Balloon Pulmonary Angioplasty (BPA)

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CTEPH is an obstructive disease

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ESC/ERS GUIDELINES

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

10. Chronic thromboembolic pulmonary hypertension (group 4)

CTEPH is a disease of obstructive PA remodelling as a consequence of major vessel thromboembolism. CTEPH has been reported with a cumulative incidence of 0.1–9.1% within the first 2 years after a symptomatic PE event.[417] The large margin of error is probably due to referral bias, a paucity of early symptoms and difficulty in differentiating acute PE from symptoms of pre-existing CTEPH.[418] Although the exact prevalence and annual incidence of CTEPH are unknown, some data suggest that this condition may occur in approximately 5 individuals per million population per year.[419]

symptoms and signs are non-specific or absent in early CTEPH, with signs of right heart failure only becoming evident in advanced disease. Thus early diagnosis remains a challenge in CTEPH, with a median time of 14 months between symptom onset and diagnosis in expert centres.[421] When present, the clinical symptoms of CTEPH may resemble those of acute PE or IPAH; in the latter context, oedema and haemoptysis occur more often in CTEPH, while syncope is more common in IPAH.[422]

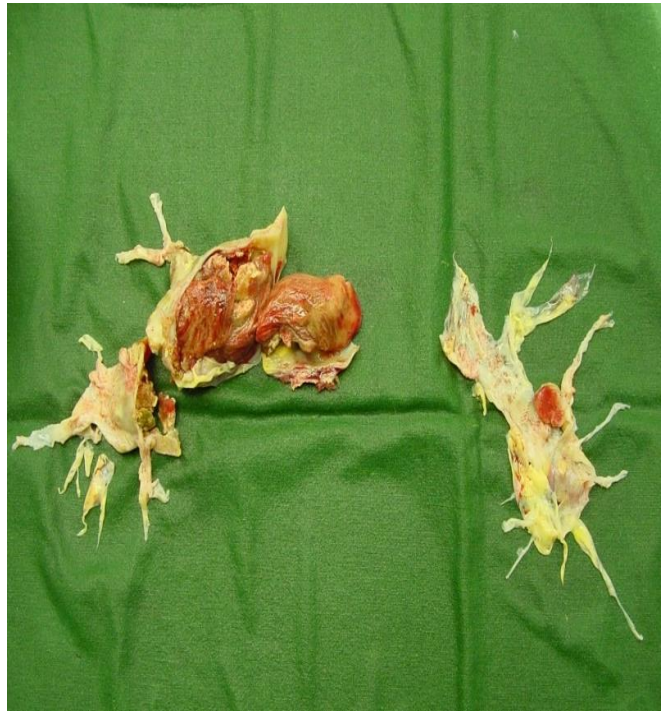
The diagnosis of CTEPH is based on findings obtained after at least 3 months of effective anticoagulation in order to discriminate this condition from 'subacute' PE. These findings are mean PAP $\geq$25 mmHg with PAWP $\leq$15 mmHg, mismatched perfusion defects on

Recommendations for PEA: ESC/ERS guidelines

Recommendations	Class[a]	Level[b]
In PE survivors with exercise dyspnoea, CTEPH should be considered	IIa	C
Life-long anticoagulation is recommended in all patients with CTEPH	I	C
It is recommended that in all patients with CTEPH the assessment of operability and decisions regarding other treatment strategies should be made by a multidisciplinary team of experts	I	C
Surgical PEA in deep hypothermia circulatory arrest is recommended for patients with CTEPH	I	C
Riociguat is recommended in symptomatic patients who have been classified as having persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon	I	B
Off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon	IIb	B
Interventional BPA may be considered in patients who are technically non-operable or carry an unfavourable risk:benefit ratio for PEA	IIb	C
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended	III	C

Rationale for PEA

- Complete removal and clearance of PA obstructions
- Reduces pulmonary arterial pressure
- Improve pulmonary perfusion, oxygenation, RV function and dead space ventilation
- Improve *life expectancy and quality of life*



Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Results From an International Prospective Registry

Joanna Pepke-Zaba, MD; Marion Delcroix, MD; Irene Lang, MD; Eckhard Mayer, MD;
Pavel Jansa, MD; David [illegible] BSc; Andrea M. D'Armini, MD;
Marco Morsolini[illegible]D; Adam Torbicki, MD;
Bent Kristens[illegible] Joan A. Barberà, MD;
Marc de P[illegible] udolf Speich, MD;
Miguel [illegible]m Hamid, MD;

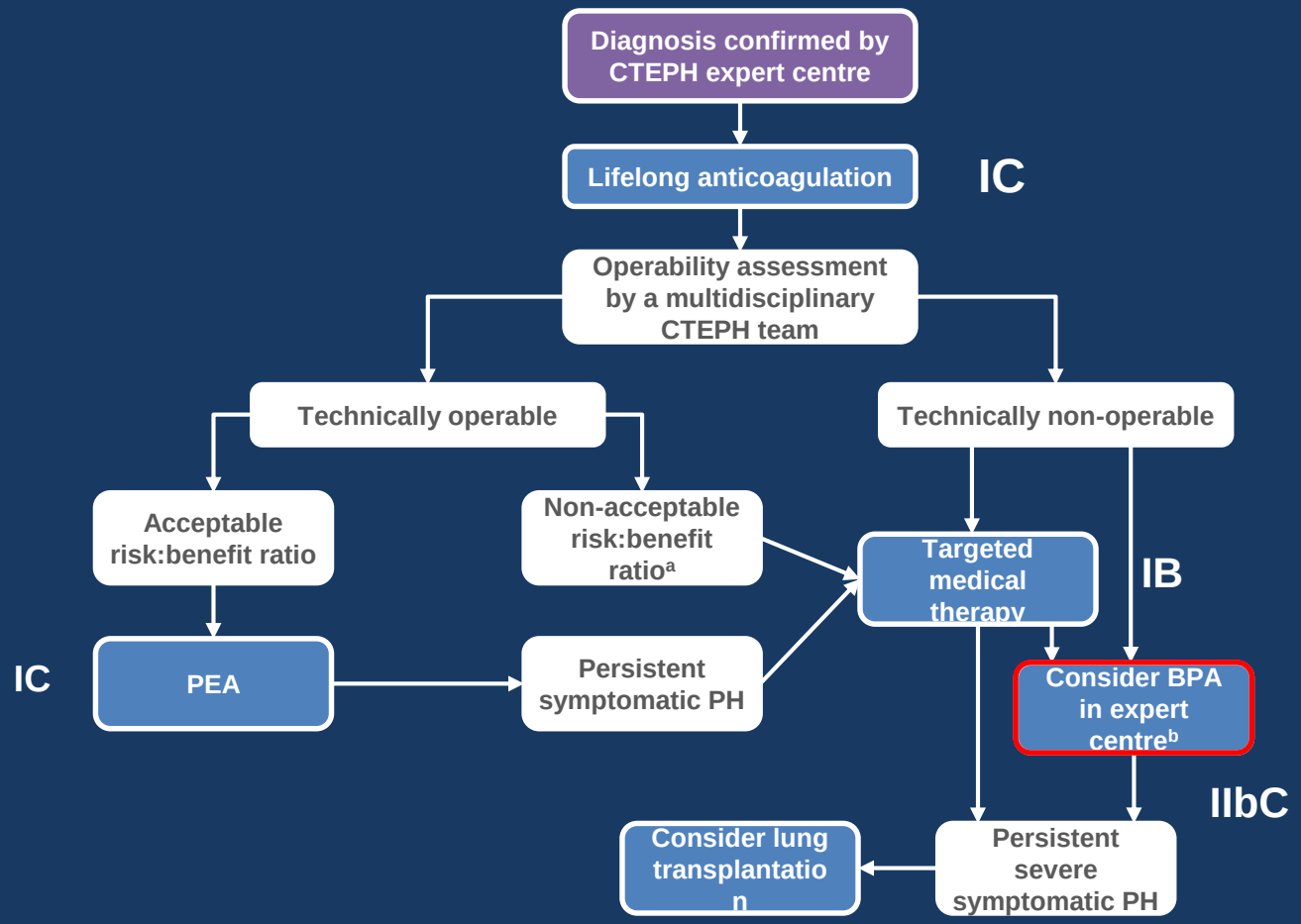
36% inoperable,
43% not operated

Background—Chronic [illegible]quel of venous thromboembolism with fatal natural history[illegible]erectomy. The clinical characteristics and current management of p[illegible] was investigated.

Methods and Results—The international [illegible] months) consecutive patients with CTEPH, from February 2007 until January 2009. Diagnosis was confirmed by rig[illegible]heart catheterization, ventilation-perfusion lung scintigraphy, computerized tomography, and/or pulmonary angiography. At diagnosis, a median of 14.1 months had passed since first symptoms; 427 patients (62.9%) were considered operable, 247 (36.4%) nonoperable, and 5 (0.7%) had no operability data; 386 patients (56.8%, ranging from 12.0%–60.9% across countries) underwent surgery. Operable patients did not differ from nonoperable patients relative to symptoms, New York Heart Association class, and hemodynamics. A history of acute pulmonary embolism was reported for 74.8% of patients (77.5% operable, 70.0% nonoperable). Associated conditions included thrombophilic disorder in 31.9% (37.1% operable, 23.5% nonoperable) and splenectomy in 3.4% of patients (1.9% operable, 5.7% nonoperable). At the time of CTEPH diagnosis, 37.7% of patients initiated at least 1 pulmonary arterial hypertension–targeted therapy (28.3% operable, 53.8% nonoperable). Pulmonary endarterectomy was performed with a 4.7% documented mortality rate.

Conclusions—Despite similarities in clinical presentation, operable and nonoperable CTEPH patients may have distinct associated medical conditions. Operability rates vary considerably across countries, and a substantial number of patients (operable and nonoperable) receive off-label pulmonary arterial hypertension–targeted treatments. **(*Circulation*. 2011; 124:00-00.)**

Interventional BPA may be considered in patients who are technically non-operable or carry an unfavourable risk to benefit ratio for PEA



[a]Technically operable patients with non-acceptable risk/benefit ratio can also be considered for BPA.
[b]In some centres medical therapy and BPA are initiated concurrently.
BPA: balloon pulmonary angioplasty, PEA: pulmonary endarterectomy

Galiè N, *et al. Eur Respir J* 2015; 46:903-75;
Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

What is Balloon Pulmonary Angioplasty (BPA)?

- BPA is an interventional treatment that uses a balloon catheter to dilate pulmonary stenosis or obstruction.

- BPA was first developed in the field of pediatric cardiology for treating congenital stenotic pulmonary arteries.

- The development of BPA for the treatment of inoperable CTEPH patients is extremely slow

- The first attempt to treat inoperable CTEPH case by BPA was performed in 1988. (Voorburg JA, et al. Chest 1988;94:1249-53)

First case series: 13 years later

Brief Rapid Communications

Balloon Pulmonary Angioplasty for Treatment of Chronic Thromboembolic Pulmonary Hypertension

Jeffrey A. Feinstein, MD, MPH; Samuel Z. Goldhaber, MD; James E. Lock, MD; Susan M. Ferndandes, PA-C; Michael J. Landzberg, MD

Background—Although pulmonary thromboendarterectomy is increasingly successful for the definitive treatment chronic thromboembolic pulmonary hypertension (CTEPH), not all patients have surgically accessible disease. Oth are poor surgical candidates because of comorbid illness. Therefore, for selected patients, we defined and implement an alternative interventional strategy of balloon pulmonary angioplasty (BPA).

Methods and Results—Eighteen patients (mean age, 51.8 years; range, 14 to 75 years) with CTEPH underwent BPA; th averaged 2.6 procedures (range, 1 to 5) and 6 dilations (range, 1 to 12). Selection of pulmonary artery segments dilation required (1) complete occlusion, (2) filling defects, or (3) signs of intravascular webs. After an average of months of follow-up (range, 0.5 to 66 months), the average New York Heart Association class improved from 3.3 1.8 ($P<0.001$), and 6-minute walking distances increased from 209 to 497 yards ($P<0.0001$). Pulmonary artery me pressures decreased from 43.0±12.1 to 33.7±10.2 mm Hg ($P=0.007$). Eleven patients developed reperfusi pulmonary edema; 3 required mechanical ventilation.

Conclusions—BPA reduces pulmonary artery hypertension in patients with CTEPH and is associated with long-te improvement in New York Heart Association class and 6-minute walking distances. BPA is a promising interventio technique that warrants randomized comparison with medical therapy in CTEPH patients who are not surgi candidates. (*Circulation*. 2001;103:10-13.)

Key Words: balloon ■ angioplasty ■ embolism ■ thrombus ■ pulmonary heart disease

- Averaged 2.6 procedures, 6 dilations
- mPAP decreased from 43.0 to 33.7 mmHg
- About 60 % of patients developed reperfusion edema (one patient died)

25 years later the 1st European publication

ORIGINAL ARTICLE

Balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension

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ABSTRACT

Objective To examine the effect of balloon pulmonary angioplasty (BPA) on chronic thromboembolic pulmonary hypertension (CTEPH) in patients with inoperable disease or persistent pulmonary hypertension after pulmonary endarterectomy.

Design Observational cohort study.

Setting Referred patients with inoperable or persistent CTEPH.

Patients Twenty consecutive CTEPH patients (10 females), aged 60±10 years.

Interventions BPA.

Main outcome measures Right heart catheterisation, functional capacity (cardiopulmonary exercise testing (CPET) and NYHA class) and blood sampled biomarkers N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T examined at the time of diagnosis and repeated in all patients 3 months after the last BPA.

to right heart strain and failure. While our understanding of the pathophysiological mechanisms remains incomplete, the prognosis of CTEPH is poor and related to the pulmonary artery pressure (PAP) and the degree of right ventricular failure.

Pulmonary endarterectomy is considered the treatment of choice in CTEPH and has curative potential.[2] However, this surgical procedure may not be offered to patients with either substantial distal vascular obstruction or significant comorbidity. Recent data from an international prospective registry demonstrated that more than a third of patients were considered inoperable.[3] Parallel with the introduction of new drugs and improved care in pulmonary arterial hypertension, inoperable CTEPH patients are increasingly being offered this same medication. However, conflicting results concerning haemodynamics and functional capacity have been published and cautious use of medical

Heart 2013;99:1415–1420.

- Averaged 3.7±2.1 procedures, 20 patients
- mPAP decreased from 45±11 to 33±10 mmHg
- About 45 % of patients developed reperfusion edema (two patients died)

The most representative results with BPA in the management of patients with inoperable CTEPH

First Author (year)	Pts	Procedures	Baseline mPAP (mmHg)	mPAP post BPA (mmHg)	Mean change (%)	Baseline PVR (WU)	PVR post BPA	Mean change (%)	n of deaths Mortality/procedures (%)
Fenstein (2001)	18	48	42±12	33±10	-21	*22±9	*17±8	-23	1/2.0
Andreassen (2013)	20	73	45±11	33±10	-27	8.8±4.0	5.9±3.6	-33	2/2.7
Kurzyna (2017)	56	157	50.7±10.8	35.6±9.3	-30**	10.3±3.7	5.9±2.8	-43**	3/1.9
Velázquez (2016)	21	75	52.4±13	37.8±10	-28	10.4±4	5.5±2	-47	1/1.3
Olsson (2017)	56	266	40±12	33±11	-18	7.4±3.6	5.5±3.5	-26	1/0.4
Mizoguchi (2012)	68	255	45.4±9.6	24±6.4	-47	11.8±4.6	4.1±1.9	-65	1/0.4
Kimura (2016)	67	405	39.3±11.0	20.0 ± 4.2	-49	9.7 ± 6.8	3.4±1.5	-65	0/0
Inami (2016)	103	350	41	21	-49	8.7	2.7	-69	1/0.3
Ogo (2016)	80	385	42±11	25±6	-40	11±5.3	5.1±2.3	-54	0/0
Kawakami (2016)	97	500	45.1±10.8	23.3±6.4	-48	12±5.7	3.9±1.9	-68	4/0.8
Aoki (2017)	84	424	38 ± 10	25 ± 6	-34	7.3 ± 3.2	3.8±1.0	-45	0/0
Ogawa (2017)	308	1408	43.2±11.0	24.3±6.4	-44	10.7±5.6	4.5±2.8	-58	8/0.6

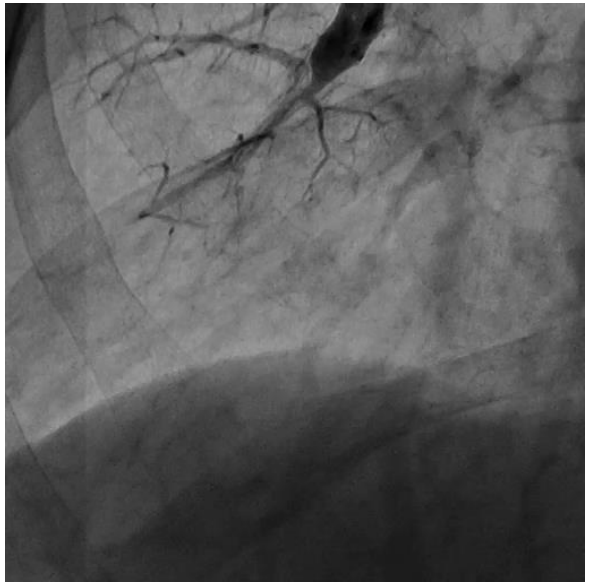
* Values for Total Pulmonary Resistance (TPR) expressed in WU · m^2

** Results from 31 patients who completed their BPA treatment or underwent at least 3 sessions

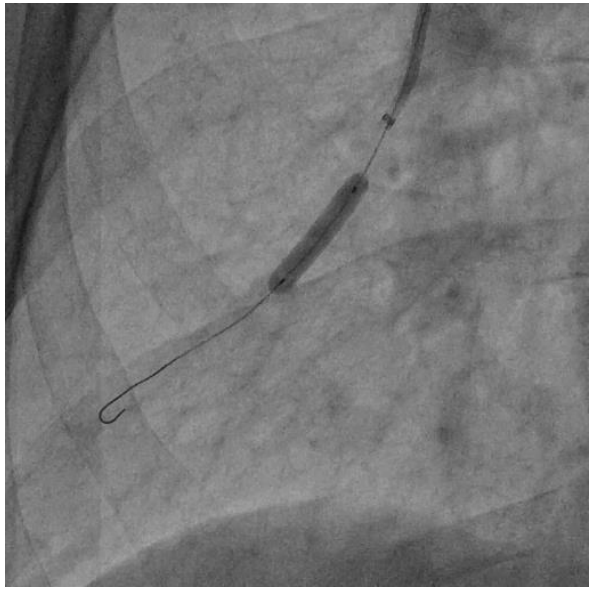
Karyofyllis, P., et al. Curr Treat Options Cardio Med (2018) 20: 13.

Balloon Pulmonary Angioplasty (BPA)

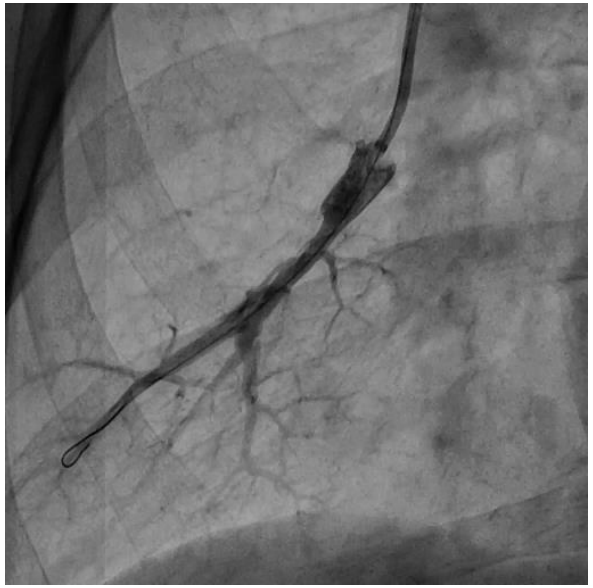
Selective PAG



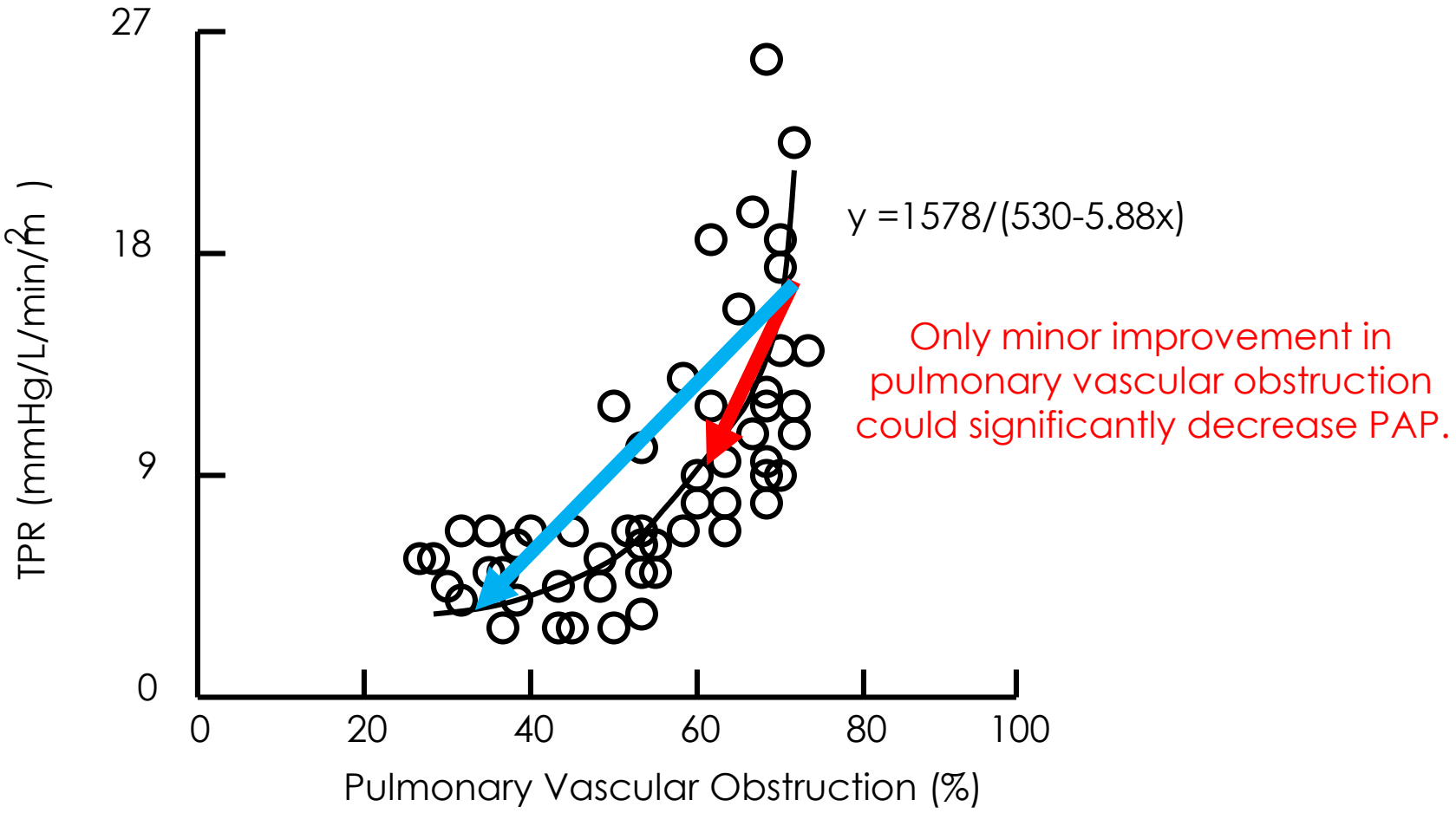
Balloon dilatation



Post BPA



Relation between pulmonary vascular obstruction and pulmonary resistance in APE



Azarian R, et al. J Nucl Med 1997; 38: 980-983

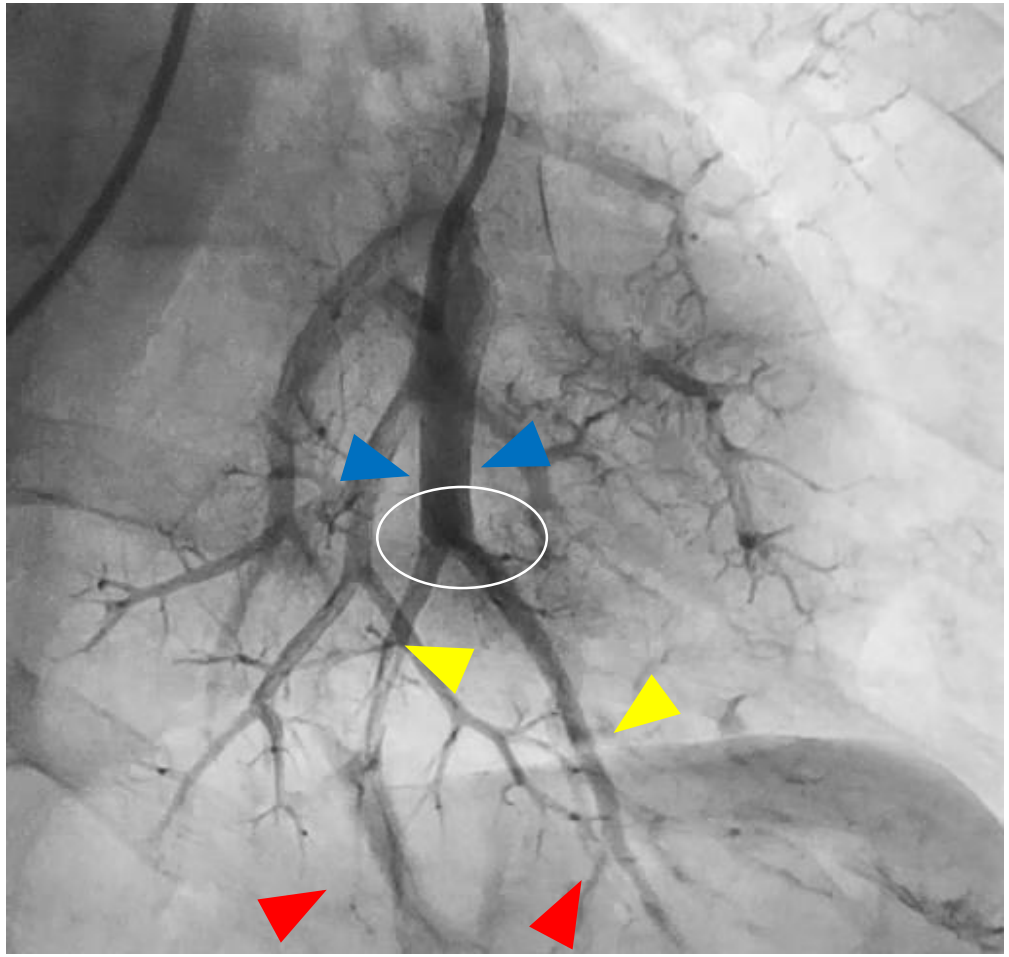
Balloon Pulmonary Angioplasty (BPA)-Contraindications

- Contraindications of BPA include iodine allergy, as the use of a contrast medium is essential in BPA.
- Additionally, in cases with renal dysfunction, the benefits of performing BPA must be weighed against the risks.
- Severity of pulmonary hypertension may not necessarily be a contraindication of BPA. Although previous reports have indicated a higher mean PAP at baseline is associated with more frequent complications, the patient prognosis will be worse without effective treatment in cases with severe hemodynamics. BPA can be expected to have more powerful effect in these patients

Recognition of the lesions

- Clearly recorded PAG with deep breath is essential in finding out lesions.
- Most frequently observed lesions are “web” and exist in almost all segments
- Most of “web” lesions only appear slightly hazy in PAGs.
- Following findings will be some help to recognize lesions.
    - lesion distal delayed flow
    - loss of capillary staining in perfused area
    - occurrence of prominent pulsatile movement of lesion proximal artery

Representative PAG of CTEPH patient



lesion distal delayed flow

loss of capillary staining of perfused area

occurrence of prominent pulsatile movement of lesion proximal artery

5 lesion types are recognized in CTEPH

Novel Angiographic Classification of Each Vascular Lesion in Chronic Thromboembolic Pulmonary Hypertension Based on Selective Angiogram and Results of Balloon Pulmonary Angioplasty

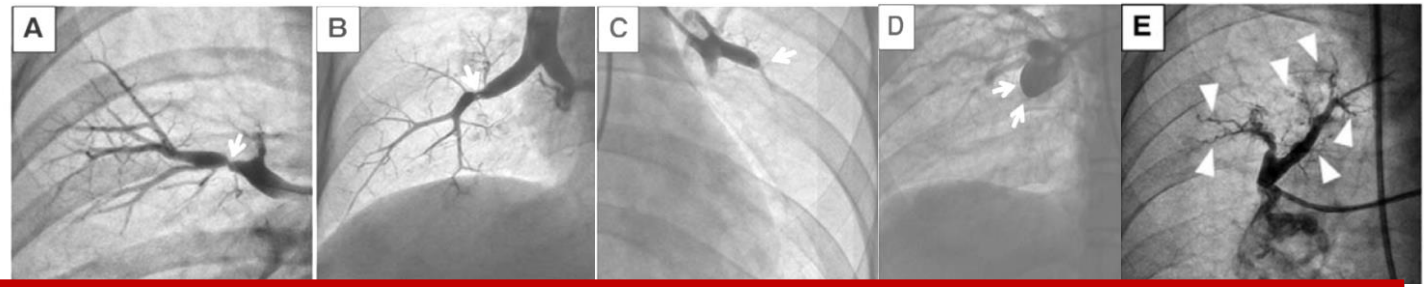
Takashi Kawakami, MD, PhD; Aiko Ogawa, MD, PhD; Katsumasa Miyaji, MD, PhD; Hiroki Mizoguchi, MD, PhD; Hiroto Shimokawahara, MD, PhD; Takanori Naito, MD; Takashi Oka, MD; Kei Yunoki, MD, PhD; Mitsuru Munemasa, MD, PhD; Hiromi Matsubara, MD, PhD

Background—Balloon pulmonary angioplasty (BPA) is an alternative therapy for patients with chronic thromboembolic pulmonary hypertension who are ineligible for standard therapy, pulmonary endarterectomy. Although there are several classifications of vascular lesions, these classifications are based on the features of the specimen removed during pulmonary endarterectomy. Because organized thrombi are not removed during balloon pulmonary angioplasty, we attempted to establish a new classification of vascular lesions based on pulmonary angiographic images. We evaluated the success and complication rate of BPA in accordance with the location and morphology of thromboembolic lesions.

Methods and Results—We reviewed 500 consecutive procedures (1936 lesions) of BPA in 97 patients with chronic thromboembolic pulmonary hypertension and investigated the outcomes of BPA based on the lesion distribution and the angiographic characteristics of the thromboembolic lesions, as follows: type A, ring-like stenosis lesion; type B, web lesion; type C, subtotal lesion; type D, total occlusion lesion, and type E, tortuous lesion. The success rate was higher, and the complication rate was lower in ring-like stenosis and web lesions. The total occlusion lesions had the lowest success rate. Tortuous lesions were associated with a high complication rate and should be treated only by operators with extensive experience with BPA.

Conclusions—We modified the previous angiographic classification and established a new classification for each vascular lesion. We clarified that the outcome and complication rate of the BPA are highly dependent on the lesion characteristics. (*Circ Cardiovasc Interv*. 2016;9:e003318. DOI: 10.1161/CIRCINTERVENTIONS.115.003318.)

Key Words: angiography ▪ angioplasty ▪ arterial pressure ▪ coronary artery disease ▪ hypertension, pulmonary



Lesion Type	A	B	C	D	E
Description of Lesion Type	Ring-Like Stenosis	Web	Subtotal	Total Occlusion	Tortuous
Number, n	248	1235	342	67	44
Bifurcation lesion, n (%)	248 (100)	1092 (88.4)	301 (88.0)	61 (91.0)	0 (0)
Distribution (upper/middle or lingular/lower)					
Right lung, n	103/7/46	215/172/367	64/42/118	6/16/24	5/3/9
Left lung, n	29/0/63	61/22/398	13/6/99	0/2/19	6/1/20
Used balloon					
Size, mm	4.0 (1.5–8)	3.5‡ (1.5–8)	3.5‡ (1.25–7)	4.0 (1.5–8)	2.0† (1.5–4.5)
Inflated pressure, atm	12 (2–22)	8‡ (2–18)	10 (2–20)	12 (3–18)	10 (2–16)
Success, n (%)	248 (100)	1219 (98.7)	296§ (86.5)	35‖ (52.2)	28 (63.6)
Complication, n (%)	4 (1.6)	27 (2.2)	53* (15.5)	4 (6.0)	19 (43.2)
Type of complication					
Balloon injury, n	3	7	5	0	0
Wire injury/perforation, n	0	12	41	4	19
Dissection of vessels, n	1	8	7	0	0

Values are presented as the median and the range. DRD indicates distal reference diameter; %DS, percent diameter stenosis; MLD; minimal lumen diameter; PRD, proximal reference diameter; QVA, quantitative vascular analysis; and RD, reference diameter.

BPA Technical Considerations

- Oxygen administration to maintain an oxygen saturation of 98% to 100%
- Anticoagulants are continued during the BPA procedure to maintain a prothrombin time international ratio between 2.0 and 3.0
- Right femoral vein (jugular) with 8F or 9F sheath and a 6-7 F long introducer sheath (70-90 cm) (Jugular vein needs 2 operators)
- Appropriate guiding catheter, 0.014-inch or 0.018-inch guidewire is used to cross the lesion
- A smaller balloon relative to the actual vessel size is selected for the initial BPA session to reduce the risk of pulmonary vessel injury and restore minimal blood flow to the occluded or stenotic pulmonary vessels
- In a subsequent session, a balloon catheter of 100-120% the size of the reference vessel diameter indicated on the angiogram is selected to optimize the dilatation of the lesion (and if previously a mean PA < 35 mmHg has been achieved, or else dilation of other untreated lesions)

BPA Technical Considerations

- There is no limitation regarding the number of lobes targeted in one session.
- The maximum time of radiographic fluoroscopy in a single session should be limited to 60 min.
- As a consequence, lesions from 4–10 sites could generally be treated in a single session.
- To enhance the therapeutic effect of BPA, it is important to make the area of reperfusion large, which requires repeated treatment with ≥ four sessions per patient depending on the treatment goal

Selection of segmental arteries

- Generally, almost all segmental arteries can be easily selected by using Judkins right type guiding catheter.

- Usage of multi purpose type guiding catheter for right PA and Amplatz left (AL1) type guiding catheter for left PA are recommended.

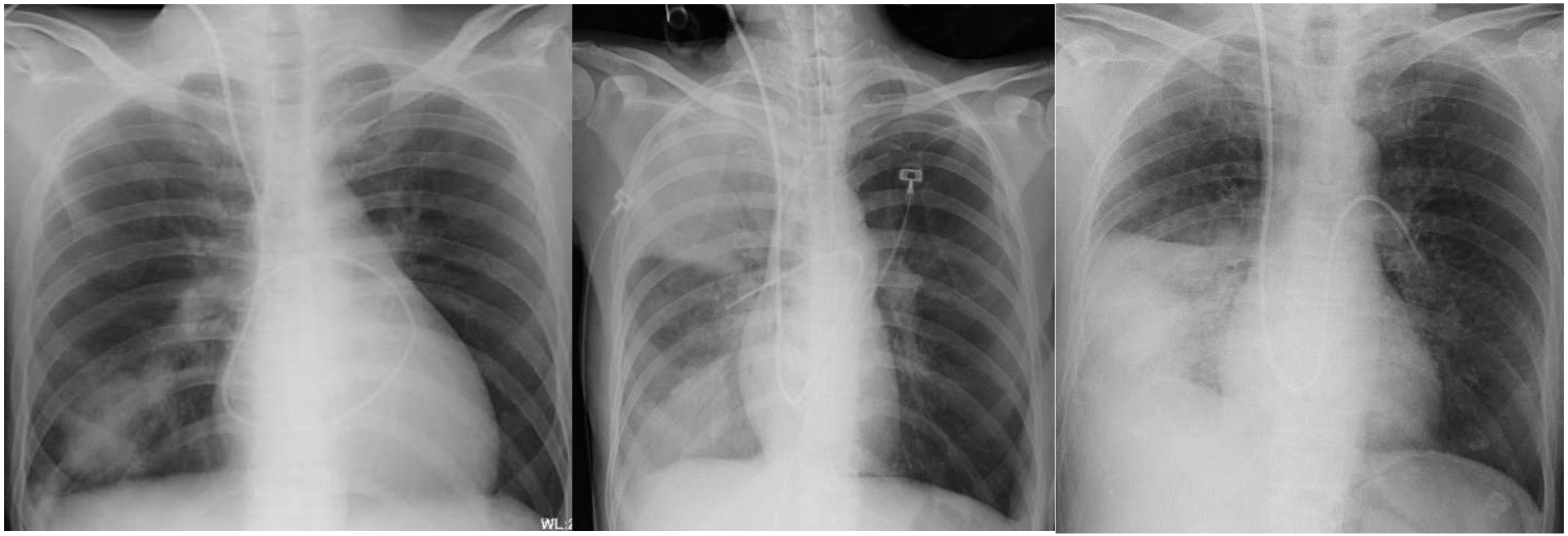
- Usage of AL 1 type guiding catheter would be necessary in selecting rt A5 and A7.

Suitable guiding catheters for each segmental pulmonary artery

Right side	Guiding Catheter	Left side	Guiding Catheter
A1	MP < JR-4	A1+2	MP < JR-4
A3	MP	A3	AL-1 < JL-4
A5	AL-1 > MP	A5	AL-1 > JL-4
A7	AL-1 > JR-4	-	-
A9	MP	A9	MP < AL-1

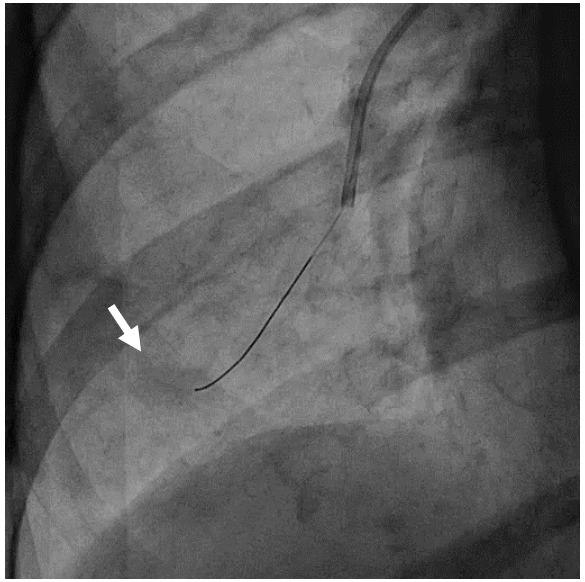
AL: Amplatz left type, JL: Judkins left type, JR: Judkins right type.

Complication; Pulmonary injury

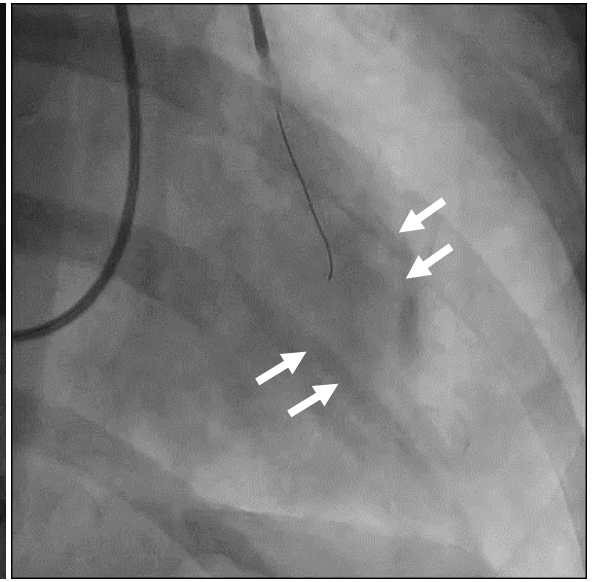


Complications	Diagnostic Criteria
Pulmonary injury	Hemoptysis
	Chest radiographic opacities
	Chest computed tomographic opacities
Pulmonary artery perforation	
Pulmonary artery rupture	

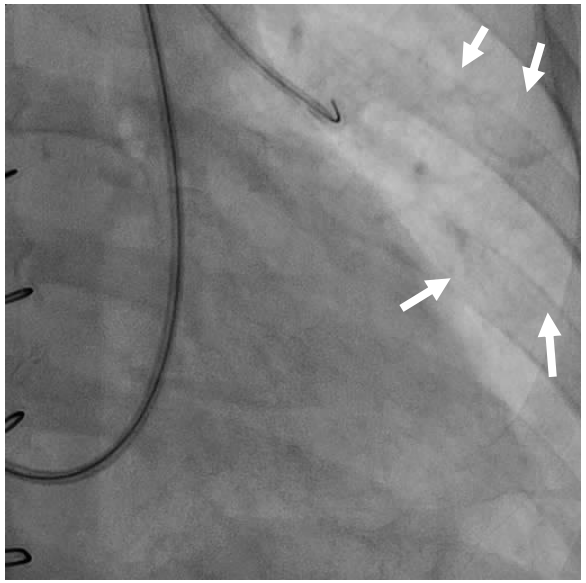
Angiographic extravasation findings of contrast medium after BPA



Wire injury



Over dilation



Pressure overload

Vascular injury due to procedural complication is the main cause of pulmonary injury.

Pulmonary injury

- The most frequent and characteristic complication of BPA is pulmonary injury.

- Pulmonary vessel injury caused by the guidewire, guiding catheter, balloon dilation, or contrast medium injection at high pressure may play a role in inducing pulmonary injury in BPA.

- It is necessary to determine how to dilate the lesion to achieve maximal therapeutic efficacy and reduce the risk of pulmonary vessel injury, which could potentially become lethal. To dilate the lesion, balloon size, vessel size, the number of organised thrombi and patient haemodynamics must be considered. Balloon size is the only one of these factors we can control.

Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension

Results of a Multicenter Registry

Aiko Ogawa, MD, PhD; Toru Satoh, MD, PhD; Tetsuya Fukuda, MD, PhD; Koichiro Sugimura, MD, PhD; Yoshihiro Fukumoto, MD, PhD; Noriaki Emoto, MD, PhD; Norikazu Yamada, MD, PhD; Atsushi Yao, MD, PhD; Motomi Ando, MD, PhD; Hitoshi Ogino, MD, PhD; Nobuhiro Tanabe, MD, PhD; Ichizo Tsujino, MD, PhD; Masayuki Hanaoka, MD, PhD; Kenji Minatoya, MD, PhD; Hiroshi Ito, MD, PhD; Hiromi Matsubara, MD, PhD

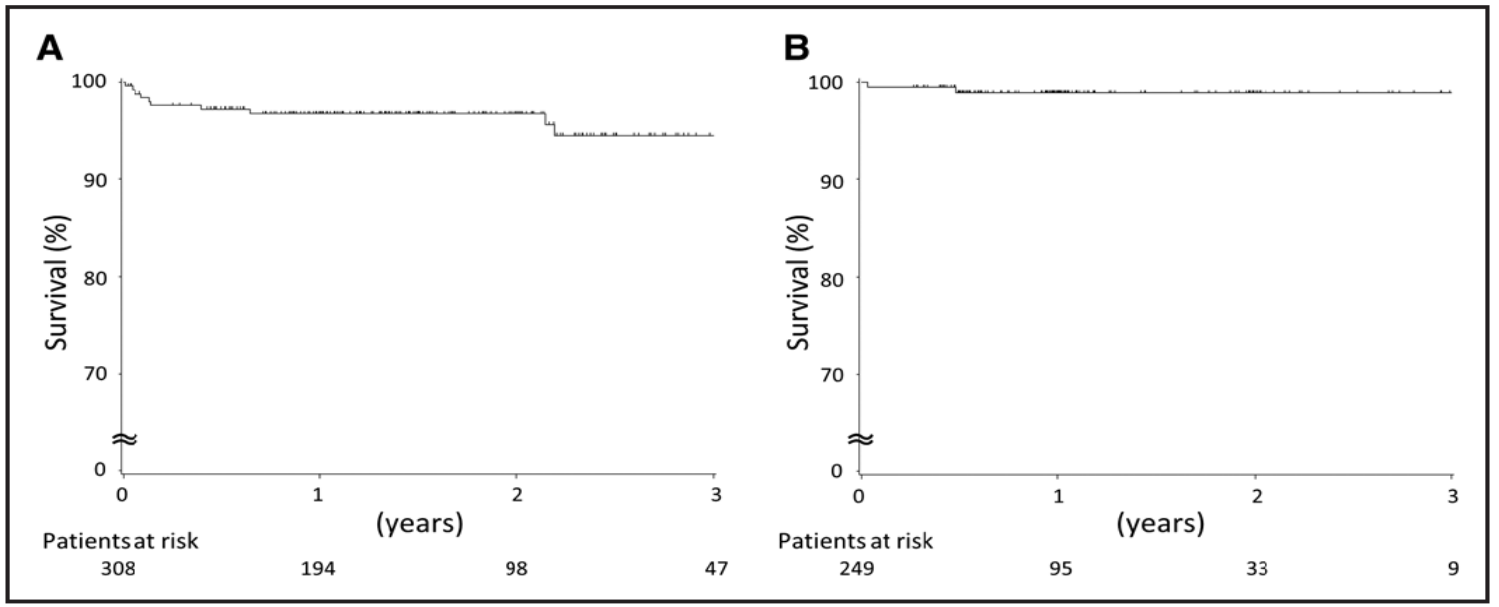
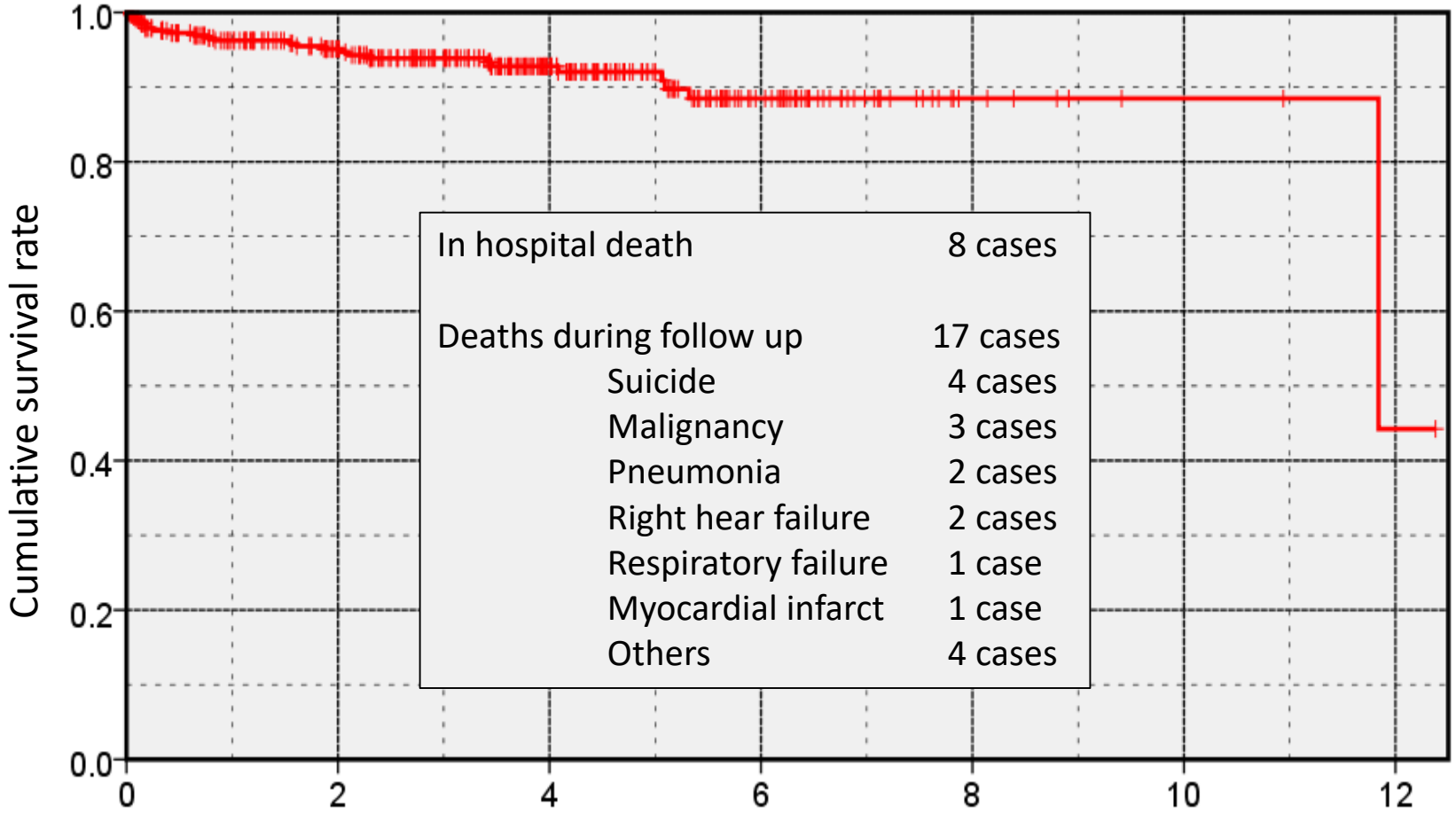


Figure 2. Long-term survival after balloon pulmonary angioplasty (BPA). **A**, Survival from the initial BPA procedure in all registered patients (n=308). **B**, Survival from the last BPA procedure in patients for whom BPA was terminated (n=249).

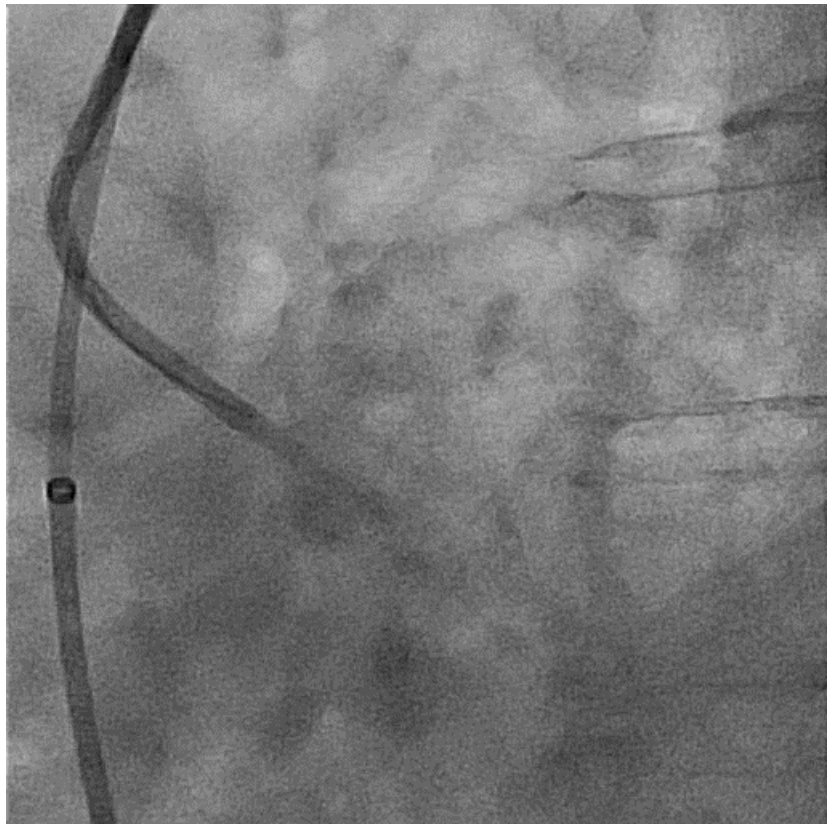
Circ Cardiovasc Qual Outcomes. 2017;10:
doi: 10.1161/CIRCOUTCOMES.117.004029

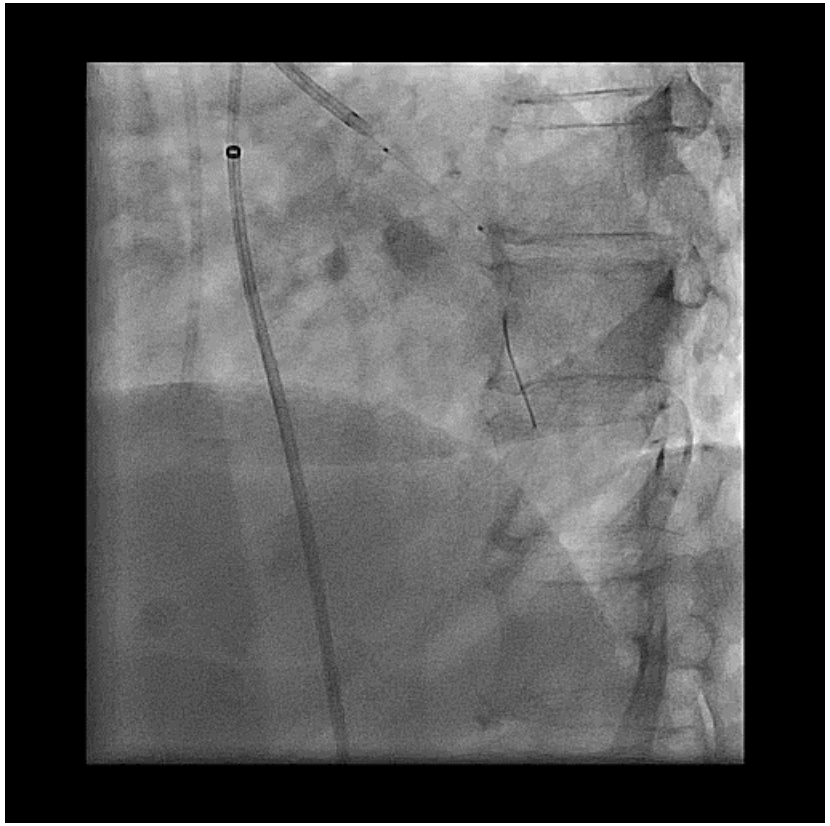
Long term survival after BPA at Okayama medical center (Nov 2004 – Mar 2017, n=329)

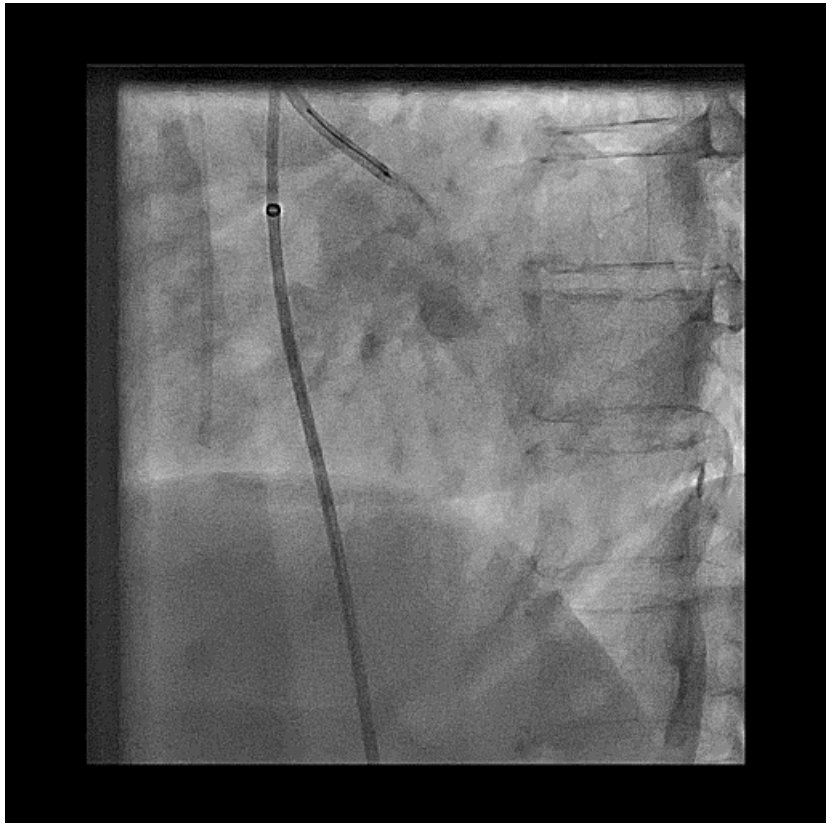


Patients at risk									
	329	276	237	193	128	81	47	8	3

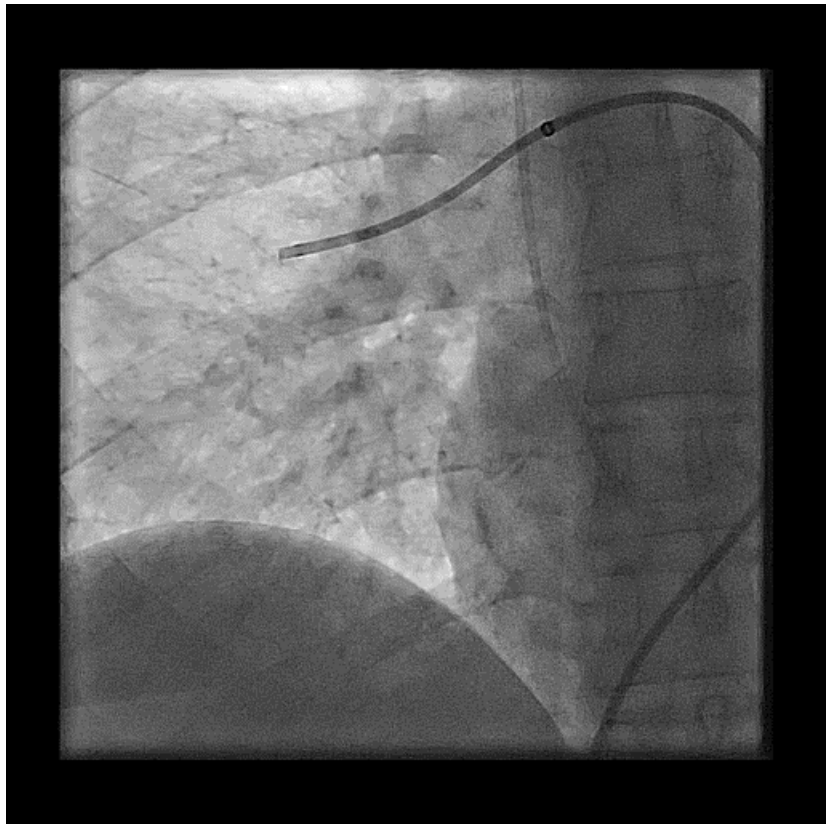
Right A10 branch (Female 48 yo)

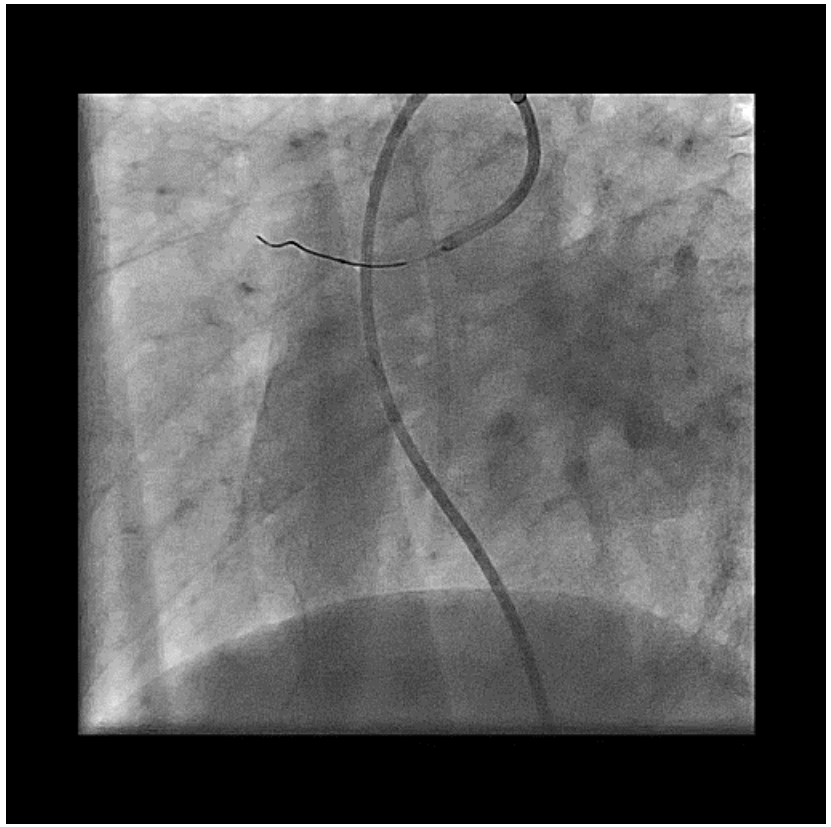


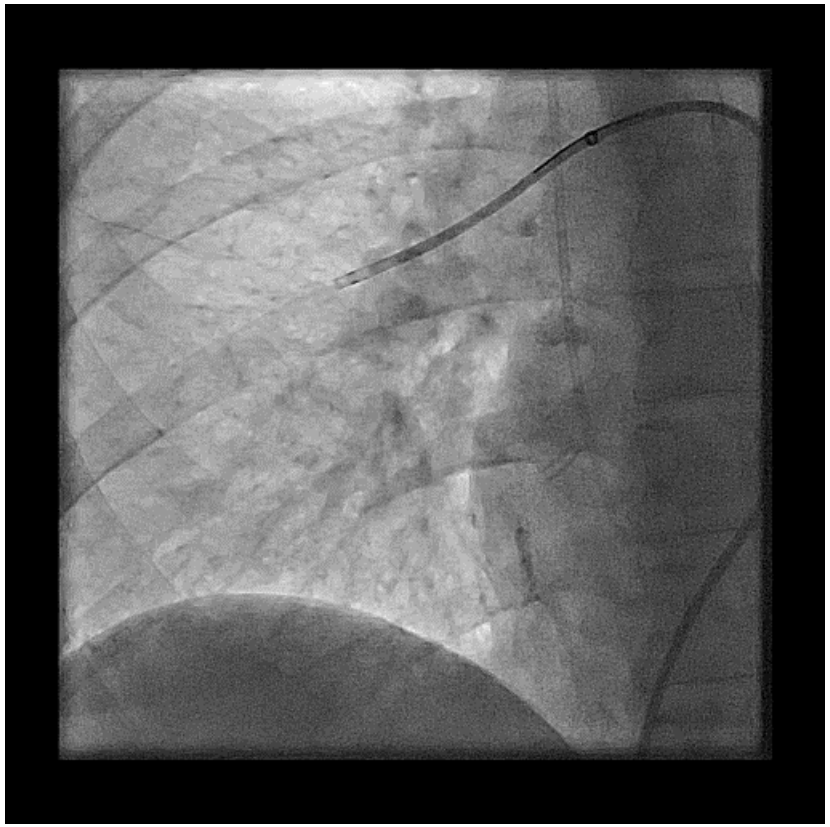




Right A4 branch

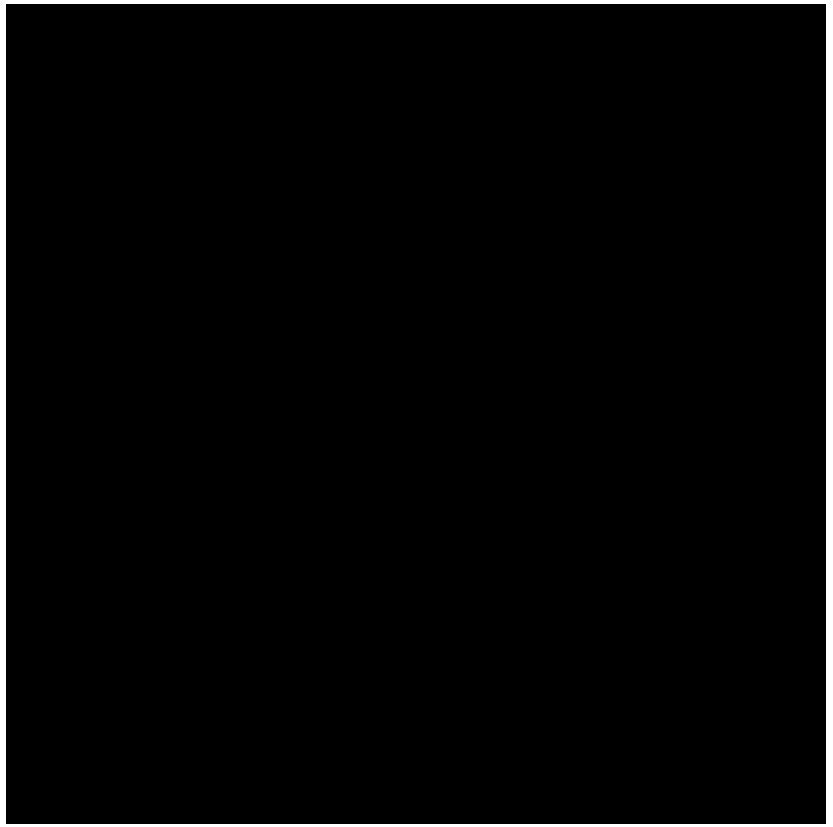


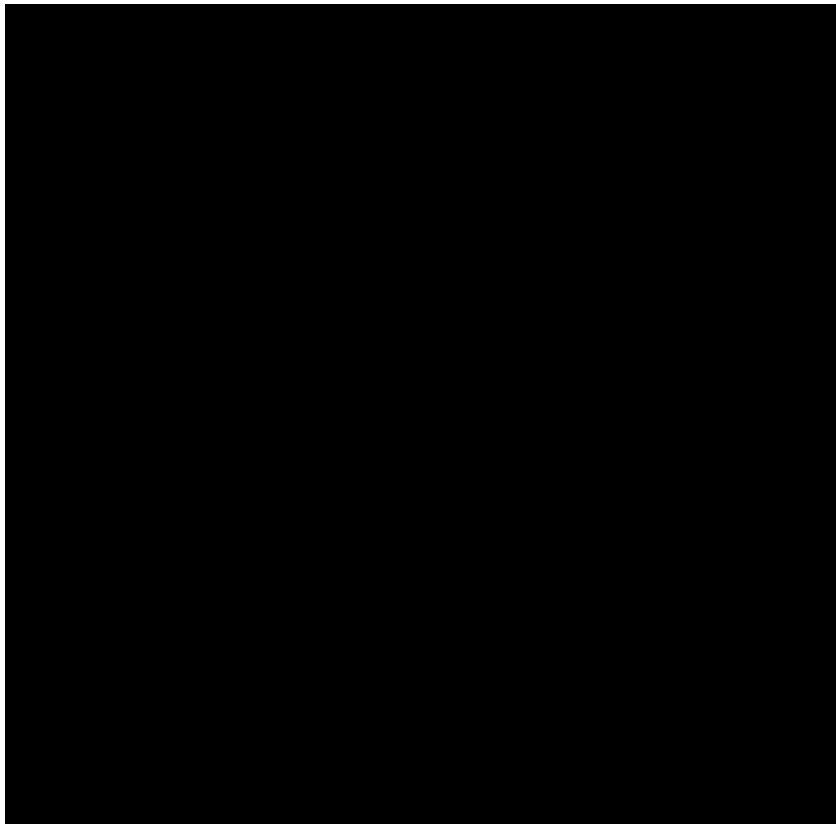




Representative case (After PEA)

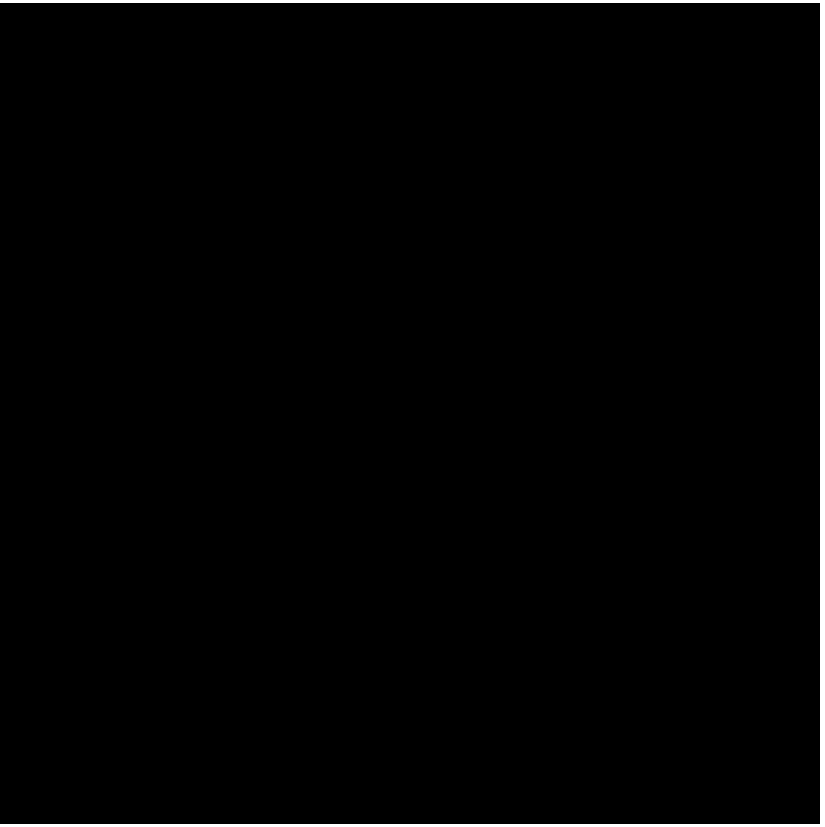
Right A10 LAO 60 view

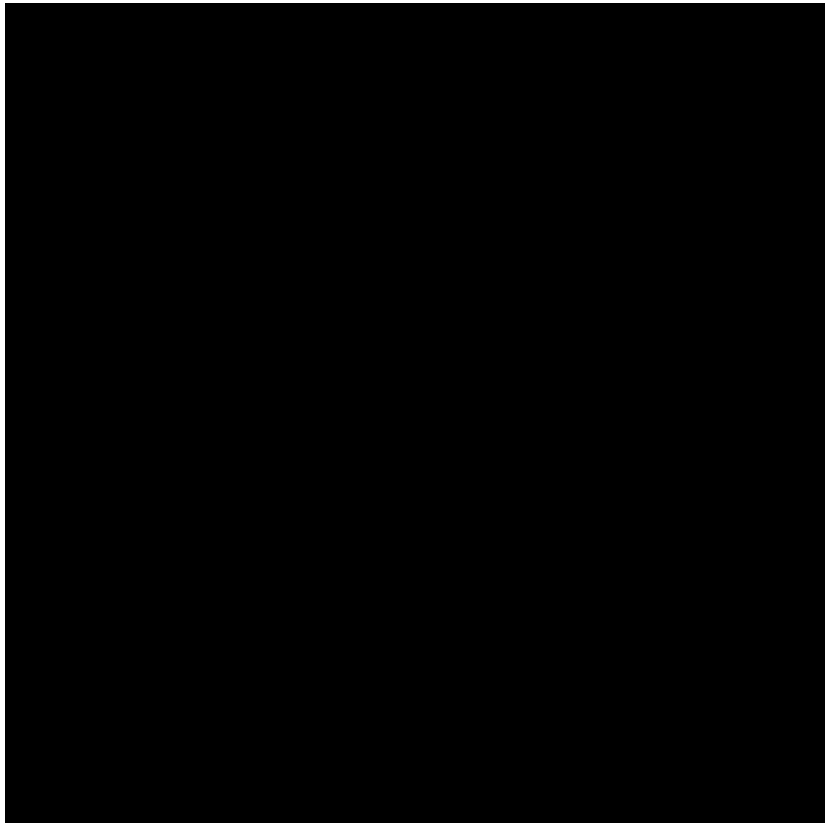


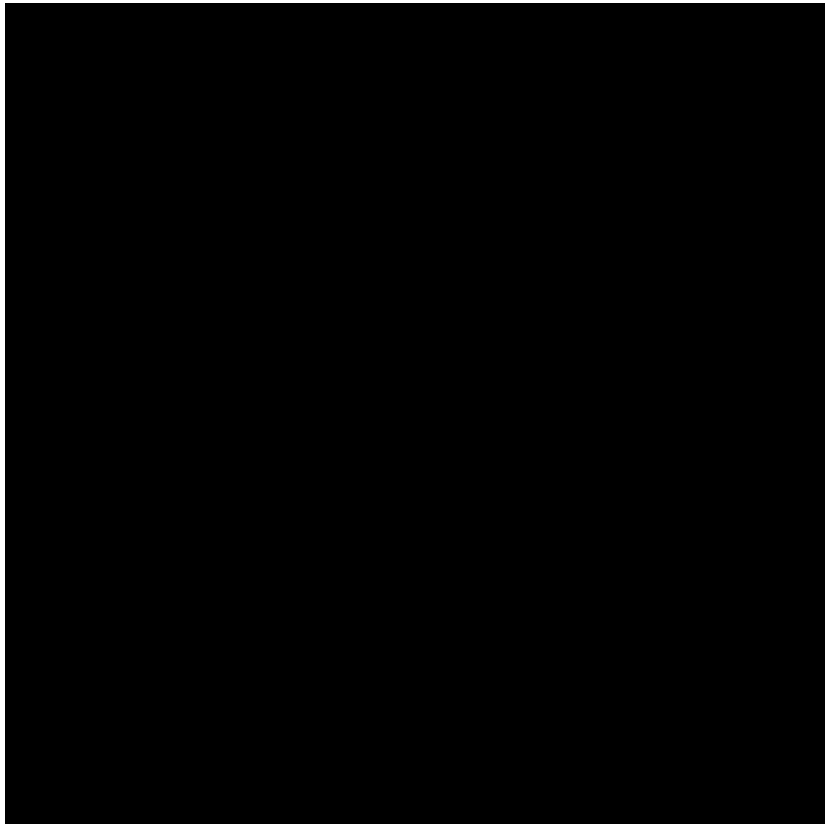


Representative case (Male 37 yo)

Left A8 branch







First Results

- 1st case/session on Dec/2016, last session 11/06/2018
- 14 pts (females 11), mean age 51±13 (28-70)
- 3 pts after PEA
- 52 sessions (1-8/pt), 261 dilated vessels, 3-12/session)
- One patient completed the BPA treatment (mPAP: 22 mmHg)

	Baseline	After BPA	Change (%)	p-value
RA (mmHg)	10.6±3.5	7.2±3	- 32	0,006
syst PAP (mmHg)	87±21	63±15	- 28	0.003
mean PAP (mmHg)	54±12	37±8	- 31	0.003
PVR (WU)	11±4	7±4	- 36	0,004
CI (l/min/m^2)	2.5±0.7	2.5±0.7		0.686
HR	83±9	74±11	- 11	0.009

Conclusions

- Balloon pulmonary angioplasty is an effective method for treating patients with CTEPH, who could not benefit from first-line surgical therapy.
- A very demanding technique in complex anatomy where biplane is mandatory
- It is not free from potentially life-threatening complications
- Further refinements of the strategy to reduce complications, improvements in the simplicity of the treatment, and evaluation of the long-term follow-up results are needed before BPA can be recommended as an established treatment for CTEPH.