JACC VOL. 85, NO. 23, 2025
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Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension

Results of an International Multicenter Prospective Registry

Irene M. Lang, MD,[a] Philippe Brenot, MD,[b] Hélène Bouvaist, MD,[c] Elie Fadel, MD,[d] Xavier Jaïs, MD,[e] Michael M. Madani, MD,[f] Stefan Guth, MD,[g] Marcin Kurzyna, MD,[h] Gérald Simonneau, MD,[i] Christoph B. Wiedenroth, MD,[g] Ehtisham Mahmud, MD,[j] Hiroto Shimokawahara, MD,[k] Riyaz Bashir, MD,[l] Marion Delcroix, MD,[m] Robert Frantz, MD,[n] Christian Gerges, MD,[a] Laurent Godinas, MD,[m] Gustavo A. Heresi, MD,[o] Pavel Jansa, MD,[p] David P. Jenkins, MD,[q] Stephen P. Hoole, MD,[q] Takeshi Ogo, MD,[r] Joanna Pepke-Zaba, MD,[q] Toru Satoh, MD,[s] Anton Vonk-Noordegraaf, MD,[t] Alison Witkin, MD,[u] David Bowers, MSc,[v] Nick H. Kim, MD,[w,*] Hiromi Matsubara, MD[k,*]

ABSTRACT

BACKGROUND Chronic thromboembolic pulmonary hypertension results from mechanical obstruction of major pulmonary artery lumina with fibrotic tissue. Main treatment has been pulmonary endarterectomy, a complex surgical procedure removing vascular obstruction. However, at least 40% of patients are not candidates for pulmonary endarterectomy because of technical inoperability, comorbidities, or limited access to surgery. Balloon pulmonary angioplasty (BPA) has emerged as an interventional treatment for these patients.

OBJECTIVES The International BPA Registry (NCT03245268) was designed to investigate BPA practice across 18 established centers in the United States, Europe, and Japan.

METHODS A total of 500 patients were prospectively and consecutively enrolled between March 2018 and March 2020, with follow-up until March 2022. Of these, 484 patients were included in the analysis set.

RESULTS Regional differences were seen in patient characteristics (fewer patients with prior pulmonary endarterectomy and more elderly women in Japan) and procedural details (less medical pretreatment, more jugular access, more segments and more occlusive lesions treated per session and patient, less conscious sedation, less contrast and less radiation, shorter intervals between BPA sessions in Japan). Female sex, procedure in Europe/United States, pulmonary hypertension medications at any time, and higher baseline pulmonary vascular resistance (PVR), calculated as transpulmonary pressure gradient divided by cardiac output, emerged as independent predictors of complications during BPA. After a median of 5 (Q1-Q3: 3-6) BPA sessions per patient within a median time of 4.9 months (Q1-Q3: 1.7-11.0 months), a 15-mm Hg (38%) decrease in mPAP, a 332 dynes/s/cm^{-5} (57%) decrease in PVR, and a 3.2% increase in arterial saturation (medians; $P < 0.001$) were observed, and there were significant improvements in functional class, 6-minute walk distance, serum levels of N-terminal probrain natriuretic peptide, and Borg dyspnea index. BPA complications occurred in 11.3% of sessions and 33.9% of patients and were mostly hemoptyses. No patient died within 30 days of BPA.

CONCLUSIONS Our data are in line with previous reports on changes of clinical and hemodynamic parameters and complication rates of BPA. Centers with more experience providing BPAs were more likely to achieve a higher percentage decrease in PVR. (JACC. 2025;85:2270-2284) © 2025 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/).

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ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2025.04.021

Chronic thromboembolic pulmonary hypertension (CTEPH) is a subset of pulmonary hypertension (PH) that results from mechanical obstruction of major pulmonary arteries with fibrotic tissue caused by misguided thrombus organization.[1] Pulmonary endarterectomy (PEA) restores patency of the pulmonary vascular tree by dissecting and removing the obstructive fibrotic intimal tissue,[2] thus alleviating right ventricular afterload and leading to excellent long-term survival.[3] However, 40% of patients in registries[4] and probably more outside of registries are not eligible for PEA, for reasons such as technical complexity, comorbidities, and patient preference. Those patients remained without mechanical treatment options until the emergence of balloon pulmonary angioplasty (BPA).

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BPA is performed in a catheterization laboratory following the standards of a classical percutaneous transluminal angioplasty with balloon dilatation of intraluminal obstructions, thus restoring antegrade flow.[5] In 2001, BPA was attempted with good success but a high complication rate[6] and was subsequently abandoned until Japanese interventionists brought it back in 2012 in a refined version,[7-9] following the principle of a staged approach, initially undersized balloons, and repeated sessions.[10] A multicenter registry of patients undergoing BPA at 7 Japanese institutions demonstrated substantial hemodynamic improvements and a relatively low complication rate.[11] Recently, BPA has been further improved technically and customized to patients in Europe and the United States mainly by the use of coronary wires and balloons.[12-17] In 2022, the European Society of Cardiology/European Respiratory Society guidelines on the diagnosis and treatment of PH[18] upgraded BPA to a Class Ib recommendation in the context of a multimodal treatment approach, including PEA and PH medications. In addition, international expert groups have published consensus documents to standardize BPA to ensure uniformity in patient selection, procedural planning, the technical approach, materials and devices, treatment goals, complications and their management, as well as patient follow-up.[5,19]

Because BPA has become a recommended component of the treatment for CTEPH[20,21] but worldwide data are lacking, the International CTEPH Association (ICA) designed a multicenter registry (NCT03245268) to investigate the complication rate of BPA, as well as changes in clinical and hemodynamic parameters after BPA, in CTEPH patients.

ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

BPA = balloon pulmonary angioplasty

CTEPH = chronic thromboembolic pulmonary hypertension

DOAC = direct oral anticoagulant

mPAP = mean pulmonary arterial pressure

NT-proBNP = N-terminal probrain natriuretic peptide

PVR = pulmonary vascular resistance

RHC = right heart catheterization

WHO FC = World Health Organization functional class

From the [a]Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria; [b]Department of Interventional Radiology, Marie Lannelongue Hospital, Paris Saclay University, Le Plessis Robinson, France; [c]Department of Cardiology, Pôle Thorax et Vaisseaux, CHU Grenoble Alpes, La Tronche, France; [d]Department of Thoracic and Vascular Surgery and Heart-Lung Transplantation, Marie Lannelongue Hospital, Paris-Saclay University, Le Plessis Robinson, France; [e]Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Respiratory and Intensive Care Medicine, Bicêtre Hospital, University of Paris-Saclay, Le Kremlin-Bicêtre, France; [f]Division of Cardiovascular and Thoracic Surgery, University of California-San Diego, La Jolla, California, USA; [g]Department of Thoracic Surgery, Kerckhoff Heart and Lung Center, Bad Nauheim, Germany; [h]Department of Pulmonary Circulation, Thromboembolic Diseases and Cardiology, Centre of Postgraduate Medical Education, European Health Centre, Otwock, Poland; [i]Assistance Publique-Hôpitaux de Paris, Service de Pneumologie, Hôpital Bicêtre, Université Paris-Sud, Laboratoire d'Excellence en Recherche sur le Médicament et Innovation Thérapeutique, and Institut National de la Santé et de la Recherche Médicale Unité 999, Le Kremlin-Bicêtre, France; [j]Division of Cardiovascular Medicine, University of California-San Diego, La Jolla, California, USA; [k]Department of Cardiology, NHO Okayama Medical Center, Okayama, Japan; [l]Department of Cardiovascular Diseases, Temple University Hospital, Philadelphia, USA; [m]Clinical Dept of Respiratory Diseases, University Hospitals of Leuven and Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), Department of Chronic Diseases and Metabolism (CHROMETA), KU Leuven - University of Leuven, Leuven, Belgium; [n]Department of Cardiovascular Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA; [o]Division of Pulmonary Medicine, Cleveland Clinic, Cleveland, Ohio, USA; [p]General University Hospital, Prague, Czech Republic (part of the European Reference Network for rare lung diseases [ERN-Lung]); [q]Royal Papworth Hospital, Cambridge, United Kingdom; [r]Division of Pulmonary Circulation, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan; [s]Health Management Center, Iruma Heart Hospital, Iruma, Saitama, Japan; [t]Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Pulmonary Medicine, and Amsterdam Cardiovascular Sciences, Pulmonary Hypertension and Thrombosis, Amsterdam, the Netherlands; [u]Division of Pulmonary and Critical Care, Massachusetts General Hospital, Boston, Massachusetts, USA; [v]School of Allied Health Sciences, University of Suffolk, Ipswich, United Kingdom; and the [w]Division of Pulmonary, Critical Care and Sleep Medicine, University of California-San Diego, La Jolla, California, USA. *These authors contributed equally to this work.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received January 31, 2025; revised manuscript received March 31, 2025, accepted April 1, 2025.

METHODS

STUDY DESIGN. The International BPA Registry prospectively collected data on patients scheduled to undergo their first BPA session at 18 specialized centers worldwide in 10 countries between March 2018 and March 2020, with follow-up until March 2022 (list of participating centers in the Supplemental Appendix). In contrast to the New International CTEPH Database that recruited between 2015 and 2016,[22] the International BPA Registry recruited 3 years later, ie, at a time at which the BPA learning curve had been completed in the larger out-of-Japan centers. Sites screened and evaluated for possible inclusion all consecutive patients who presented at their hospitals, were diagnosed with CTEPH, and were scheduled to undergo BPA. Patients were diagnosed according to clinical guidelines.[18] Local Institutional Review Boards or independent ethics committees approved the protocol, and written informed consent was obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki and registered in the clinicaltrials.gov database (NCT03245268). It was led by the International CTEPH Association, whose members are physicians and surgeons who specialize in the treatment of patients with CTEPH. Expert centers participating in the project were selected by the members of the International CTEPH Association Executive Board.

Data on patient characteristics, diagnosis, and treatment approaches were collected at enrollment and during assessments routinely performed for CTEPH patients in clinical practice. Baseline right heart catheterization (RHC) was the last available RHC before the first scheduled BPA session. The frequency and type of assessments at follow-up were determined by the treating physicians, according to the real-world, noninterventional study design, and according to current consensus.[23] Case selection and event reporting were adjudicated within each center by the multidisciplinary team using harmonized unified criteria, without external audit.

This study was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting observational studies.[24] The data underlying this paper are the property of the International CTEPH Association.

AIMS. The primary objective of the International BPA registry was to investigate the complication rate of BPA in CTEPH patients. Secondary objectives were to assess change of pulmonary vascular resistance (PVR) from baseline, to compare patient selection for BPA across regions and sites, to compare BPA-related complications and the changes seen after BPA in patients on and off concomitant PH medications, and to compare BPA techniques across regions and sites.

INCLUSION CRITERIA. To qualify for inclusion, patients had to be diagnosed with CTEPH or chronic thromboembolic pulmonary disease (CTEPD) without PH, confirmed by RHC demonstrating mean pulmonary arterial pressure (mPAP) ≥25 mm Hg for CTEPH, or <25 mm Hg in combination with exercise limitations for CTEPD without PH, and have abnormal imaging confirming CTEPD as recommended[18] after ≥3 months of anticoagulation.

Patients had to be naïve to BPA treatment and scheduled to undergo their first BPA session ≥1 day after enrollment.

BALLOON PULMONARY ANGIOPLASTY. BPA was performed according to a recent consensus.[5,7,8] The severity of lung injury was classified on a 4-point scale as: 1) without hypoxemia; 2) mild (supplemental O_2); 3) moderate (noninvasive ventilation); or 4) severe (mechanical ventilation ± extracorporeal membrane oxygenation). Hemodynamic assessment was performed according to PH guidelines[18] before each BPA session and after the last recorded BPA.

DATA HANDLING. The International CTEPH Association Executive Board acted as the Data Quality Committee and periodically assessed the data to ensure data quality. The raw data set comprised 500 patients (Supplemental Figure 1). No values were imputed for missing data.

"Final BPA" for a given patient was defined as the last procedure recorded in this registry for which the investigator indicated that no further sessions were planned.

Predefined subgroups were CTEPH or CTEPD without PH, geographic region, sex, medical therapy before BPA, and PEA surgery before BPA. Additional analyses were performed by center-adjudicated operability, because patients considered ineligible for surgery can either be technically inoperable because of the distal nature of their lesions, be operable but refuse surgery, or be operable with an unfavorable risk/benefit ratio for surgery.

Based on the inclusion criteria, 10 European patients, 4 U.S. patients, and 2 Japanese patients were classified as having CTEPD without PH. Because of their small numbers, they were not analyzed separately.

STATISTICAL ANALYSIS. Results are expressed as median (Q1-Q3) for continuous variables, or as

absolute numbers and percentages for categorical variables. Subgroups were compared using Student's *t*-test or 1-way analysis of variance (or their nonparametric alternatives) for continuous variables and the chi-square test for categorical variables. The reported *P* values are to be interpreted in the exploratory sense.

The reduction in PVR following BPA is illustrated through a heatmap, where percentage reduction in PVR from baseline to after final BPA is presented in 10-percentage-point increments, highlighting the proportion of patients in selected comparator subgroups with that percentage decrease.

Multivariable binary logistic regression identified factors associated with complications. Variables identified as significantly associated with an increased risk of complication in a preliminary univariable analysis were considered for inclusion as covariates in the multivariable model to provide risk-adjusted ORs, along with further baseline variables that emerged as appropriate covariates through preliminary stepwise modeling. The final selection of covariates for the multivariable regression took into account their clinical relevance, and was guided by the principle of ensuring at least ten events per adjustment variable.

A Kaplan-Meier analysis of patient survival since the initial BPA procedure was carried out, with the endpoint being either PH-related or all-cause death, as recorded in the registry. Patients not experiencing these events were right-censored at their last recorded follow-up visit or at the point of discontinuation for other reasons. Differences in survival between subgroups were analyzed by the log-rank test.

The recruitment of 500 patients would allow the study to measure the percentage of patients with a binary outcome event (such as death or complication) with a 2-sided 95% CI of approximately ±4.4%.

IBM SPSS software version 27 was used.

RESULTS

PATIENT BASELINE CHARACTERISTICS. Of the 500 patients enrolled, 484 patients entered the final analysis (Table 1). Two patients with incomplete baseline data, 2 patients not meeting the inclusion criteria, and 12 patients who never underwent BPA were excluded from the analyses, leaving 484 patients who had undergone at least 1 BPA session, 406 of which had completed follow-up until registry closure.

Across the entire cohort, the majority of patients were Caucasian (73.1%), median age was 65 years, and 40.9% were men. The main reason for BPA was technically inoperable CTEPH in 70.7% of patients. Median mPAP and PVR at baseline were 42 mm Hg and 604 dynes/s/cm^{-5}, respectively. Median time from diagnosis to first BPA was 5.6 months, and PH medication was initiated in 71.9% of patients before first BPA.

Subgroups by geographical regions. Main demographics were similar between Europe and the United States, with the exception of a higher body mass index in the United States. Time from diagnosis to first BPA was shorter in Japan (median 2.1 months vs 6.8 months in Europe and 7.8 months in the United States). Japanese patients were predominantly women (75.5% vs 53.7% in Europe and 58.0% in the United States). Baseline mPAP and arterial oxygen saturation (SaO_2) were lower in Japan (37 mm Hg vs 46 mm Hg in Europe and 39 mm Hg in the United States, and 91% vs 92% in Europe and 94% in the United States, respectively) (Table 1).

Subgroups by sex. Across the entire cohort, 77.9% of women and 67.2% of men were in World Health Organization functional class (WHO FC) 3 or 4. Except for a mild difference in mean right atrial pressure, baseline hemodynamics were not different between sexes (Supplemental Table 1A).

Subgroups by PH medication before first BPA. PH medication was initiated before the first BPA in 71.9% of patients, with a significantly greater proportion in Europe and the United States than in Japan (77.6% and 76.1% vs 52.0%; $P < 0.001$), mainly soluble guanylate cyclase stimulator (sGC) given to 75.9% of patients (Table 1). Patients on PH medication before the first BPA were characterized by a longer time from diagnosis to first BPA (7.2 months vs 3.2 months), higher levels of the N-terminal probrain natriuretic peptide (NT-proBNP) (973 pg/mL vs 253 pg/mL) and higher PVR (655 dynes/s/cm^{-5} vs 472 dynes/s/cm^{-5}) than patients who did not receive medical therapy (Supplemental Table 1B).

Subgroups by operability. The proportion of patients undergoing BPA due to inoperability was similar in Japan, Europe, and the United States (71.6% vs 72.1% vs 64.8%). Inoperable patients tended to be younger (age 65 years vs 68 years; $P = 0.016$). Other baseline characteristics were broadly similar.

PROCEDURAL DETAILS. A total of 2,327 BPA sessions were performed in 484 patients, of whom 459 had more than 1 BPA session and 427 had a final BPA session. At most centers, 2 operators performed a single routine session; the number of operators per site ranged from 1 to 4 (Supplemental Table 2). In Japan, BPA was performed mainly by interventional cardiologists (98.6%), whereas in Europe and the United States, PH physicians were the main operators

TABLE 1 Patient Characteristics

	Whole Cohort (N = 484)	Japan (n = 102)	Europe (n = 294)	United States (n = 88)	*P* Value
Age at diagnosis, y	65 (52-73)	69 (55-76)	65 (52-71)	59 (49-71)	<0.001
Male	198 (40.9)	25 (24.5)	136 (46.3)	37 (42.0)	<0.001
Ethnicity					<0.001
Caucasian/White	354 (73.1)	0	282 (95.9)	72 (81.8)	
Black	13 (2.7)	1 (1.0)	6 (2.0)	6 (6.8)	
Asian	103 (21.3)	101 (99.0)	1 (0.3)	1 (1.1)	
Other	7 (1.4)	0	0	7 (8.0)	
Not available	7 (1.4)	0	5 (1.7)	2 (2.3)	
Body mass index, kg/m^2	26.0 (23.2-29.8)	23.4 (21.0-27.2)	26.1 (23.4-29.8)	28.4 (24.1-34.7)	<0.001
Time from diagnosis to first BPA, mo	5.6 (2.5-13.7)	2.1 (0.9-4.3)	6.8 (3.4-14.2)	7.8 (2.3-25.4)	<0.001
mRAP, mm Hg	6 (4-10)	4 (2-6)	7 (5-11)	7 (4-10)	<0.001
mPAP, mm Hg	42 (34-50)	37 (31-44)	46 (37-53)	39 (31-47)	<0.001
PAWP, mm Hg	9 (6-12)	7 (4-10)	9 (7-12)	10 (8-13)	<0.001
CO determined by					<0.001
Fick	76 (15.7)	18 (17.6)	27 (9.2)	31 (35.6)	
Thermodilution	407 (84.1)	84 (82.4)	267 (90.8)	56 (64.4)	
Not indicated	1	0	0	1	
Cardiac index, L/min/m^2	2.4 (2.0-2.9)	2.7 (2.2-3.3)	2.3 (1.8-2.7)	2.6 (2.2-2.9)	<0.001
PVR, dynes/s/cm^{-5}	604 (400-852)	548 (367-722)	676 (472-960)	457 (308-627)	<0.001
Arterial oxygen saturation %, SaO_2	92 (88-9)5	91 (86-93)	92 (88-95)	94 (92-97)	<0.001
Reason for BPA					0.004
Inoperable	342 (70.7)	73 (71.6)	212 (72.1)	57 (64.8)	
Operable but refused	28 (5.8)	12 (11.8)	11 (3.7)	5 (5.7)	
Operable but unfavorable	50 (10.3)	13 (12.7)	26 (8.8)	11 (12.5)	
Post-PEA residual defects	64 (13.2)	4 (3.9)	45 (15.3)	15 (17.0)	
Decision for BPA by, ≥1 choice possible					n/a
PH physician	452 (93.4)	100 (98.0)	270 (91.8)	82 (93.2)	
Surgeon	305 (63.0)	53 (52.0)	235 (79.9)	17 (19.3)	
Interventional cardiologist	354 (73.1)	94 (92.2)	234 (79.6)	26 (29.5)	
Interventional radiologist	178 (36.8)	8 (7.8)	158 (53.7)	12 (13.6)	
Noninterventional radiologist	87 (18.0)	8 (7.8)	79 (26.9)	0	
PH medication at baseline					<0.001
On medication	320 (66.1)	44 (43.1)	213 (72.4)	63 (71.6)	
Drug naive	164 (33.9)	58 (56.9)	81 (27.6)	25 (28.4)	
PH medication initiated before first BPA, ≥1 choice possible	348 (71.9)	53 (52.0)	228 (77.6)	67 (76.1)	<0.001
sGC, % of patients with PH drugs	264 (75.9)	47 (88.7)	169 (57.5)	48 (54.5)	
PDE5i	63 (18.1)	2 (3.8)	46 (15.6)	15 (17.0)	
ERA	91 (26.1)	4 (7.5)	63 (21.4)	24 (27.3)	
PCA	19 (5.5)	3 (5.7)	8 (2.7)	8 (9.1)	
IP agonist	2 (0.6)	0	1 (0.3)	1 (1.1)	
Any combination	91 (26.2)	7 (13.2)	59 (20.1)	25 (28.5)	
PH medication initiated after first BPA, ≥1 choice possible	22 (4.5)	5 (4.9)	14 (4.8)	3 (3.4)	0.851
sGC, % of patients with PH drugs	20 (90.9)	4 (80.0)	14 (100)	2 (66.7)	
PDE5i	1 (4.5)	1 (20.0)	0	0	
ERA	2 (9.1)	0	2 (14.3)	0	
PCA	0	0	0	0	
IP agonist	1 (4.5)	0	0	1 (33.3)	
Any combination	2 (9.1)	0	2 (14.3)	0	

Continued on the next page

TABLE 1 Continued

	Whole Cohort (N = 484)	Japan (n = 102)	Europe (n = 294)	United States (n = 88)	*P* Value
Patients with at least 1 follow-up after final BPA	378 (781)	91 (89.2)	249 (84.7)	38 (43.2)	
PH medication at last recorded follow-up after final BPA, ≥1 choice possible					
sGC	165 (43.7)	16 (17.6)	133 (53.4)	16 (42.1)	
PDE5i	39 (10.3)	2 (2.2)	32 (12.9)	5 (13.2)	
ERA	61 (16.1)	4 (4.4)	48 (19.3)	9 (23.7)	
PCA	8 (2.1)	1 (1.1)	5 (2.0)	2 (5.3)	
IP agonist	2 (0.5)	0	1 (0.4)	1 (2.6)	
Any combination	48 (12.7)	3 (3.3)	38 (15.3)	7 (18.4)	0.007
No therapy	156 (41.3)	71 (78.0)	70 (28.1)	15 (39.5)	<0.001[a]

Values are median (Q1-Q3) or n (%). Categorical data is compared using the chi-square test, and continuous data is compared using Student's *t*-test or analysis of variance, or their nonparametric alternatives. Exploratory *P* values are for the comparison between the 3 regions; $P < 0.05$ indicates a rejection of the null hypothesis that the variable is distributed similarly in each region. [a]*P* value for "no therapy" vs "any therapy."

BPA = balloon pulmonary angioplasty; CO = cardiac output; ERA = endothelin receptor antagonist; IP agonist = prostacyclin receptor agonist; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; PAWP = mean pulmonary arterial wedge pressure; PCA = prostacyclin analogue; PDE5i = phosphodiesterase 5 inhibitor; PEA = pulmonary endarterectomy; PH = pulmonary hypertension; PH medication = treatment with pulmonary hypertension drugs; PVR = pulmonary vascular resistance; sGC = soluble guanylate cyclase stimulator.

(Table 1). Femoral access was used in 99.6% and 95.4% of sessions in European and U.S. patients, respectively, whereas in Japan, roughly one-half of the BPAs were from a neck access. In Japan, only local anesthesia was used, whereas in Europe and the United States, conscious sedation was used in 22.8% and 46.2% of sessions, respectively (Table 2). Routine intravascular imaging use including intravascular

TABLE 2 Procedural Details, by Geographic Region

	Total Cohort	Japan	Europe	United States	*P* Value
Number of BPA sessions per patient (patients with final BPA, n = 427)	5 (3-6)	5 (4-6)	5 (3-6)	4 (2-6)	0.055
Time (months) from first BPA to final BPA (patients with final BPA, n = 427)	4.9 (1.7-11.0)	4.7 (1.4-9.0)	4.5 (1.9-11.3)	5.5 (1.7-12.2)	0.075
Time between consecutive BPA sessions, d	39 (6-74)	7 (5-60)	43 (7-76)	40 (7-94)	<0.001
Time (months) from final BPA to follow-up RHC (patients with follow-up RHC after final BPA, n = 319)	6.14 (3.61-8.51)	6.44 (5.78-9.19)	5.91 (3.35-8.41)	2.91 (2.71-3.71)	0.027
Number of segments treated per session (across all sessions: n = 2,327)	3 (2-5)	5 (3-7)	3 (2-4)	3 (2-4)	<0.001
Number of segments treated per patient (patients with final BPA: n = 427)	13 (9-15)	16 (14-17)	12 (8-15)	10 (5-12)	<0.001
Number of occlusive lesions opened per patient (patients with final BPA: n = 427)	4 (2-7)	8 (3-11)	4 (2-7)	2 (1-3)	<0.001
Access route (across all sessions: n = 2,327)					<0.001
Neck	277 (11.9%)	254 (49.9%)	6 (0.4%)	17 (4.6%)	
Groin	2,050 (88.1%)	255 (50.1%)	1,440 (99.6%)	355 (95.4%)	
Anesthesia (across all sessions: n = 2,327)					<0.001
Local only	1,821 (78.5%)	509 (100%)	1,112 (77.2%)	200 (53.8%)	
Sedation as needed	421 (18.1%)	0	328 (22.8%)	93 (25.0%)	
Mod-deep sedation	79 (3.4%)	0	0	79 (21.2%)	
General anesthesia	0	0	0	0	
Missing, n	6	0	6	0	
Intravenous contrast volume per session, mL (across all sessions: n = 2,327)	200 (130-255)	135 (100-170)	220 (150-280)	200 (150-270)	<0.001
Radiation exposure, mSv (across all sessions: n = 2,327)	9.0 (3.2-19.5)	0.7 (0.2-13.1)	13.3 (6.3-25.4)	5.4 (3.0-9.0)	<0.001
Fluoroscopy time, min (across all sessions: n = 2,327)	37 (26-46)	44 (34-53)	35 (25-43)	53 (37-66)	<0.001
Length of hospital stay per BPA session, d (across all sessions: n = 2,327)	4 (2-5)	3 (2-4)	4 (2-5)	4 (2-5)	0.032

Values are median (Q1-Q3) or n (%). Exploratory *P* values are for the comparison between the 2 comparator regions; $P < 0.05$ indicates a rejection of the null hypothesis that the variable is distributed similarly in each region. Effective dose [mSv] = DAP [Gy/cm^2] · 0.25.

BPA = balloon pulmonary angioplasty; Mod-deep sedation = moderate to deep sedation; RHC = right heart catheterization.

TABLE 3 Exercise Capacity, Biomarkers and Hemodynamics Before BPA, and After the Final BPA Session

	Pre-BPA	After Final BPA	*P* Value
Number of patients with a follow-up visit after final BPA	378	378	
WHO FC			<0.001
I	5 (1.3)	88 (23.8)	
II	89 (23.5)	212 (57.3)	
III	257 (68.0)	66 (17.8)	
IV	27 (7.1)	4 (1.1)	
Missing, n	0	8	
Change in WHO FC since baseline			
Improved		251 (67.8)	
Same		110 (29.7)	
Worse		9 (2.4)	
Missing, \n\		8	
6-min walk distance, m	356 (269-433)	410 (348-506)	<0.001
Increase in 6-min walk distance since baseline, m		54 (1-110)	
NT-proBNP, pg/mL	641 (179-1,911)	157 (70-337)	<0.001
Decrease in NT-proBNP since baseline, pg/mL		329 (33-1,355)	
Borg dyspnea index, treated as continuous	4 (2-5)	2 (0.5-4)	<0.001
Decrease in Borg dyspnea index since baseline		1 (0-2)	
Number of patients with follow-up RHC after final BPA	319	319	
Arterial oxygen saturation, SaO_2, %	92 (88-95)	95 (92-97)	<0.001
mRAP, mm Hg	6 (4-10)	5 (3-7)	<0.001
mPAP, mm Hg	43 (34-50)	25 (20-31)	<0.001
Decrease in mPAP since baseline, mm Hg		15 (7-23)	
% decrease in mPAP since baseline		37.9 (20.6-50.0)	
PVR, dynes/s/cm^{-5}	619 (432-872)	244 (182-357)	<0.001
Decrease in PVR since baseline, dynes/s/cm^{-5}		332 (147-569)	
% decrease in PVR since baseline		57.0 (37.6-71.4)	
PAWP, mm Hg	9 (6-11)	9 (7-12)	0.014
Cardiac index, L/min/m^2	2.4 (2.0-2.9)	2.7 (2.4-3.2)	<0.001

Values are median (Q1-Q3) or n (%). Data are shown for all patients with a follow-up visit after their "final" BPA. A "final" BPA is where no further BPA sessions are planned or anticipated. 427 of 484 patients in the registry analysis cohort had a BPA session noted as "final"; 378 of these had a follow-up visit after their final BPA, and 319 had a follow-up RHC after their final BPA.

NT-proBNP = N-terminal probrain natriuretic peptide; WHO FC = World Health Organization functional class; other abbreviations as in Table 1.

ultrasound, optical coherence tomography, or pressure wire was reported by 9 centers (Supplemental Table 2). Time between consecutive BPA sessions was 39 days with no differences by patient subgroups, but significantly shorter intervals in Japan (**Table 2**).

The median number of segments treated per session was 5 in Japan and 3 in Europe and the United States, corresponding to 16 segments treated per patient with a final BPA in Japan, 12 segments per patient with a final BPA in Europe, and 10 segments per patient with a final BPA in the United States (all $P < 0.001$) (**Table 2**). In 8.5% of sessions, both right and left lung segments were treated in a single session. In Japan, this concerned 22.0% of sessions, whereas in Europe and the United States, 5.0% and 3.5% of sessions, respectively, involved bilateral BPA in a single session ($P < 0.001$). Medians of intravenous contrast volume per session were greater in Europe and the United States than in Japan, as was effective radiation dose.

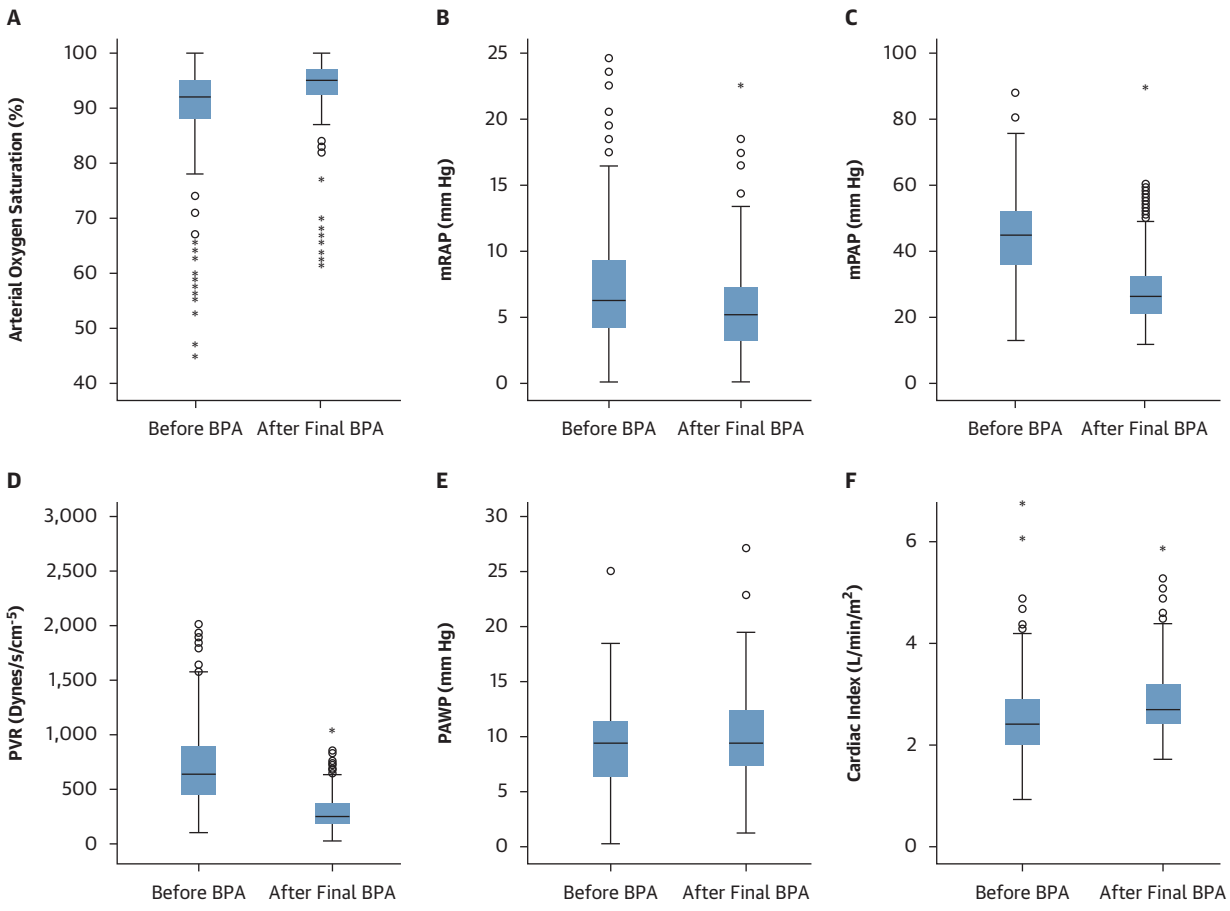
There were no sex-specific differences in procedural details, except that radiation dose and contrast volume were lower in women, regardless of geographic distribution (Supplemental Table 3A). Time from first to final BPA was longer in patients with PH drugs initiated before first BPA than in patients without PH drugs before BPA (Supplemental Table 3B).

All patients were anticoagulated at baseline (36% of sites used vitamin K antagonists [VKA], 57% used direct oral anticoagulants [DOACs], and 7% used heparins). In preparation for a BPA session, anticoagulation was switched by 50% of sites; of these, 43% switched to low molecular weight heparin, 28% to DOAC, and 29% to no anticoagulation. During BPA, 70% of sites used unfractionated heparin (of these, 60% at an activated coagulation time of 200-250 seconds vs 40% who used 2,000 IU unfractionated heparin as bolus, with additional 1,000 IU/h), and 30% used DOAC only. After completion of BPA, 70% of sites continued to treat their patients with DOAC and 30% with VKA.

CHANGES IN CLINICAL AND HEMODYNAMIC PARAMETERS FOLLOWING BPA. Median follow-up time was 26.3 months from enrollment to censoring or discontinuation. Follow-up was recorded in 378 patients after their final BPA session. A closer analysis of these patients showed that there were no major differences in baseline characteristics compared with patients who had no follow-up visit after their final BPA, with a trend toward more severe WHO functional classes in those with follow-up visits (Supplemental Table 4). Therefore, follow-ups were not likely biased toward those who were better. WHO FC, 6-minute walk distance (6MWD), NT-proBNP, and Borg dyspnea index significantly improved from baseline ($P < 0.001$) (**Table 3**). In the majority of patients, PVR decreased by at least 330 dynes/s/cm^{-5}, and mPAP by at least 15 mm Hg. These changes were similar across geographical regions (Supplemental Figure 2, Table 5).

A follow-up RHC after the final BPA session was recorded in 319 patients. Hemodynamics improved significantly after BPA with a 57% decrease in PVR from baseline (**Figure 1**, Supplemental Table 5, **Central Illustration**). Patients with ≥5 lesions opened were more likely to experience a high percentage decrease in PVR, as were patients with a baseline mPAP ≥40 mm Hg. Centers with more prior experience of

FIGURE 1 Selected Hemodynamic Parameters Before and After Final BPA



(A) Arterial oxygen saturation ($P < 0.001$), (B) mean right atrial pressure (mRAP) ($P < 0.001$), (C) mean pulmonary arterial pressure (mPAP) ($P < 0.001$), (D) pulmonary vascular resistance (PVR) ($P < 0.001$), (E) mean pulmonary arterial wedge pressure (PAWP) ($P = 0.014$), and (F) cardiac index ($P < 0.001$) of all patients with a follow-up right heart catheterization after their final balloon pulmonary angioplasty (BPA) (n = 319) were analyzed.

providing BPAs were more likely to achieve a higher percentage decrease in PVR (**Central Illustration**). Overall, 51.7% of patients had a final mPAP ≥25 mm Hg, and 13.5% (all from Europe or the United States) had a final mPAP ≥38 mm Hg.

USE OF PH MEDICATIONS. Of 378 patients with at least 1 follow-up visit after final BPA, 58.7% were on PH medications at their last recorded follow-up. In Japan, 78.0% were off PH medications, whereas in Europe, the proportion was 28.1% and in the United States it was 39.5%. PH medications at baseline and at last recorded follow-up after final BPA are illustrated in Supplemental Figure 3A by monotherapy vs combination, and in Supplemental Figure 3B by sGC vs other PH medication. Patients pretreated with sGC had been on medication for a median of 6.6 months before enrollment, and patients pretreated with other PH medications had been on treatment for a median of 11.6 months before enrollment.

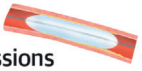
BPA-RELATED COMPLICATIONS. Any complication (thoracic or nonthoracic) occurred in 11.3% of sessions and in 33.9% of patients (**Table 4**). These percentages were markedly lower in Japan compared with Europe and the United States (4.5% vs 14.1% and 9.7% of sessions and 12.7% vs 42.2% and 30.7% of patients, respectively).

Thoracic complications, ie, lung injury most commonly within 3 hours after the start of BPA, predominantly acute hemoptysis, or pulmonary artery dissection, occurred in 9% of sessions and 28.7% of patients. Hemoptysis required balloon tamponade in 2% of sessions and pulmonary artery embolization in 0.6% of sessions (**Table 4**). No patient required

CENTRAL ILLUSTRATION **The International BPA Registry: Overview and Main Results**

The International Balloon Pulmonary Angioplasty (BPA) Registry

500 patients enrolled prior to their first BPA from 18 chronic thromboembolic pulmonary hypertension (CTEPH) centers worldwide → 484 in final analysis, undergoing 2,327 BPA sessions



Primary objective: Assess world-wide practice of BPA in CTEPH patients

Outcomes: BPA complications; functional/hemodynamic changes from baseline

	Change in pulmonary vascular resistance (PVR) from baseline to after final BPA					
	No change or increase	1-19% decrease	20-39% decrease	40-59% decrease	60-79% decrease	≥80% decrease
All patients	6.1%	7.3%	15.4%	24.7%	35.6%	10.9%
Male	6.7%	8.4%	14.2%	29.4%	27.7%	13.4%
Female	5.7%	6.8%	16.1%	21.8%	40.5%	9.3%
Body mass index <25 kg/m^2	6.7%	5.9%	11.6%	27.5%	34.2%	14.1%
Body mass index ≥25 kg/m^2	7.2%	7.9%	17.8%	22.4%	34.8%	9.9%
No lesions opened	11.9%	10.2%	18.7%	25.5%	30.5%	3.4%
1-4 lesions opened	7.4%	8.5%	16.0%	28.7%	28.7%	10.7%
≥5 lesions opened	4.2%	4.2%	12.6%	21.0%	41.2%	16.8%
Baseline mean pulmonary arterial pressure ≤40 mmHg	10.4%	10.4%	24.4%	27.5%	24.5%	2.9%
Baseline mean pulmonary arterial pressure >40 mmHg	2.8%	5.1%	8.5%	22.6%	44.0%	16.9%
Center with <200 previous BPAs	2.6%	14.1%	21.8%	33.3%	23.1%	5.1%
Center with 200-999 previous BPAs	10.7%	3.6%	11.6%	20.5%	39.3%	14.3%
Center with ≥1,000 previous BPAs	4.2%	5.9%	15.0%	22.5%	40.8%	11.7%

% of cases: >0 to <10 | 10 to <20 | 20 to <30 | ≥30

Key findings

0% in-hospital mortality post-BPA

BPA complications (mostly mild hemoptysis) in 11.3% of sessions and 33.9% of patients

Greater PVR ↓ after BPA with
- ≥5 lesions opened
- baseline mean pulmonary arterial pressure >40 mmHg
- centers having more prior experience of providing BPAs

Lang IM, et al. JACC. 2025;85(23):2270-2284.

The heatmap shows percentage decrease in pulmonary vascular resistance (PVR) from baseline to after final balloon pulmonary angioplasty (BPA) session, in 20-percentage-point increments, highlighting the proportion of patients in selected comparator subgroups with that percentage decrease. Because the greatest effect derives from opening of type C and D lesions,[14,32,33] data on successfully opened occlusive lesions were included. The heatmap shows that the modal decrease in PVR after BPA is around the 60%-79% class overall. Patients with ≥5 lesions opened were more likely to experience a high percentage decrease in PVR (mean 56% decrease in PVR [95% CI: 50%-61%] vs mean 45% decrease [95% CI: 41%-50%] for <5 lesions opened), as were patients with a baseline mean pulmonary artery pressure [mPAP] >40 mm Hg (mean 59% decrease in PVR [95% CI: 55%-62%] vs mean 40% decrease [95% CI: 34%-45%] for mPAP ≤40 mm Hg). Centers with more prior experience of providing BPAs (counted in BPA sessions) were more likely to achieve a higher percentage decrease in PVR (mean 52% decrease in PVR [95% CI: 48%-56%] for ≥200 previous BPAs vs mean 46% decrease in PVR [95% CI: 41%-51%] for <200 previous BPAs). Other factors shown in the heatmap were not significantly associated with percentage decrease in PVR. BMI = body mass index.

TABLE 4 BPA-Related Complications

	Whole Cohort		Japan		Europe		United States	
	Per Session (n = 2,327)	Per Patient (n = 484)	Per Session (n = 509)	Per Patient (n = 102)	Per Session (n = 1,446)	Per Patient (n = 294)	Per Session (n = 372)	Per Patient (n = 88)
Any complication (thoracic or nonthoracic)	263 (11.3)	164 (33.9)	23 (4.5)[a]	13 (12.7)[b]	204 (14.1)	124 (42.2)	36 (9.7)	27 (30.7)
Any thoracic complication, ≥1 choice possible	210 (9.0)	139 (28.7)	23 (4.5)[a]	13 (12.7)[b]	159 (11.0)	103 (35.0)	28 (7.5)	23 (26.1)
Lung injury	73	56	9	6	59	45	5	5
Hemoptysis	147	98	21	12	102	67	24	17
Pulmonary artery dissection	9	9	0	0	9	9	0	0
Lung injury, early (<3 h)	55		8		45		2	
Lung injury, late (≥3 h)	16		1		13		2	
Severity of lung injury								
Without hypoxemia	21		2		17		2	
Mild	36		7		27		2	
Moderate	14		0		14		0	
Severe	0		0		0		0	
Unknown	2		0		0		1	
Hemoptysis, acute	126		21		85		20	
Hemoptysis, delayed	21		0		17		4	
Management								
No direct intervention	86		2		65		19	
Local balloon tamponade	48		8		37		3	
Bronchial artery embolization	0		0		0		0	
Pulmonary artery embolization	16		13		3		0	
Any nonthoracic complication (≥1 choice possible)	69 (3.0)	52 (10.7)	0	0	61 (4.2)	45 (153)	8 (2.2)	7 (8.0)
Access site complications	23	20	0	0	21	18	2	2
Contrast-induced nephropathy	11	8	0	0	9	6	2	2
Contrast medium allergy	11	8	0	0	8	6	3	2
Other	26	22	0	0	23	19	3	3

Values are n (%) or n. No thrombosis or infectious complications occurred. [a]$P < 0.001$ for Japan vs Europe/United States per session. [b]$P < 0.001$ for Japan vs Europe/United States per patient.

Abbreviations as in Table 2.

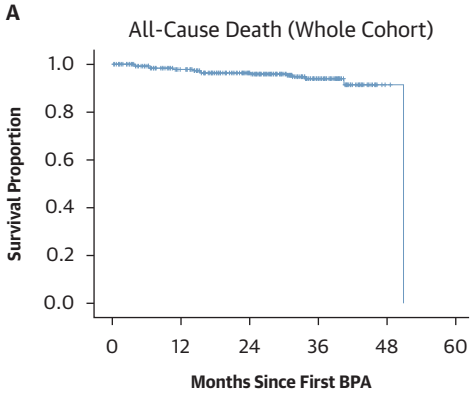
extracorporeal membrane oxygenation and/or intubation to manage a complication. No patient died of a BPA-related complication.

Nonthoracic complications such as access site complications, contrast-induced nephropathy, and contrast medium reactions occurred in 3.0% of sessions and 10.7% of patients.

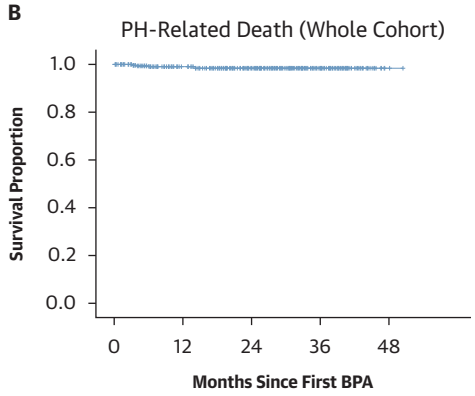
Multivariable binary logistic regression was used to identify factors associated with thoracic complication. On risk adjustment, 3 patient-related variables retained their significant association with a greater likelihood of thoracic complications (PH medication at any time) (OR: 3.62 [95% CI: 1.34-9.78]), female sex (OR: 2.24 [95% CI: 1.44-3.51]), and higher baseline PVR (OR: 1.23 [95% CI: 1.02-1.45]). Centers in Japan had a reduced risk compared with those in Europe (OR: 0.28 [95% CI: 0.14-0.54]) or the United States (OR: 0.38 [95% CI: 0.17-0.84]) (Supplemental Figure 4). As a sensitivity analysis, to ensure variation among the 18 centers was fully taken into account, a mixed effects model including center as a random effect was run. No substantive difference in the predictors were found: PH medication at any time (OR: 3.77 [95% CI: 1.38-10.32]), female sex (OR: 2.02 [95% CI: 1.29-3.16]), and baseline PVR (OR: 1.27 [95% CI: 1.06-1.51]).

BPA AFTER PEA. Prior PEA was recorded in 13.8% of patients. Age at diagnosis of these patients was lower than that of patients without prior PEA (56 years vs 66 years). Time from diagnosis to first BPA was longer (28.5 months vs 4.6 months). Baseline functional class and hemodynamics were not different, with the exception that SaO_2 was slightly better in patients with prior PEA (Supplemental Table 1B).

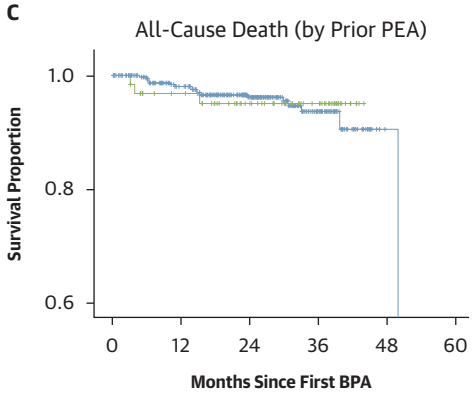
FIGURE 2 Patient Survival Since First BPA



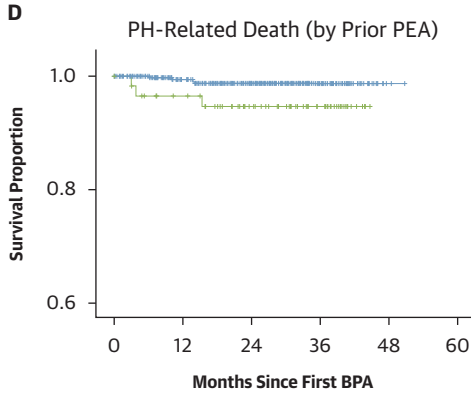
Interval Start (Months)	0	12	24	36	48
Entering	484	398	277	90	2
Deaths	9	7	3	1	1
Censored	77	114	184	87	1



Interval Start (Months)	0	12	24	36	48
Entering	484	398	277	90	2
Deaths	4	3	0	0	0
Censored	82	118	187	88	2



Interval Start (Months)	0	12	24	36	48
No PEA Before BPA (Blue Line)					
Entering	417	340	236	70	2
Deaths	7	6	3	1	1
Censored	70	98	163	67	1
PEA Before BPA (Green Line)					
Entering	67	58	41	20	
Deaths	2	1	0	0	
Censored	7	16	21	20	



Interval Start (Months)	0	12	24	36	48
No PEA Before BPA (Blue Line)					
Entering	417	340	236	70	2
Deaths	2	2	0	0	0
Censored	75	102	166	68	2
PEA Before BPA (Green Line)					
Entering	67	58	41	20	
Deaths	2	1	0	0	
Censored	7	16	21	20	

Kaplan-Meier curves for all-cause death (A and C) and pulmonary hypertension (PH)–related death (B and D) in the entire study cohort (A and B) and in patients with prior pulmonary endarterectomy (PEA) (C and D). Panel C shows no significant difference between groups (log rank test; $P = 0.983$), whereas panel D shows a significant difference between groups (log rank test; $P = 0.030$). BPA = balloon pulmonary angioplasty.

In patients with and without prior PEA, similar improvements in WHO FC and 6MWD and similar decreases in NT-proBNP and Borg dyspnea index were observed after final BPA. Hemodynamic improvements after final BPA were also broadly similar, except for a slightly greater percent increase in SaO_2 since baseline in patients with no PEA before BPA, and lower final wedge pressure (Supplemental Table 5). At last follow-up after final BPA, 55.7% of patients with no prior PEA vs 78.3% of patients with a prior PEA were on PH medications.

LONG-TERM OUTCOMES. Among 484 patients who underwent BPA, there were 21 all-cause deaths and only 7 PH-related deaths (**Figures 2A and 2B**). Three-year overall survival since first BPA was 94.1% (**Figure 2A**), with no significant difference for those with prior PEA (log-rank test; $P = 0.983$) (**Figure 2C**), but patient survival in terms of PH-related death since first BPA was significantly worse in patients with prior PEA (log-rank test; $P = 0.030$) (**Figure 2D**).

Neither type (sGC vs other PH medication vs none) nor timing of PH medication (before first BPA vs after first BPA vs no medication) could be shown to have an impact on survival subsequent to BPA.

DISCUSSION

The data from the worldwide International BPA Registry demonstrate that following BPA, significant improvements in hemodynamics, SaO_2, WHO FC, 6MWD, NT-proBNP, and Borg dyspnea index were observed, both for BPA as an initial treatment in patients not eligible for PEA, and after prior PEA. These changes may translate into meaningful practical clinical benefits such as improved patient-reported quality of life,[25,26] less hospitalizations, less oxygen use, and less PH medications.[27]

Complications occurred in 11.3% of sessions and 33.9% of patients, and were mostly hemoptysis. No patient died within 30 days of BPA. Results are generalizable to broader clinical practice if centers manage their learning curves by proctorship or educational programs,[28] with the goal to complete 85 patients[28] or 126 sessions,[7] and if there is a sufficient caseload (number of cases/y).

REGIONAL CHARACTERISTICS. The BPA registry enrolled 500 patients from 18 sites across 3 continents, 484 of which were included in the final analysis set. Expert site selection guaranteed that decisions were made by a multidisciplinary team, and that the BPA learning curve had been completed.[18] Although changes in clinical and hemodynamic parameters following BPA were evident in the whole cohort and complications occurred in all geographical regions, significant differences were observed between Caucasian and Japanese patients despite the correction for center experience. Anthropomorphic differences (more elderly women, milder hemodynamics, and shorter delay between diagnosis and BPA in Japan), but also other aspects (fewer patients with prior PEA, less medical pretreatment, more neck access, more segments and more occlusive lesions treated per session and patient, less conscious sedation, less contrast per session, less radiation in Japan, shorter intervals between BPA sessions), and other patient factors[29] may account for this observation.

CHANGES IN HEMODYNAMICS. Hemodynamics were assessed at a median of 6.1 months after final BPA. This practice is related to the gradual improvement in perfusion of ballooned vascular segments.[30,31] Because the greatest effect derives from opening of type C and D lesions,[14,32,33] data on successfully opened occlusive lesions were included in the **Central Illustration**. Hemodynamic changes following BPA were impressive, with a 57% decrease in PVR from baseline for the whole cohort, an achievement that parallels data from recent randomized controlled trials in Europe and Japan.[16,34] Final PVRs were 206 dynes/s/cm^{-5} in Japan vs 264 dynes/s/cm^{-5} in Europe and 266 dynes/s/cm^{-5} in the United States, which is similar to immediate postoperative PVR in the first and second European CTEPH registries (256 dynes/s/cm^{-5} vs 258 dynes/s/cm^{-5} in Pepke-Zaba et al[4] and Guth et al[35]). However, direct comparison between PEA and BPA[36] was not the goal of this registry. A dedicated randomized controlled comparative effectiveness trial is underway for patients who are suitable for both PEA and BPA (NCT05110066).

Postinterventional PH, defined as mPAP ≥25 mm Hg,[3] was present in 51.7% of patients, which mirrors the 51% of patients with mPAP ≥25 mm Hg after PEA in the Cambridge series at the 3- to 6-month review.[37] This observation may be interpreted in 2 ways: first, one may assume that PEA and BPA both address significant vascular obstruction, and/or second, the definition of PH after mechanical treatments of CTEPH needs a revision that takes into account postinterventional microvascular disease and elevated left ventricular filling pressures.[38] In addition, postinterventional assessment should probably include an exercise component.

THE ROLE OF PH DRUGS. One of the criticisms of BPA success is that its results are commonly reported with concomitant medical treatments, which is not a

practice in PEA data reporting. In the BPA registry, 68.6% of patients were on PH drugs at baseline, and 58.7% at the last recorded follow-up after final BPA. As expected, the percent increase in CO from baseline was significantly greater in patients on PH drugs than in those without (16.4% vs 3.7%; $P = 0.002$), despite equal changes in PVR, highlighting a net impact of BPA on mPAP, rather than on CO.

The data show that while successful BPA should allow for medical therapies to be stopped, the majority of treatments given at baseline were continued. Although PH medications given at any time during the registry did not significantly affect the percent decrease in PVR from baseline (60.1% in patients on sGC vs 51.2% in patients without PH medications), they enhanced the increase in CI. PH-related death since first BPA was not affected by PH medication given at any time (data not shown).

COMPLICATIONS. One of the goals of the refinement of the BPA technique by Japanese interventionists[7-9] was the reduction of complications.[6] Since 2013, Japanese operators have been proctoring in Europe and the United States and have helped establish most centers involved in the BPA registry. As a consequence, complications were reduced since the second CTEPH registry (11.3% vs 12% complications per session[35]), and 30-day mortality was 0% vs 1.1%.[22] Lung injury occurred in 15.3% of patients in Europe, 5.7% of U.S. patients, and 5.9% of Japanese patients, which constitutes low numbers compared with previous reports.[5] We recommend that every BPA operator should be familiar with the technique of pulmonary artery embolization using gelatine, which is particularly effective in stopping major hemoptysis.[39]

Predictors of BPA-related thoracic complications were female sex, PH medications, region outside of Japan and high PVR. Female sex is an accepted risk factor for percutaneous interventional procedure-related adverse outcomes.[40] One of the reasons that PH medications in the present registry were associated with more rather than less complications[16] may be that they were given to patients with the highest PVR. PVR >560 dynes/s/cm^{-5} and mPAP >40 mm Hg have been reported as thresholds increasing the likelihood of BPA-related complications.[5]

LONG-TERM OUTCOME. BPA 3-year survival was 94.1%, which is similar to the Japanese registry (94.5%)[11] and the French experience (95.1%),[12] and better than in the Polish multicenter registry (92.4%) that recruited between July 2013 and June 2019.[13]

There were only 7 PH-related deaths, making the estimation of HRs unreliable. Preliminary analysis suggests that predictors of all-cause death for patients undergoing BPA include higher WHO FC, higher NT-proBNP, and a longer time from diagnosis to first BPA. This will be the subject of future more detailed research, eg, in the currently ongoing international TEAM (TrEatment Approach in the Multimodal Era; NCT05629052).

STUDY LIMITATIONS. Because the registry started enrolling in 2018, the PH definition in use at that time, namely a threshold of 25 mm Hg for mPAP, was employed. The case report form included questions on intubation and PEA, but information on complication-related hospitalizations was not collected in the registry.

There was limited availability of follow-up RHCs, which were only recorded in 66.5% of patients because of the COVID-19 pandemic. We cannot make conclusions on drug choices and drug effects. Sequential RHCs were not prespecified; therefore, the magnitude of hemodynamic improvements by treated segments cannot be reported. We cannot exclude that changes seen following BPA were partially caused by medical therapy in those patients who started PH medications after the first BPA. In light of the variation observed in the use of medication after BPA, future research to elucidate optimal medication management strategies should be supported, because clear recommendations are currently not available.

SEX AND GENDER CONSIDERATIONS. In this study, we used the term "sex" to refer to the biological classification of participants as male or female based on physiological and genetic characteristics. We acknowledge that sex is distinct from gender, which encompasses social and cultural roles, behaviors, and identities.

CONCLUSIONS

Despite differences in patients and practice approaches, meaningful changes of PVR were observed from baseline, with 0% 30-day mortality and 94.1% 3-year survival. Complications occurred in 11.3% of sessions, but were classified as mild in the majority of cases. These results were achieved with a multidisciplinary approach that is likely to have influenced treatment selection and outcomes toward patient-centered rather than procedure-centered medicine.

ACKNOWLEDGMENTS The authors thank Simone Lerch and Sonja Mariotti (ICA, Switzerland) for project management. The authors acknowledge the inclusion of patients from Keio University. The International BPA Registry is owned and managed by the International CTEPH Association. The association is headed by an Executive Board, composed of CTEPH

experts. The Executive Board of the association was responsible for the design of the registry, provided input into the analyses, decided on medical interpretation, and oversaw the development of the manuscript.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The ICA received financial support from Bayer Pharma AG to run the registry. The sponsor was not involved in the management of nor in decisions related to the Registry, and had no access to the database. Dr Lang was an investigator in trials involving the following drug companies, and also had relationships including consultancy service, research grants, and membership of scientific advisory boards: AOP-Health, Actelion-Janssen, Merck Sharp & Dohme, United Therapeutics, Pulnovo, Medtronic, Neutrolis, and Sanofi. Dr Brenot has received compensation for scientific symposia from Merck Sharp & Dohme. Dr Jaïs has received grants from Janssen; and has received speaker fees and/or consultant honoraria from Merck Sharp & Dohme. Dr Madani has received consultancy fees and royalties from Wexler Surgical; and has received consultancy fees from Actelion/Janssen and Johnson and Johnson. Dr Guth has received speaker fees and/or consultant honoraria from Actelion/Janssen, Bayer AG, Merck Sharp & Dohme, and Pfizer. Dr Kurzyna has provided consultancy services, received research grants, served as scientific advisory board member, and served as an investigator in clinical trials for drug companies including AOP-Health, Actelion-Janssen, Merck Sharp & Dohme, United Therapeutics, Pfizer, and Ferrer. Dr Wiedenroth has received speaker fees and/or consultant honoraria from Actelion/Janssen, AOP Orphan Pharmaceuticals AG, Bayer AG, BTG, Merck Sharp & Dohme, OrphaCare, and Pfizer. Dr Shimokawahara has received lecture fees from Bayer Yakuhin and Nippon Shinyaku; and has received research funding from Bayer Yakuhin. Dr Bashir has been funded by National Heart, Lung, and Blood Institute; and has an equity interest in Thrombolex Inc. Dr Delcroix has received speaker and consultant fees from Ferrer, Gossamer Bio, Janssen, and Merck Sharp & Dohme, unrelated to current work and all paid to her institution. Dr Frantz has received consulting fees from Gossamer Bio, Insmed, Merck and Liquidia; has participated in a Data Safety Monitoring or Advisory Board of Aerovate Pharmaceuticals; has received royalties or licenses from UpToDate; has received grants that were paid to his institution from National Heart, Lung, and Blood Institute and Gossamer Bio; is a member of the Pulmonary Hypertension Association Scientific Leadership Council; and holds stocks in Merck. Dr Gerges has received compensation for scientific symposia from AstraZeneca, AOPHealth, Cordis, Janssen, and Merck Sharp & Dohme; has received speaker fees from AOPHealth, AstraZeneca, Janssen, and Ferrer; and has received an educational grant from OrphaCare. Dr Godinas has received consultant/speaker honoraria from Merck Sharp & Dohme, Johnson and Johnson, Biotest, and Chiesi. Dr Heresi has received funds for investigator-initiated research as well as fees for advisory boards and non-promotional nonbranded speaking from Bayer Healthcare; and has received fees for advisory boards from Johnson and Johnson. Dr Jansa is a paid consultant and speaker for numerous pharmaceutical companies and has received financial grants from Johnson and Johnson, AOP Health, Bayer Healthcare, Merck Sharp & Dohme, and Arena Pharmaceuticals Inc. Dr Jenkins has received speaker fees and consultancy fees from Janssen. Dr Hoole has received speaker fees/honoraria from AstraZeneca. Dr Pepke-Zaba has received research grant from Merck Sharp & Dohme; has received consulting fees from Gossamer and Johnson and Johnson; and has received support for attending meetings and/or travel from Johnson and Johnson. Dr Witkin has received consultancy fees from Janssen Pharmaceuticals. Dr Kim has received consultant/speaker honoraria from Bayer, Gossamer Bio, Johnson and Johnson, Merck, Pulnovo, and United Therapeutics. Dr Matsubara has received grants from Nippon Shinyaku; has received honoraria for lectures from AOP Health, Bayer, Janssen, Kaneka Medix, Mochida, Merck Sharp & Dohme, Nippon Shinyaku, and Nipro; has received payments for expert testimony from Merck Sharp & Dohme; and has participated in advisory board meetings for Bayer, Janssen, Mochida, and Merck Sharp & Dohme. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Irene M. Lang, Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria. E-mail: irene.lang@meduniwien.ac.at. X handle: @IreneMLang.

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KEY WORDS balloon pulmonary angioplasty, balloon pulmonary angioplasty outcomes, balloon pulmonary angioplasty-related complication, chronic thromboembolic pulmonary hypertension

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.