congenital heart disease and lung disease. None of the patients had any other diseases that caused hypoxemia or pulmonary hypertension. All patients underwent pulmonary angiography and had at least 1 of the following features: ring-like stenosis lesions; web lesions; subtotal lesions; total occlusion lesions; or tortuous lesions.[9] All patients were diagnosed as inoperable by a multidisciplinary CTEPH team because of the location and surgical accessibility of the thrombi, age, and/or comorbidities, and they were treated with warfarin and >1 pulmonary hypertension-targeted drug.

This study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Institutional Review Board of the National Hospital Organization Okayama Medical Center (approval H22-RINKEN-01), and written informed consent was obtained from each patient before the procedure. The study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline.[10]

BPA PROCEDURES AND DATA COLLECTION. The BPA procedures and periprocedural managements were described elsewhere.[9,11,12] Briefly, we used a 0.014-inch guidewire (ie, Chevalier 14 floppy, FMD; B-pahm, Japan Lifeline) to cross the targeted lesion. The appropriate balloon size was determined based on the lesion type and vessel diameter, as measured by pulmonary angiography and intravascular ultrasound. Respiratory care after BPA was performed according to the patient's condition. We reviewed data, including charts, laboratory results, and catheter reports. We used right heart catheterization data obtained within 1 week before the BPA procedure. In terms of the BPA procedural data, 3 cardiologists evaluated the hemodynamic data and carefully reviewed the angiography during BPA.

DEFINITION OF VASCULAR INJURY DURING BPA. We previously described representative angiographic findings of vascular injury as belonging to the following BPA-related vascular injury types: type A, focal type; type B, stain and pooling type; and type C, diffuse blooming type (Supplemental Figure 1).[8]

FIGURE 1 Hierarchically Systematic Treatment Strategy for Vascular Injury During BPA

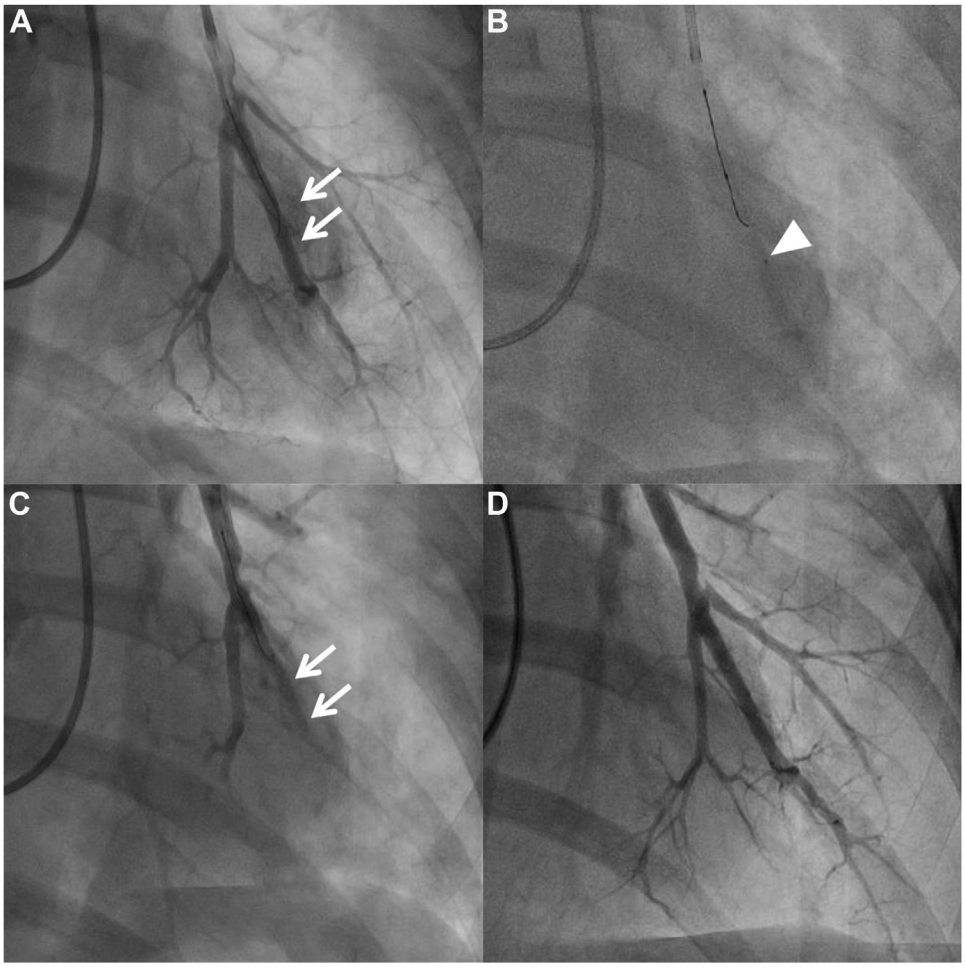


First, general treatments were reversal of heparin and high-flow oxygen administration. After the assessment of the patient's condition (stable or unstable) and culprit lesion of bleeding during the general treatment (10 minutes), the occlusion of the proximal vessel to the bleeding site by the guiding catheter or balloon was performed. Gelatin sponge embolization was performed in patients with continuous symptoms even after several vessel occlusion attempts (total occlusion time: 10 minutes). In cases of an ambiguous or unstable patient condition, gelatin sponge embolization was considered for first-line bailout. Invasive positive pressure ventilation (IPPV) or non-IPPV and venoarterial extracorporeal membrane oxygenation (VA ECMO) were considered as necessary. BPA = balloon pulmonary angioplasty.

Furthermore, our previous study demonstrated that the occurrence of vascular injury could not be rejected only on the basis of the absence of angiographic findings of extravasation. Therefore, clinically apparent vascular injury was defined based not only on procedures with angiographic signs, but also on respiratory and hemodynamic symptoms. Sudden respiratory distress (cough, bloody sputum, or significant hypoxia, defined as a decrease in oxygen saturation [SpO_2] by ≥5% from preoperative status) or sudden hemodynamic defects (an increase in heart rate of >20 beats/min from the initial status during BPA) were considered to be physical signs suggestive of vascular injury regardless of the presence of typical angiographic findings.

TREATMENT OF VASCULAR INJURY. Clinically apparent vascular injury during BPA was treated using a hierarchically systematic strategy (Figure 1). First, general treatment, such as reversal of heparin and high-flow oxygen administration was performed. During the general treatment (10 minutes), we assessed the patient's condition (stable or unstable) and culprit lesion of bleeding. In cases of stable conditions and apparent detection of the culprit lesion, occlusion of the proximal vessel to the bleeding site by the wedge of the guiding catheter (vessel diameter <2.0 millimeters) or inflating balloon (vessel diameter ≥2.0 millimeters) was the next step of treatment. However, if continuous symptoms could not be improved even after several vessel occlusion attempts (total occlusion time: 10 minutes), gelatin sponge embolization (GSE) was performed. In cases of an ambiguous bleeding site or unstable patient conditions, the use of this approach was considered for first-line bailout. In cases of severe hypoxemia or hemodynamic instability, noninvasive

FIGURE 2 A Representative Case Treated Using GSE



(A) Pulmonary angiography showing extravasation of the contrast medium from the pulmonary artery **(arrows):** the left lower lobe A9 after ballooning. **(B)** Gelatin sponge embolization (GSE) via a selective microcatheter in the culprit pulmonary artery (the tip of the microcatheter is indicated by an **arrowhead**). **(C)** The pulmonary artery is opacified with a delay immediately after embolization **(arrows). (D)** Pulmonary angiography performed 3 months later without additional balloon pulmonary angioplasty showing recanalization of the embolized pulmonary artery without stenosis.

or invasive positive pressure ventilation and venoarterial extracorporeal membrane oxygenation were considered.

GSE is a promising technique for vascular injury in endovascular and surgical treatments.[13,14] The preparation requires a piece of gelatin sponge (Serescue, Nippon Kayaku), saline, and contrast medium at a ratio of 4:1 in 10 mL syringes, creating a total mixture of 5 mL. Details are shown in Video 1. Following this, a slow injection of the mixture of GSE via a selective microcatheter (Prominent, Tokai Medical Product, Inc) or guiding catheter into the culprit pulmonary artery branch is performed. An appropriately sized balloon to occlude all flow in the affected artery, thereafter, is inflated proximally. Selective pulmonary angiography of the embolized vessel at the following BPA session is then performed (**Figure 2,** Video 2). The original stenotic lesion is treated again as necessary.

OUTCOMES. To determine the optimal treatment strategy for vascular injury during BPA, we compared patient and procedural characteristics between treatment with GSE (GSE group) and conventional treatment with vessel occlusion by guiding or balloon catheter without GSE (conventional group). After that, we evaluated the clinical course of vascular

injury during BPA with the systematic treatment strategy using a stepwise algorithmic approach. Additionally, to assess the safety and efficacy of GSE on pulmonary hemodynamics and oxygenation in early phase, we investigated the following time-dependent changes in hemodynamic status: SpO_2, fraction of inspired oxygen (FiO_2), SpO_2/FiO_2, heart rate, pulmonary arterial pressure (PAP), cardiac index, and pulmonary vascular resistance (PVR) during the periprocedural period (before procedure, after bleeding, after GSE [at the end of the procedure], and at follow-up). These parameters were assessed using right heart catheterization. Patients in whom these parameters could not be assessed because of invasive cardiopulmonary support during the procedure were excluded from these analyses. Finally, to evaluate the safety of GSE, we compared the use of mechanical ventilation (noninvasive or invasive positive pressure ventilation) after the procedure and all-cause mortality after the final GSE or angioplasty within the study period between GSE group and conventional group.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD, and categorical variables are presented as numbers and percentages. In per-patient analyses, the difference between GSE group and conventional group was examined using Student's *t*-test for continuous variables and Fisher exact test for categorical variables. In per-procedure analyses, we used mixed-effect linear or logistic regression models with compound symmetry correlation matrix to account for the within-participant correlation. Time-dependent changes in hemodynamic parameters (SpO_2, FiO_2, SpO_2/FiO_2, heart rate, mean PAP, cardiac index, and PVR) during periprocedural periods and at follow-up in GSE group were also assessed using mixed-effect linear regression models. The Kaplan-Meier method and log-rank test were used to compare the cumulative mortality rate between the 2 groups. In the GSE group, the time 0 was defined as the date of the last angioplasty with GSE. In conventional group, that was defined as the date of the last angioplasty with vascular injury during the study period. We computed a propensity score for with or without GSE using a logistic regression model with the covariates: age; sex; body mass index; log-transformed B-type natriuretic peptide; World Health Organization functional class III or IV; previous deep vein thrombosis; cancer history; coagulation disorder; hemodynamic data before the procedure (heart rate, systolic and diastolic blood pressure, SpO_2, mean right atrial pressure, mean PAP, cardiac index, and PVR); and medication (vitamin K antagonist, direct oral anticoagulant, soluble guanylyl cyclase inhibitor, phosphodiesterase 5 inhibitor, endothelin receptor antagonist, and epoprostenol). In per-patient survival analyses, HR and 95% CI for all-cause death was quantified using a Cox regression model with the propensity score as a covariate. In per-procedural safety analyses, odds ratio and 95% CI for mechanical ventilator after the procedure was quantified using a mixed-effect logistic regression model with the propensity score and compound symmetry correlation. All comparisons and analyses were 2-sided, with statistical significance set at $P < 0.05$. All analyses were performed using R (version 3.6.3, The R Foundation for Statistical Computing) and Stata/SE (version 16, StataCorp).

RESULTS

BASELINE CHARACTERISTICS. Between November 1, 2012 and November 30, 2015, 956 consecutive BPA procedures were performed in 207 patients with inoperable CTEPH (Supplemental Figure 2). Eighty-one patients (140 procedures) who underwent treatment of vascular injury were included in this study. Two patients (7 procedures) in whom invasive ventilation had been implemented before and during the procedures were excluded. A total of 79 patients (133 procedures) was included in the analyses. Baseline characteristics between GSE group (n = 27 [32 procedures]) and conventional group (n = 52 [101 procedures]) are shown in **Table 1**. Mean patient age was 62.8 years; patients were predominantly female (83.5%); and 41.8% of patients were in World Health Organization functional classes III and IV. Hemodynamic parameters before procedures were as follows: mean PAP, 35.7 mm Hg; cardiac index, 2.33 L/min/m^2; and PVR, 8.6 WU. No significant difference was observed between the 2 groups, except diastolic blood pressure, SpO_2, and endothelin receptor blocker as a baseline medication. The distribution of a propensity score of GSE group and conventional group are shown in Supplemental Figure 3.

The procedural characteristics and details of these treatments are shown in **Table 2**. Intravascular ultrasound was used in most of the procedures. Overall, the most frequent site of bleeding culprit was the right lower lobe; the most frequent angiographic finding of vascular injury was the focal type; and the most frequent angiographic lesion type of vascular injury was the web lesion. On the other hand, 12.8% of these injuries could not be detected by angiography. There were no significant

TABLE 1 Baseline Characteristics[a]

	Overall (N = 79)	GSE Group (n = 27)	Conventional Group (n = 52)	*P* Value
Age, y	62.8 ± 12.2	64.4 ± 12.0	62.0 ± 12.4	0.40
Male	13 (16.5)	6 (22.2)	7 (13.5)	0.50
Body mass index, kg/m^2	22.1 ± 3.4	22.3 ± 4.1	22.0 ± 3.1	0.73
BNP, pg/mL	101.8 ± 187.4	129.8 ± 206.5	87.3 ± 177.0	0.34
WHO functional class				0.69
I	1 (1.3)	0	1 (1.9)	
II	45 (57.0)	14 (51.9)	31 (59.6)	
III	27 (34.2)	10 (37.0)	17 (32.7)	
IV	6 (7.6)	3 (11.1)	3 (5.8)	
Previous venous thromboembolism	28 (35.4)	9 (33.3)	19 (36.5)	0.97
Pulmonary embolism	18 (22.8)	4 (14.8)	14 (26.9)	0.35
Deep vein thrombosis	10 (12.7)	5 (18.5)	5 (9.6)	0.44
Cancer history	10 (12.7)	4 (14.8)	6 (11.5)	0.95
Coagulation disorder	5 (6.3)	0	5 (9.6)	0.24
Hemodynamic data				
Heart rate, beats/min	75.6 ± 12.2	73.9 ± 11.7	76.4 ± 12.5	0.39
Systolic blood pressure, mm Hg	113.0 ± 17.3	110.4 ± 12.0	114.4 ± 19.5	0.34
Diastolic blood pressure, mm Hg	66.8 ± 11.4	62.2 ± 8.5	69.1 ± 12	0.009
SpO_2, %	90.0 ± 5.6	87.9 ± 6.1	91.2 ± 5.1	0.012
Mean right atrial pressure, mm Hg	5.7 ± 3.6	5.7 ± 4.2	5.6 ± 3.3	0.88
Mean PAP, mm Hg	35.7 ± 12.2	36.9 ± 13.4	35.1 ± 11.6	0.55
Cardiac index, L/min/m^2	2.33 ± 0.77	2.27 ± 0.44	2.35 ± 0.90	0.66
PVR, WU	8.6 ± 4.6	9.1 ± 4.6	8.4 ± 4.6	0.51
Medication				
Vitamin K antagonist	78 (98.7)	26 (96.3)	52 (100)	0.74
Direct oral anticoagulant	1 (1.3)	1 (3.7)	0	0.74
Soluble guanylyl cyclase inhibitor	7 (8.9)	3 (11.1)	4 (7.7)	0.93
Phosphodiesterase 5 inhibitor	36 (45.6)	16 (59.3)	20 (38.5)	0.128
Endothelin receptor antagonist	39 (49.4)	19 (70.4)	20 (38.5)	0.014
Epoprostenol	2 (2.5)	1 (3.7)	1 (1.9)	>0.99

Values are mean ± SD or n (%). [a]In case of patients with multiple treatment history of vascular injury, only values at the earliest balloon pulmonary angioplasty procedure were analyzed.

BNP = B-type natriuretic peptide; GSE = gelatin sponge embolization; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance; SpO_2 = oxygen saturation; WHO = World Health Organization.

differences in almost all procedural characteristics between the 2 groups. In GSE group, culprit vessel occlusion by balloon catheter as an initial treatment for vascular injury was significantly greater than in the conventional group.

ALGORITHM OF TREATMENT STRATEGY FOR VASCULAR INJURY. The Central Illustration describes our treatment results based on the systematic strategy for vascular injury. All vascular injuries presented with cough and elevated heart rate. More than one-half of these cases presented with bloody sputum and oxygen desaturation. More than one-half of the injuries showed improvements with general treatment alone. Conversely, continuous or worsening symptoms during general treatment were observed in 56 procedures (42%). Of these, conventional treatment of proximal vessel occlusion by a guiding or balloon catheter was performed in 47 procedures (35%) in which culprit vessels were detected and patient condition remained stable. In the remaining 9 procedures (7%), GSE was performed immediately because of undetectable culprit lesion or unstable patient conditions. In 47 procedures with conventional treatment, 24 procedures obtained successful bailout, whereas 23 procedures required additional GSE treatment. Consequently, 32 procedures (24%) required GSE treatment. Of these, 31 procedures obtained successful bailout; however, only 1 case was not improved by our treatment strategy and required invasive cardiopulmonary support. In total, the successful bailout rate of both conventional and GSE treatments for vascular injury was 98%. After successful bailout, invasive positive pressure ventilation was required in 4 procedures and both invasive ventilation and extracorporeal membrane oxygenation in 1 procedure. All patients eventually

TABLE 2 Procedural and Treatment Characteristics of Vascular Injury

	Overall (N = 133)	GSE Group (n = 32)	Conventional Group (n = 101)	*P* Value
No. of previous BPA procedures	4.19 ± 4.46	3.69 ± 4.05	4.35 ± 4.59	0.28
No. of treated arteries per procedure	4.06 ± 2.36	3.62 ± 1.81	4.20 ± 2.50	0.77
No. of treated segments per procedure	4.30 ± 2.92	4.44 ± 2.86	4.27 ± 2.95	0.22
Maximum balloon diameter, mm	3.06 ± 1.42	3.33 ± 2.27	2.97 ± 0.98	0.058
Artery diameter, mm	4.21 ± 1.87	4.47 ± 2.97	4.12 ± 1.32	0.41
Balloon-to-artery ratio[a]	0.75 ± 0.13	0.76 ± 0.13	0.74 ± 0.13	0.70
No. of wires per procedure[b]	1.14 ± 0.36	1.09 ± 0.30	1.15 ± 0.38	0.46
Fluoroscopy time/procedure, min	47.3 ± 18.5	44.4 ± 15.4	48.2 ± 19.3	0.30
Amount of contrast medium per procedure, mL	103.6 ±42.5	102.0 ± 42.8	104.1 ± 42.6	0.82
Intravascular ultrasound use	125 (94.0)	31 (96.9)	94 (93.1)	0.15
Culprit vessel site				
Right upper lobe	19 (14.3)	8 (25.0)[c]	11 (10.9)	0.093
Right middle lobe	17 (12.8)	4 (12.5)[c]	13 (12.9)	0.98
Right lower lobe	46 (34.6)	13 (40.6)[c]	33 (32.7)	0.45
Left upper lobe	30 (22.6)	3 (9.4)[c]	27 (26.7)	0.055
Left lower lobe	12 (9.0)	4 (12.5)[c]	8 (7.9)	0.44
Recovery before the detection of culprit	9 (6.8)	0[c]	9 (8.9)[d]	0.99
Angiographic signs of vascular injury				
Focal type	56 (42.1)	12 (37.5)	44 (43.6)	0.56
Stain and pooling type	40 (30.1)	11 (34.4)	29 (28.7)	0.44
Diffuse blooming type	20 (15.0)	4 (12.5)	16 (15.8)	0.49
Absent	17 (12.8)	5 (15.6)	12 (11.9)	0.29
Angiographic lesion type (injured site)				
Ring-like stenosis	4 (3.0)	0	4 (4.0)	0.45
Web	65 (48.9)	19 (59.4)	46 (45.5)	0.98
Subtotal	41 (30.8)	8 (25.0)	33 (32.7)	0.11
Total occlusion	15 (11.3)	5 (15.6)	10 (9.9)	0.61
Tortuous	0	0	0	NA
Unclassified because of undetected culprit	8 (6.1)	0	8 (7.9)	0.99
Treatment details				
General treatment alone	86 (64.6)	9 (28.1)[e]	77 (76.2)	0.059
Guiding catheter wedge	12 (9.0)	7 (21.9)[e]	5 (5.0)	0.13
Balloon occlusion	35 (26.3)	16 (50.0)[e]	19 (18.8)	<0.001
GSE	32 (24.0)	32 (100)	NA	NA

Values are mean ± SD or n (%). [a]Balloon-to-artery ratio was calculated by maximum balloon diameter divided by culprit artery diameter measured by intravascular ultrasound before ballooning (in the case of complete occlusion, no assessment). [b]Number of wires used in the procedure. [c]At the vessel site of injection of gelatin sponge. [d]Recovery by the general treatment before detection of culprit. [e]The number and percentage describe the initial treatment of GSE.

BPA = balloon pulmonary angioplasty; GSE = gelatin sponge embolization; NA = not applicable.

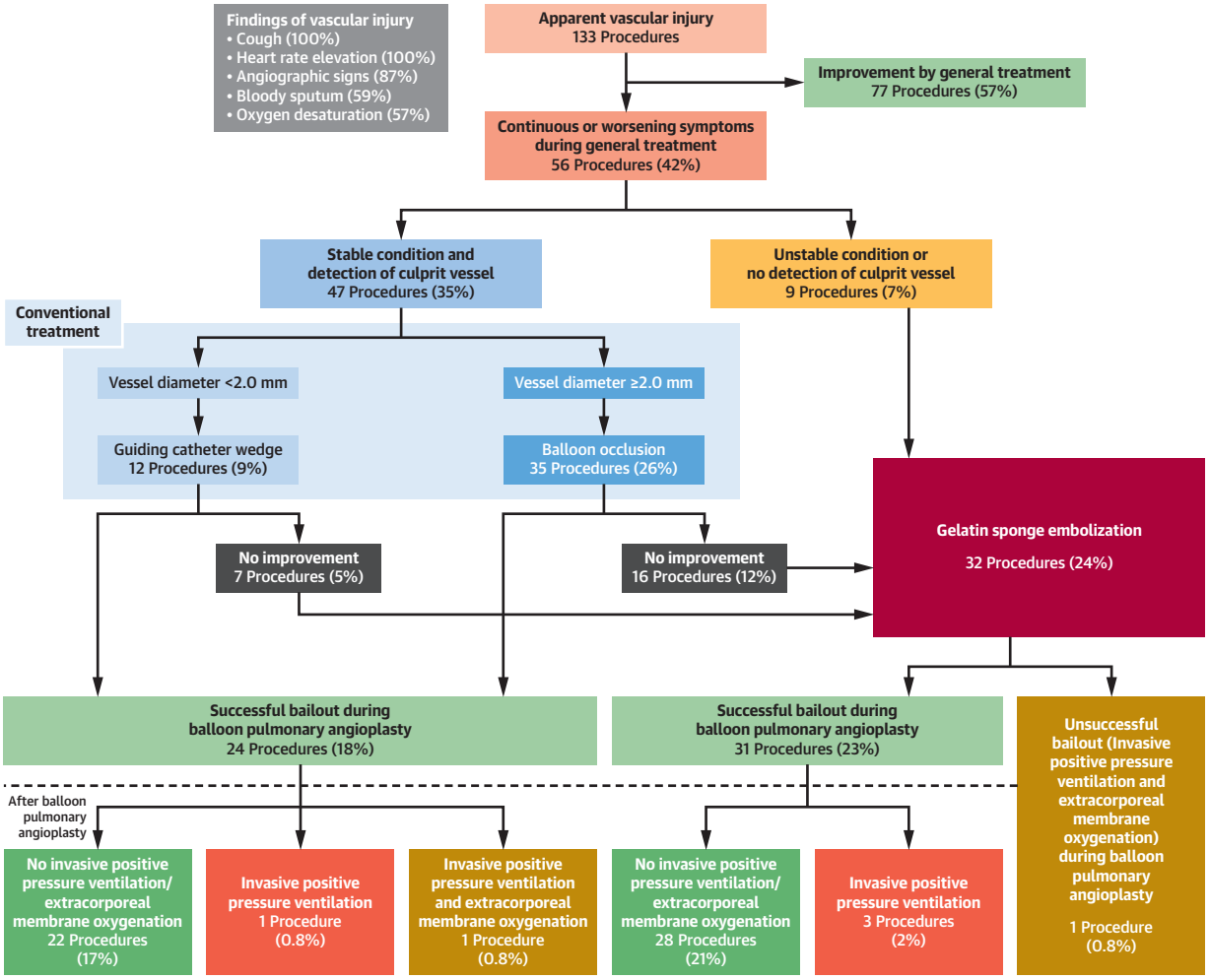
recovered from lung injury after BPA caused by vascular injury.

HEMODYNAMIC CHANGE AMONG BEFORE AND AFTER GSE. Among 32 procedures in GSE group, time-dependent changes in the hemodynamic parameters (SpO_2, FiO_2, SpO_2/FiO_2, heart rate, mean PAP, cardiac index, and PVR) were assessed. One patient who could not be assessed for these parameters because of invasive cardiopulmonary support during the procedure was excluded from these analyses. Significant differences were observed in the time-dependent changes in SpO_2, FiO_2, and SpO_2/FiO_2 (**Table 3,** Supplemental Figure 4). In each parameter, there was a significant improvement in oxygenation after embolization compared with after bleeding. Between before and after GSE, furthermore, a significant improvement was observed in mean PAP and PVR, whereas improvement was not observed in heart rate.

SAFETY OUTCOMES. Angiographic follow-up after embolization was performed in 30 of 32 procedures (93.8%) in the GSE group (median follow-up duration: 68 [IQR: 36-135] days) (**Figure 2,** Video 2). Of these, additional treatment of the original stenotic lesion after GSE was attempted in 16 cases and succeeded in 13 cases.

No patient died within 30 days after vascular injury in both GSE and conventional treatment groups

CENTRAL ILLUSTRATION **Results of a Treatment Strategy for Vascular Injury During BPA**



Ejiri K, et al. JACC: Asia. 2022;2(7):831–842.

More than one-half of the injuries showed improvements with general treatment alone. Continuous or worsening symptoms during general treatment were observed in 56 procedures (42%). In 47 procedures with conventional treatment, 24 procedures obtained successful bailout, whereas 23 procedures required additional gelatin sponge embolization (GSE) treatment. Consequently, 32 procedures (24%) required GSE treatment. Of these, 31 procedures obtained successful bailout; however, only 1 case was not improved by our treatment strategy and required invasive cardiopulmonary support. In total, the successful bailout rate of both conventional and GSE treatments for vascular injury was 98%. After successful bailout, invasive positive pressure ventilation was required in 4 procedures and both invasive ventilation and extracorporeal membrane oxygenation in 1 procedure. BPA = balloon pulmonary angioplasty.

(Supplemental Table 1). In the GSE group, despite recovery from lung injury, in-hospital death occurred in 1 patient because of malignant syndrome and rhabdomyolysis during invasive ventilation with general anesthesia. One patient died 4 months later because of worsening of right heart failure. The cumulative mortality rates between the 2 groups were 15.6% (95% CI: 3.0-28.5) and 8.2% (95% CI: 2.0-15.5) (median follow-up duration: 6.6 [IQR: 5.1-8.0] years; log-rank $P = 0.30$) (**Figure 3**). In a Cox regression model adjusted for the propensity score, there was no significant difference in all-cause mortality between the 2 groups (adjusted HR: 1.47; 95% CI: 0.25-8.69; $P = 0.67$) (Supplemental Table 1).

DISCUSSION

This is the first report to systematically describe the treatment of vascular injury during BPA using contemporary interventional techniques in patients with CTEPH. Although only a small number of patients were treated with GSE in this series, it is the

TABLE 3 Time-Dependent Change in Hemodynamic Parameters Before and After GSE (N = 31)

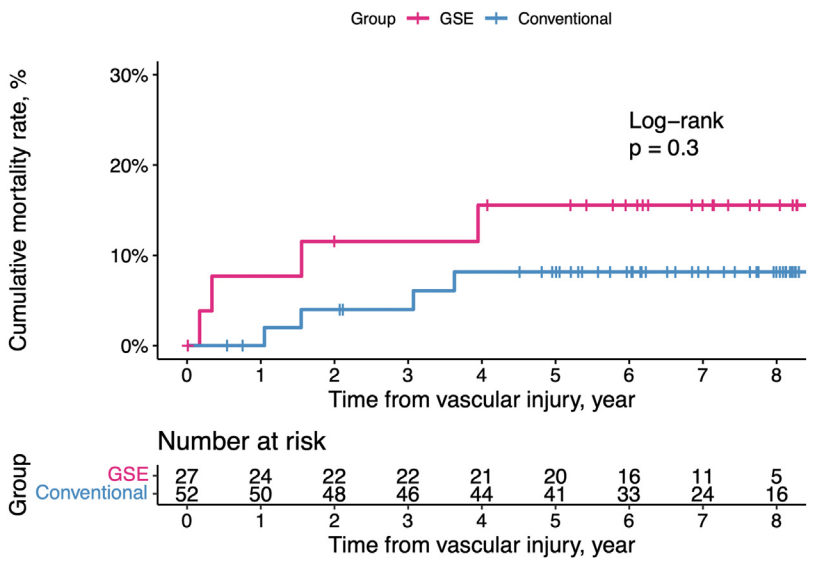
	Before Procedure	After Bleeding	After GSE	At Follow-Up[a]	*P* Value
SpO_2, %	99.4 ± 1.5	94.8 ± 8.5	99.1 ± 2.0	89.6 ± 6.7	<0.001
FiO_2	0.56 ± 0.15	0.85 ± 0.09	0.76 ± 0.20	0.26 ±0.16	<0.001
SpO_2/FiO_2	188.8 ± 49.5	112.7 ± 18.8	150.2 ± 85.2	390.6 ± 84.8	<0.001
Heart rate, beats/min	73.8 ± 13.2	88.2 ± 17.3	75.1 ± 16.6	77.1 ± 15.7	0.71
Mean PAP, mm Hg	36.3 ± 12.9	NA	33.8 ± 12.6	31.4 ± 10.7	0.016
Cardiac index, L/min/m^2	2.24 ± 0.45	NA	NA	2.28 ± 0.47	0.68
PVR, WU	9.3 ± 4.5	NA	NA	7.5 ± 3.9	0.007

Values are mean ± SD. [a]Median follow-up duration was 63 (IQR: 8-92) days.
FiO_2 = fraction of inspired oxygen; SpO_2 = oxygen saturation, other abbreviations as in Table 1.

largest description of the use of this technique for addressing vascular injury during BPA for CTEPH from one of the most experienced BPA centers in the world. In this study, we defined clinically apparent vascular injuries based on angiographic signs and clinical symptoms. A total of 42% of the patients required specific treatment with temporary vessel occlusion or GSE, despite general treatment such as reversal of heparin and high-flow oxygen administration. In cases where the bleeding-culprit vessel could not be detected or those where the patients' conditions were unstable, GSE proved to be a promising technique without adverse effects on hemodynamic and respiratory conditions during the perioperative period.

The refined BPA strategy has been shown to be effective for patients with inoperable CTEPH and has been adopted in the European Society of Cardiology/European Respiratory Society guidelines.[15] Our previous report also suggested that the main cause of lung injury was vascular injury related to BPA procedures.[8,16] The development of a bailout

FIGURE 3 The Cumulative Mortality Rate After Vascular Injury During BPA



Pink and blue lines show the cumulative mortality rate between patients with GSE (GSE group) and those with conventional treatment without GSE (conventional group). In the GSE group, the time 0 was defined as the date of the last procedure with GSE. In the conventional group, that was defined as the date of the last angioplasty with vascular injury during the study period. No patient died within 30 days after vascular injury in both GSE and conventional treatment groups (Supplemental Table 1). The cumulative mortality rates between the 2 groups were 15.6% (95% CI: 3.0-28.5) and 8.2% (95% CI: 2.0-15.5) (median follow-up duration: 6.6 years; log-rank $P = 0.30$). Abbreviations as in Figures 1 and 2.

JACC: ASIA, VOL. 2, NO. 7, 2022
DECEMBER 2022:831–842

technique for vascular injury, therefore, was needed to prevent lung injury after BPA, especially when the conventional treatment failed. Balloon occlusion or wedging a guiding catheter is adequate for minor injuries; however, they cannot address a major vascular injury. The efficacy of coil embolization for pulmonary artery rupture has been reported;[17] however, the embolized vessel cannot be recanalized. Although covered stent therapy can seal a catastrophic rupture,[18] it is not ideal for the tortuous pulmonary vascular anatomy and cannot address distal wire perforations or bleeding from more obscure points. Inami et al[19] reported the management of vascular injury during BPA using catheter techniques, including balloon occlusion and embolization. In addition to the previous report, our study could suggest a more systematic treatment strategy for vascular injury during BPA and its short- and long-term effect on patient prognosis.

In our study, more than one-half of the procedures with clinically apparent vascular injury were improved by general treatment alone, such as by reversal of heparin and high-flow oxygen administration. As we have previously reported, vascular injury during BPA is caused by procedural complications such as wire perforation, overdilation by the balloon, and pressure overload by injection;[8] general treatment is thought to be effective in stopping bleeding in cases where such vascular injuries are minor. When these treatments cannot improve symptoms and patient conditions, the detection of bleeding culprit vessels by selective pulmonary angiography is important to perform conventional treatment by vessel obstruction with a catheter. In this study, one-half of the vascular injuries treated with conventional treatment without GSE obtained a successful bailout. In cases with clear evidence of bleeding vessels and stable patient condition, vessel occlusion by a catheter can be expected to treat vascular injury. On the other hand, in about one-half of the procedures, no improvement was observed with conventional treatment alone. In such situations, GSE, a therapeutic option for vascular injury that can immediately approach a wide range of pulmonary arteries and stop bleeding, is promising regardless of the detection of culprit vessels.

GSE is one of the most widely used treatments for preventing arterial bleeding.[13] Similarly, this treatment has been used for addressing vascular injury during BPA. A gelatin sponge fills the vascular tree with arterial thrombosis[13] and achieves rapid hemostasis. When the gelatin sponge would embolize all culprit pulmonary arteries, it is effective regardless of whether the bleeding point is identifiable. After GSE, significant improvement was observed in the time-dependent changes in respiratory and hemodynamic conditions. Thus, stopping bleeding immediately using the GSE technique during BPA can maintain the effectiveness of BPA treatment by minimizing the worsening of respiratory and hemodynamic status caused by vascular injury during BPA. These results suggest that GSE treatment is an effective bailout technique to prevent the worsening of vascular injury during BPA that cannot be managed with conventional treatment alone. Importantly, because bioresorbable gelatin sponge particles can be absorbed within 2 to 6 weeks,[20] the culprit vessel can be subsequently recanalized and is therefore amenable for retreatment with BPA. Thus, GSE can treat vascular injury without any treatment disturbances after bleeding. In most cases, our treatment strategy could obtain successful bailout of vascular injury during BPA. Although invasive cardiopulmonary support was required in a case even after GSE, all patients could achieve survival within 30 days after vascular injury. On the other hand, the cumulative mortality rate in conventional group in this study was clinically comparable to those in the previous reports,[21-23] whereas that in the GSE group appeared to be lower. No significant difference in all-cause mortality was observed between the 2 groups; however, limited sample size and safety outcomes might contribute to not attaining statistical significance in this study. Although our treatment strategy could facilitate the establishment of vascular injury management during BPA, it is still important to minimize the incidence of vascular injury during BPA by further refinement of the procedures.

STUDY LIMITATIONS. First, this was a retrospective observational study conducted in a single center, which is one of the most experienced BPA centers in the world. However, the number of study participants was limited, and thus low statistical power might contribute the results of this study. Specifically, it is possible that significant difference in the study outcomes, especially in all-cause mortality between GSE group and control group exists. The findings of this study, therefore, should be interpreted as exploratory in nature. Second, no causal inference between each treatment option of vascular injury and safety outcome was possible because of the hierarchical relationship between the severity of vascular injury

and its treatment; however, to minimize other confounding factors, we evaluated the safety and efficacy of the treatment strategy using a stepwise algorithmic approach and regression models adjusted for a propensity score with or without GSE. Third, this study included only Asian patients, and thus generalizability of findings of this study might be limited. Finally, selection bias and residual confounding bias were inevitable in this type of observational study. To overcome these potential limitations, further multicenter prospective study is warranted.

CONCLUSIONS

We identified a treatment strategy for clinically apparent vascular injuries during BPA. Although most of the vascular injuries could be treated by general treatment or conventional interventional techniques, in about one-fourth of the vascular injuries needed additional treatment. GSE could stop bleeding and stabilize hemodynamic and respiratory parameters without any adverse effects in such cases. Nonetheless, the cumulative mortality rates in patients with GSE and in those without did not significantly differ. The hierarchically systematic treatment strategy including GSE would be promising for obtaining a successful bailout of clinically apparent vascular injury during BPA in patients with CTEPH; however, the findings of this study should be interpreted as exploratory in nature because the number of study participants was limited. In addition to further multicenter prospective study, refinement of whole treatment strategy to minimize the risk of vascular injury is warranted.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: We identified a systematic treatment strategy for clinically apparent vascular injuries during BPA for CTEPH. General treatment or conventional interventional techniques including proximal vessel occlusion using a guiding or balloon catheter is effective in most of the vascular injuries. In the remaining injuries without detected culprit lesions or improvement with such treatment, GSE could immediately stop bleeding and improve patient condition without adverse effect in short- and long-term follow-up.

TRANSLATIONAL OUTLOOK: In addition to multicenter prospective study, refinement of the entire treatment strategy to minimize the risk of vascular injury is warranted.

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KEY WORDS BPA, CTEPH, gelatin sponge embolization, treatment strategy, vascular injury

APPENDIX For supplemental figures, table, and videos, please see the online version of this paper.