Hot topics in pulmonary hypertension (group 4):
Interventional Treatment

Balloon Pulmonary Angioplasty

Okayama Medical Center
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Disclosure Statement of Financial Interest

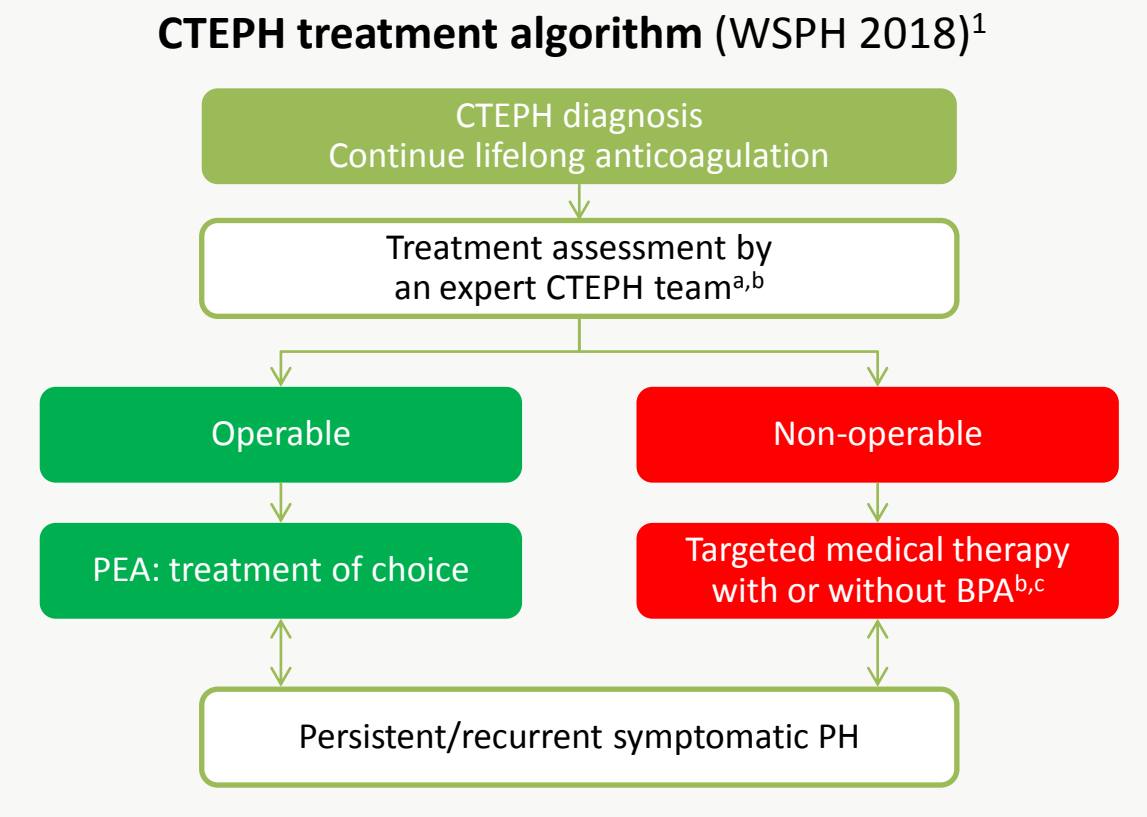
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship
Consulting Fees/Honoraria

Company
- Actelion Pharmaceuticals, Ltd;
  AOP orphan Pharmaceuticals AG;
  Bayer, Ltd;
  GSK;
  Pfizer Japan, Inc;
  Nippon Shinyaku, Co, Ltd;
  Kaneka Medix Corporation;
  United therapeutics.

CTEPH management options[1]

- PEA is the treatment of choice in patients with operable CTEPH[1,2]
- However, PEA is not an option for every patient, and some experience persistent or recurrent symptomatic PH following PEA[3–6]
  - For such patients, medical therapy is an option[1,2]
  - BPA may also be considered[1]
- A critical step in the CTEPH treatment algorithm remains operability assessment by an experienced CTEPH team[2,3]



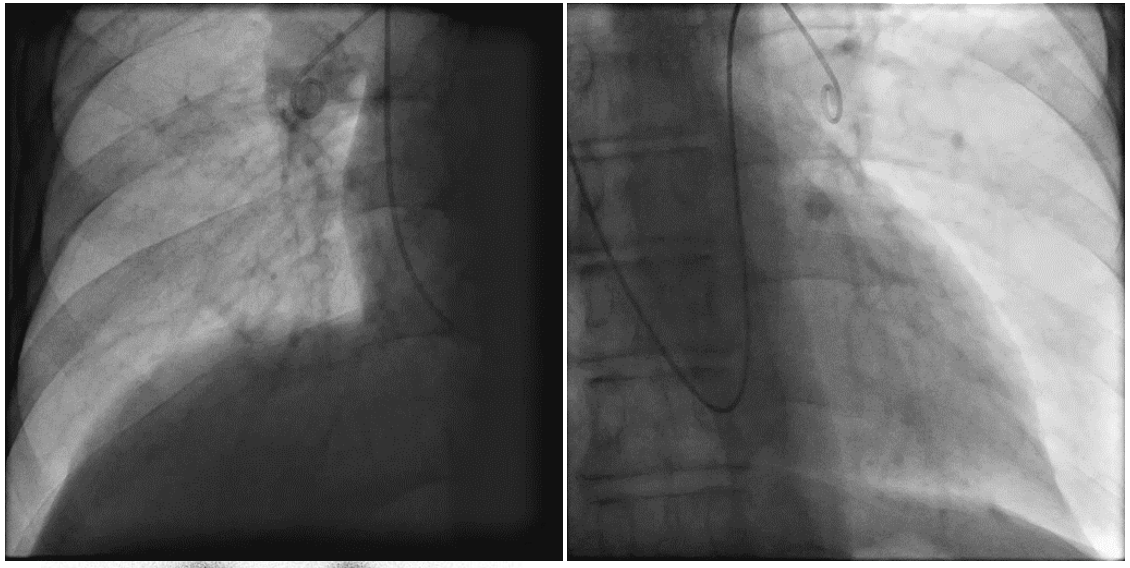
[a]Multidisciplinary: PEA surgeon, PH expert, BPA interventionist, and radiologist. [b]Treatment assessment may differ depending on the level of expertise. [c]BPA without medical therapy can be considered in selected cases.

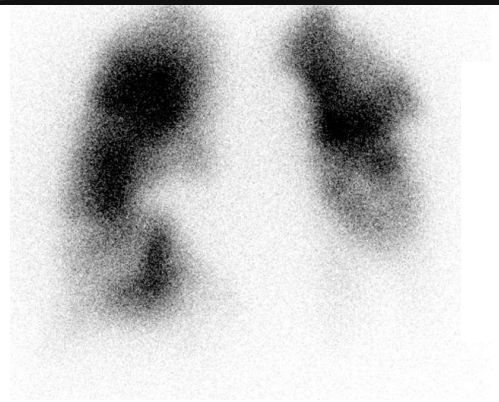
BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; WSPH, World Symposium on Pulmonary Hypertension.

1. Kim NH *et al. Eur Respir J.* 2019;53:pii.1801915. 2. Galiè N *et al. Eur Respir J.* 2015;46:903–975. 3. Jenkins D *et al. Eur Respir Rev.* 2017;26:pii.160111. 4. Pepke-Zaba J *et al. Circulation.* 2011;124:1973–1981. 5. Mayer E *et al. J Thorac Cardiovasc Surg.* 2011;141:702–710. 6. Cannon JE *et al. Circulation.* 2016;133:1761–1771.

Pulmonary endarterectomy; PEA

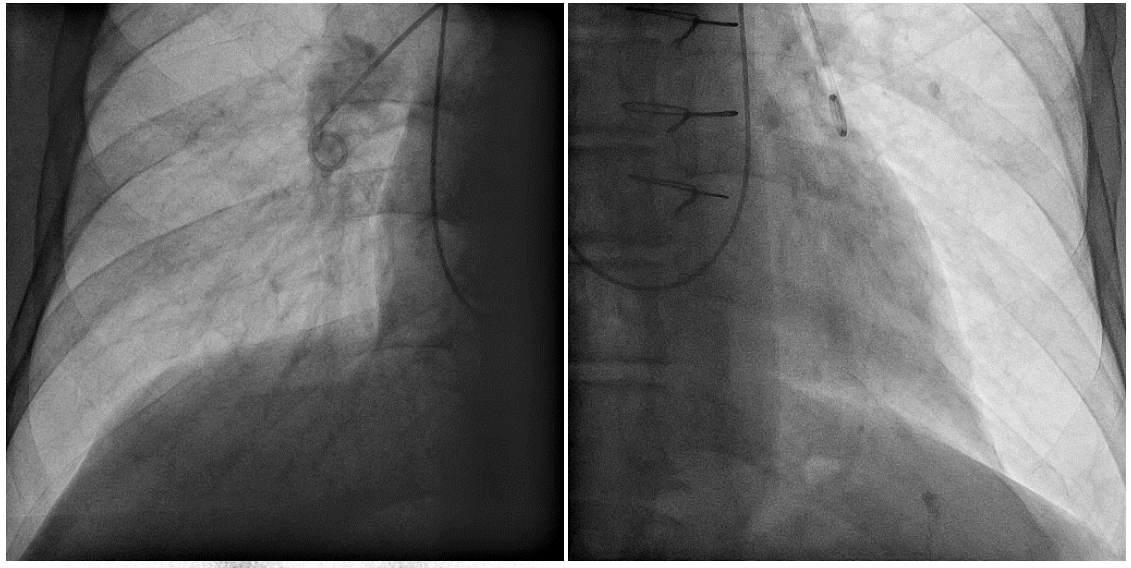
Before PEA

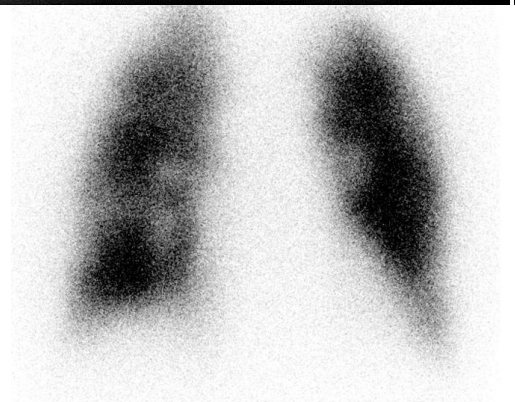




PAP 60/19 (38) mmHg
CO 4.06 L/min
CI 2.33 L/min/m^2
PVR 6.9 wood unit
SpO_2 85 % (room air)

After PEA





PAP 16/7 (11) mmHg
CO 3.38 L/min
CI 2.01 L/min/m^2
PVR 1.8 wood unit
SpO_2 100 % (room air)

PAP; pulmonary artery pressure, CO; cardiac output, CI; cardiac index, PVR; pulmonary vascular resistance, SpO_2: percutaneous oxygen saturation;

RCTs of pulmonary hypertension-targeted medical therapy in CTEPH[1]

Study drug / trial	Duration (weeks)	Subjects (n)	NYHA FC	6MWD baseline (m)	6MWD effect (m)	PVR baseline (dyn•sec•cm^{-5})	PVR effect (%)
Bosentan BENEFIT[2]	16	157	II–IV	342 ± 84	+2^{NS}	783 (95% CI 703–861)	–24
Riociguat CHEST-1[3]	16	261	II–IV	347 ± 80	+46	787 ± 422	–31
Macitentan MERIT-1[4]	16 (24*)	80	II–IV	352 ± 81	+34	957 ± 435	–16

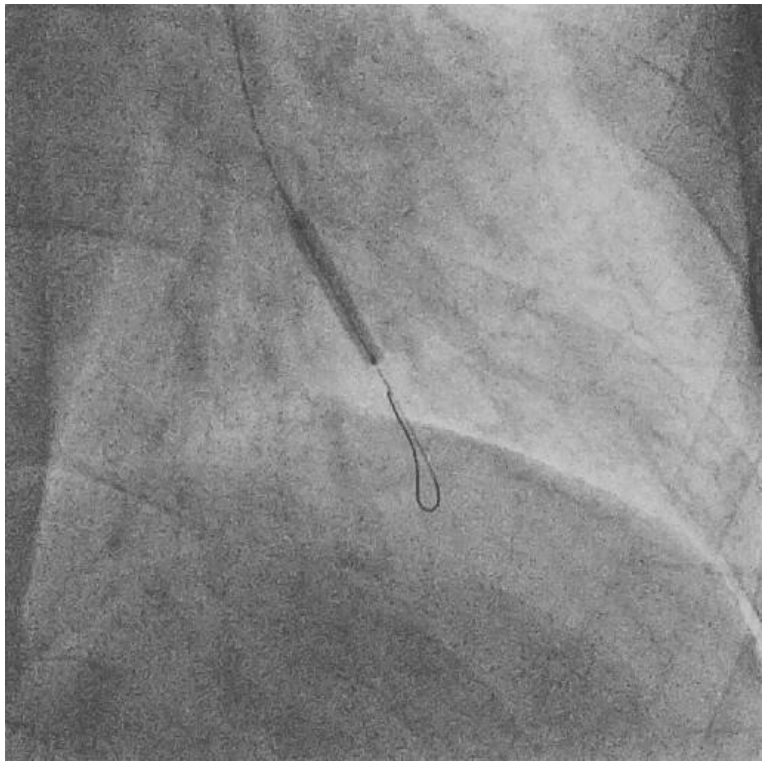
Data are presented as n or mean ± SD, unless otherwise stated.

*6MWD measured at 24 weeks. All three trials had an adjudication process for operability.
6MWD, six-minute walking distance; NS: non-significant; NYHA FC, New York Heart Association Functional Class; RCT, randomized controlled trial.
1. Kim NH *et al. Eur Respir J.* 2019;53:pii.1801915. 2. Jais X *et al. J Am Coll Cardiol* 2008; 52:2127–2134. 3. Ghofrani HA *et al. N Engl J Med.* 2013;369:319–329.
4. Ghofrani HA et al. Lancet Respir Med 2017;5:785–794.

Balloon Pulmonary Angioplasty (BPA)

Before BPA

Balloon dilation



Immediately after BPA

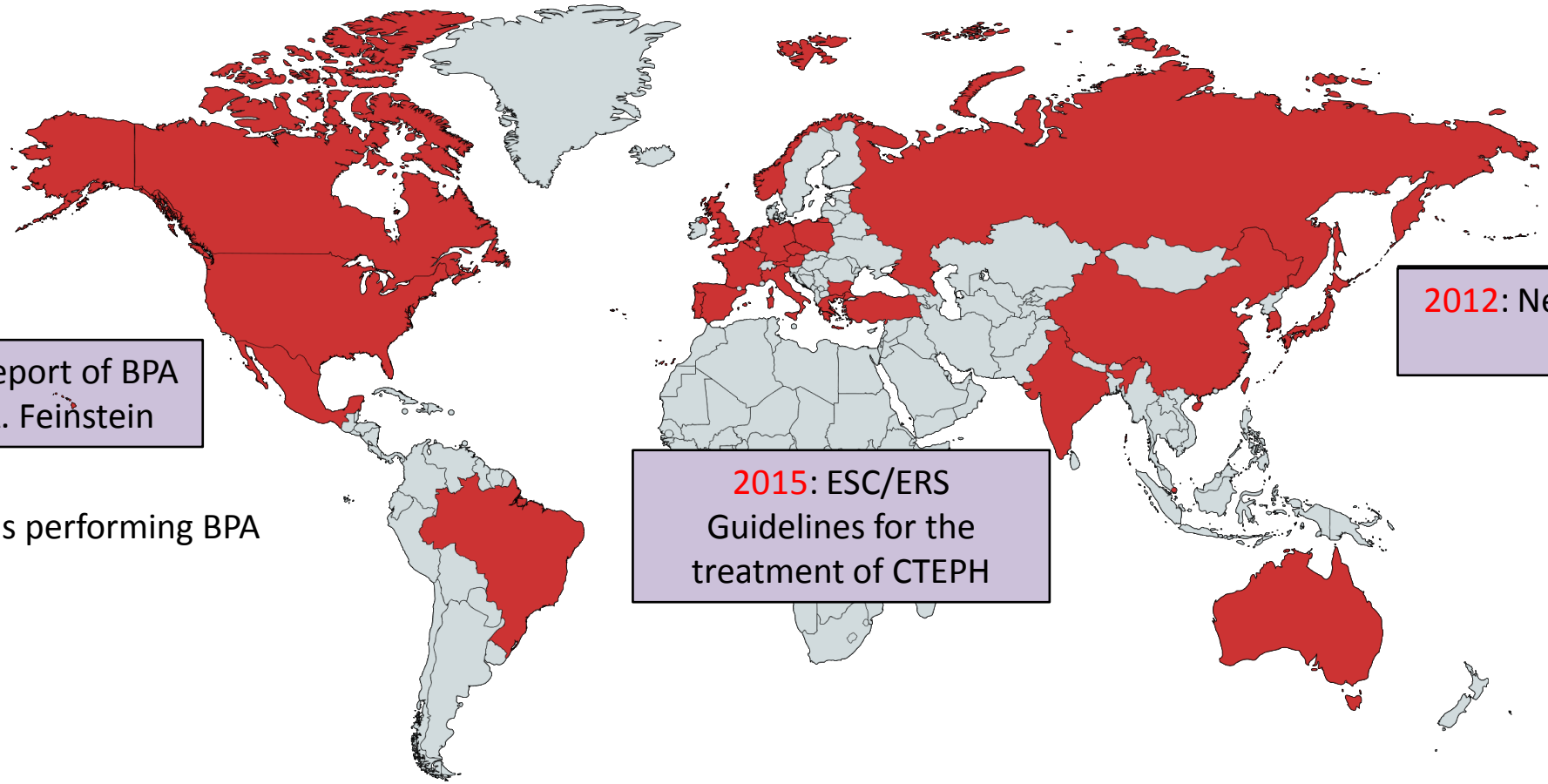
Timeline of BPA

2000 — 2005 — 2010 — 2015 — 2020

Angiography/IVUS-guided BPA (Larger balloon based on IVUS)

IVUS/lesion-type-guided BPA

Angiography-guided BPA (small size balloon)



2001: First report of BPA by Jeffrey A. Feinstein

Countries performing BPA

2015: ESC/ERS Guidelines for the treatment of CTEPH

2012: Next series of BPA reports

ESC, European Society of Cardiology; ERS, European Respiratory Society; IVUS, intravascular ultrasound.

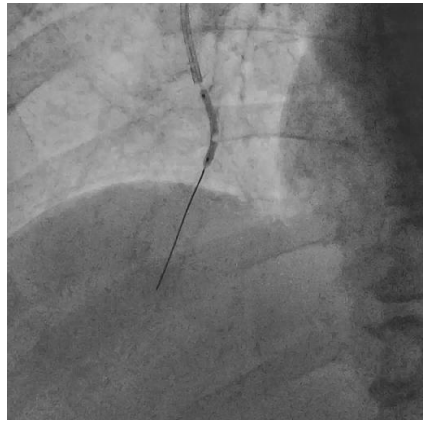
History of BPA strategy in our hospital

	Initial strategy (2004–Oct 2012)	Previous strategy (Nov 2012–Sep 2014)	Current strategy (Oct 2014–now)
Number of patients	120	122	123
Objective	Normalization of hemodynamics	Minimize the complication while keeping the efficacy	Total revascularization without complication
Balloon size (Initial treatment)	Selecting balloon size as large as possible based on IVUS findings	Limiting balloon size based on IVUS findings and mPAP	Selecting minimal balloon size
Balloon size (Second treatment)		Limiting balloon size based on IVUS findings and mPAP	Selecting optimized balloon size
Target vessels in a session	2 vessels	4–5 vessels	As many as possible
Imaging modality	IVUS	IVUS	Only angiography
Number of sessions	4–5	6–8	4–6

Staged lesion dilatation

Initial procedure

Before

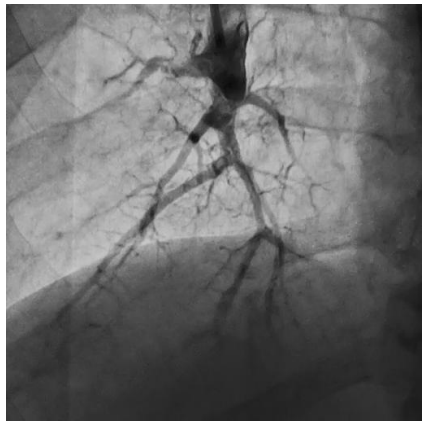


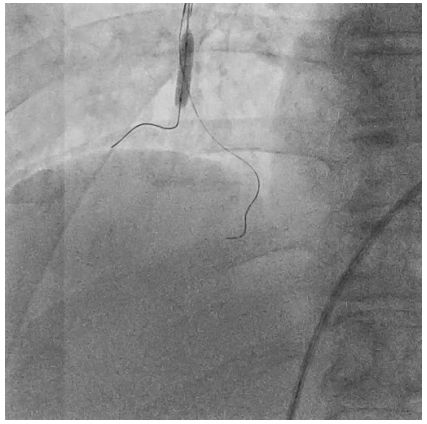
Balloon

After

A smaller balloon relative to the actual vessel size is selected to reduce the risk of complication and restore minimal blood flow to the occluded pulmonary vessels.

Second procedure (1 month later)





A larger size of balloon is selected to optimize the dilatation of the lesion if necessary.

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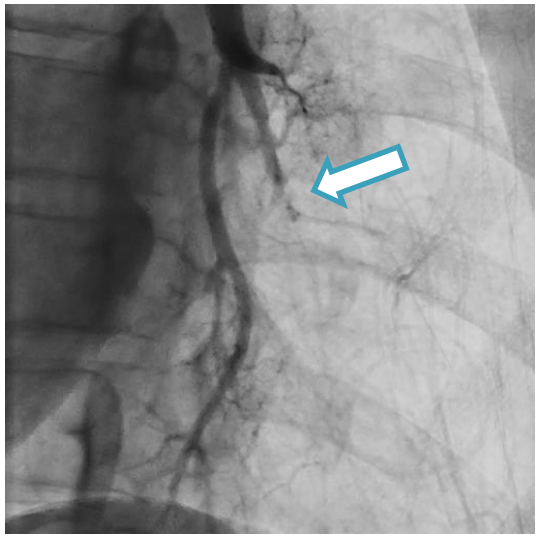
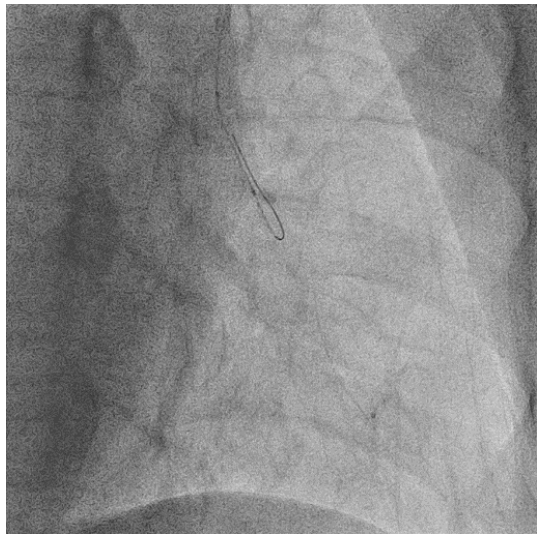
Simple technique

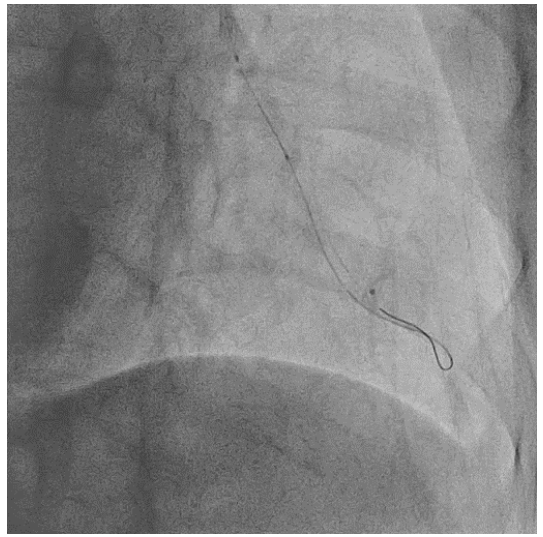
1. Pulmonary angiogram



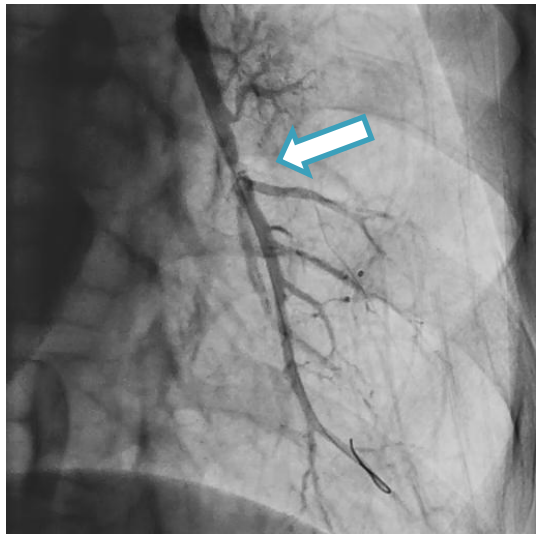
2. Passing the guidewire



3. Balloon dilatation



4. Final pulmonary angiogram



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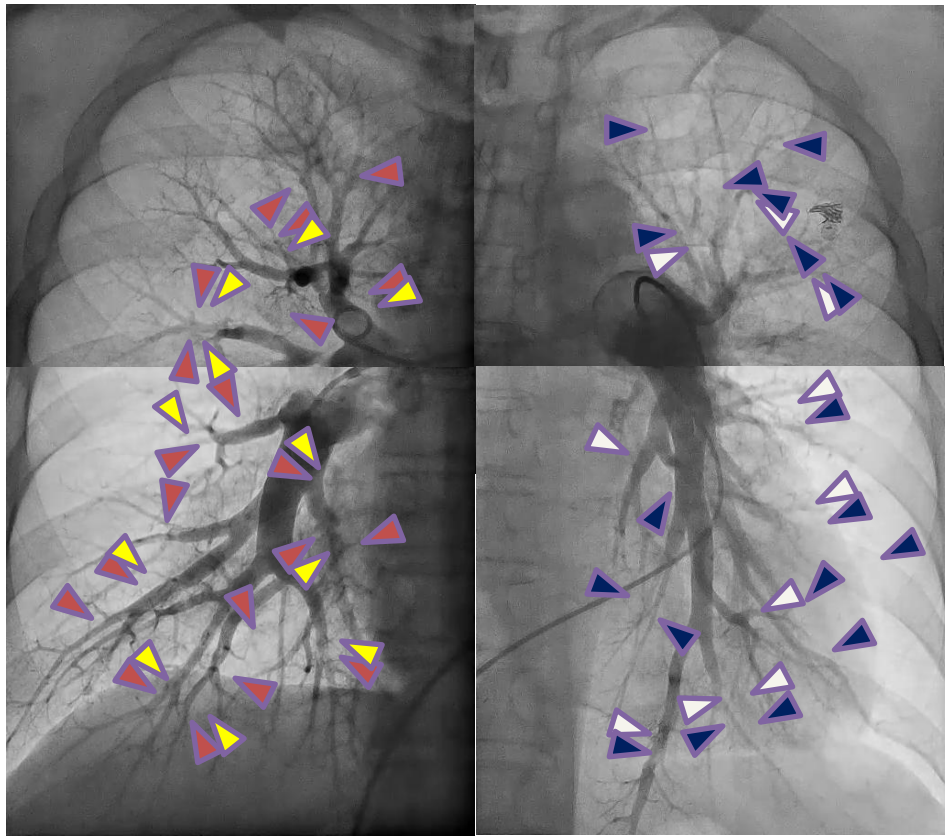
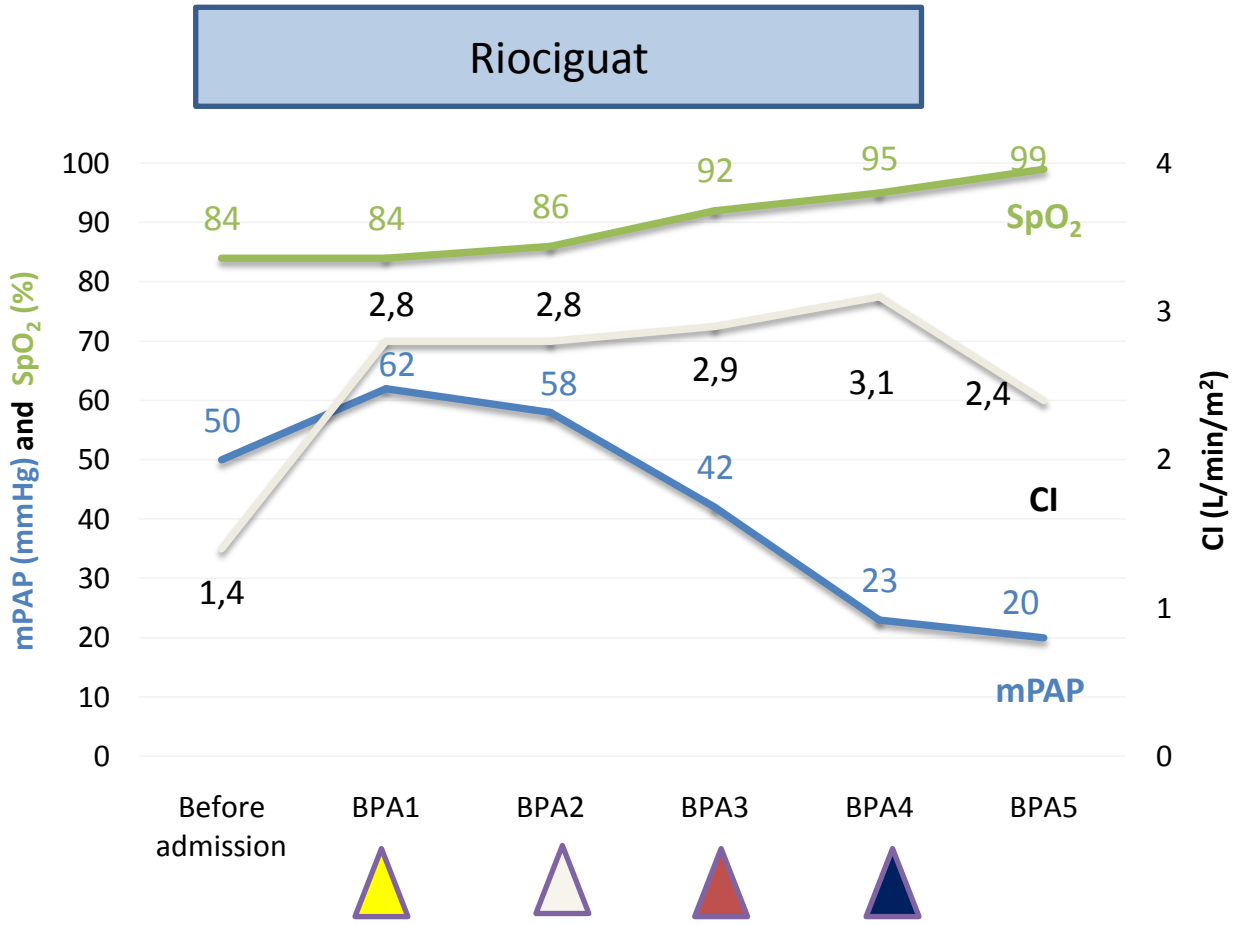
Systematic procedures



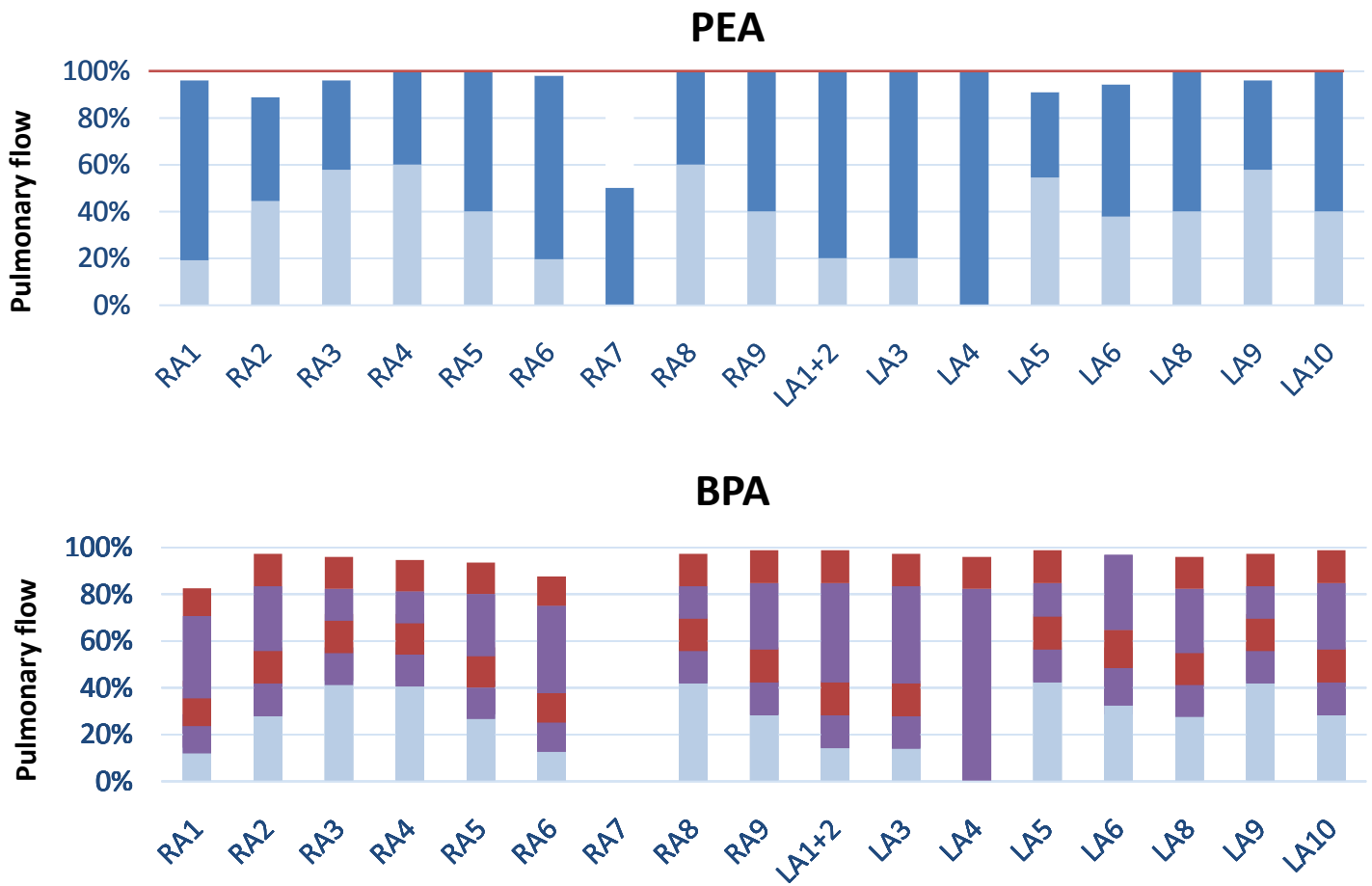
PAWP 7 mmHg , PAP 111/35(62) mmHg, RAP 8 mmHg, CI 2.83 L/min/m^2, PVR 10.1 Wood units, SpO_2 84%

PAWP, pulmonary arterial wedge pressure; RAP, right atrial pressure.



Using only small size of balloon could reduce therapeutic efficacy.

Concept of current BPA strategy



LA, left pulmonary artery; RA, right pulmonary artery.

Three key concepts starting with S in current BPA strategy

Staged lesion dilatation

Reduce the risk of complication

Simple technique

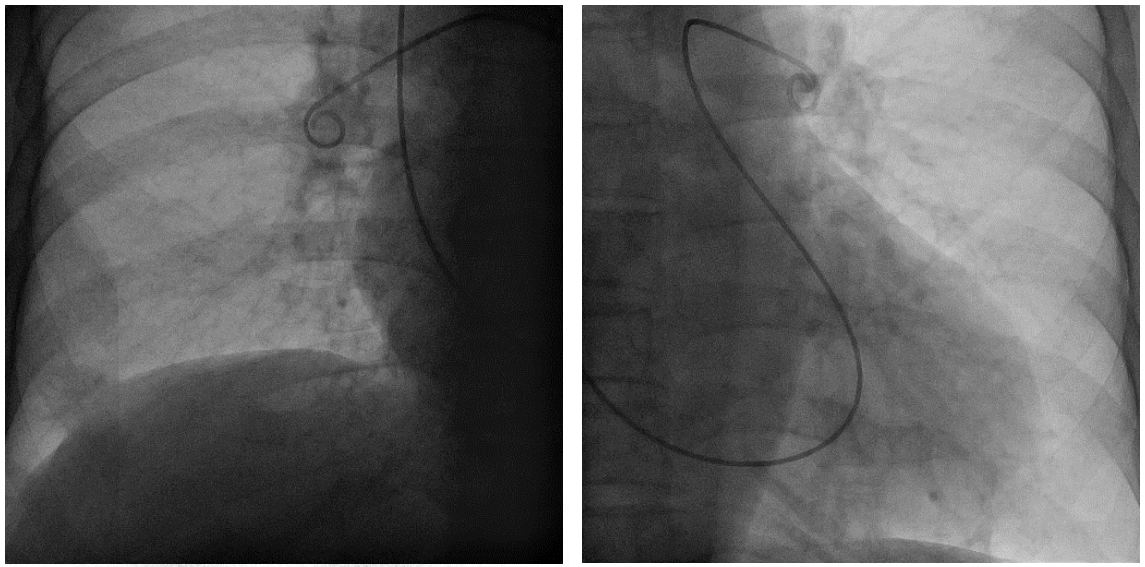
Reduce the cost
Reduce the radiation exposure
Reduce the contrast medium

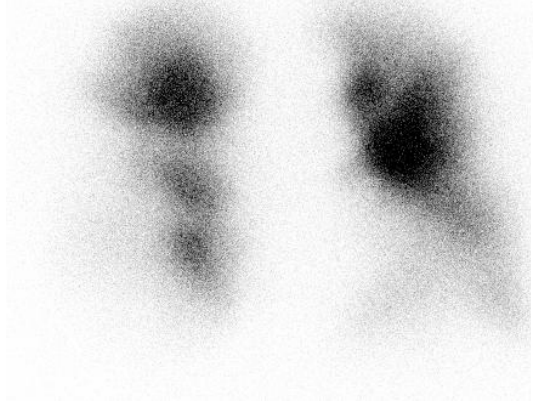
Systematic procedure

Maintain the efficacy
Improvement of oxygenation

Pulmonary balloon angioplasty; BPA

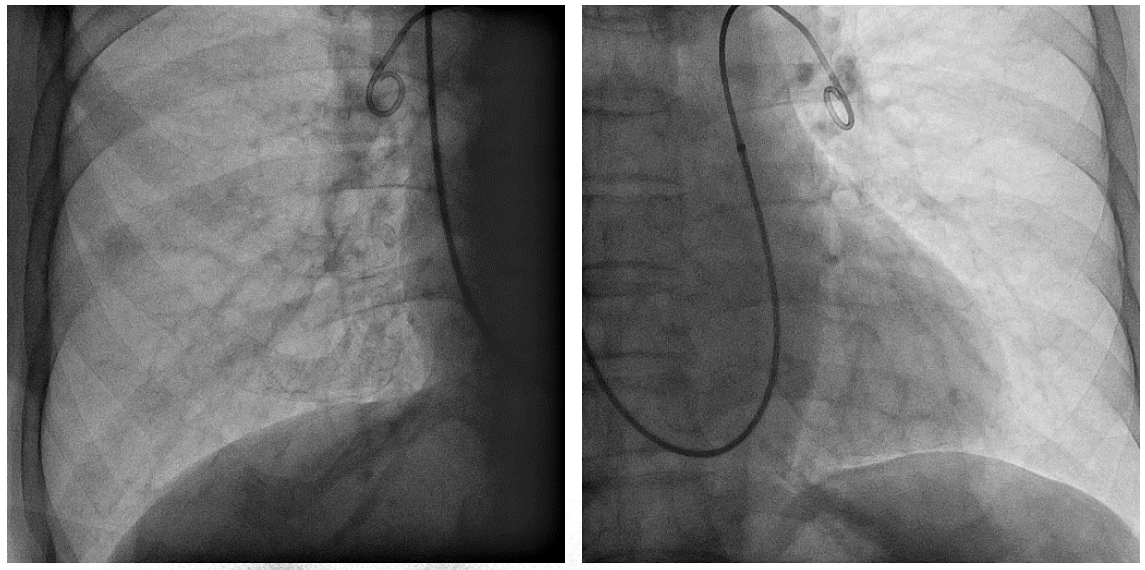
before

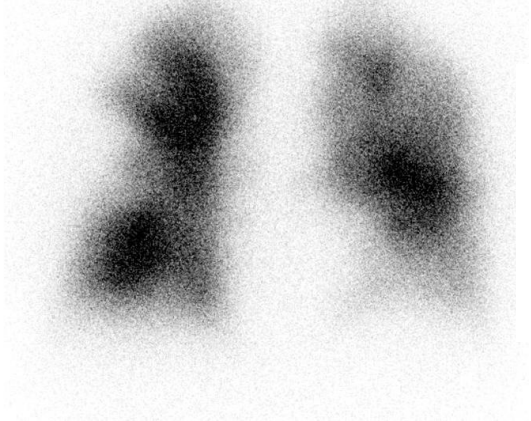




PAP 88/27 (48) mmHg
CO 2.80 L/min
CI 1.90 L/min/m^2
PVR 12.9 wood unit
SpO_2 80% (room air)

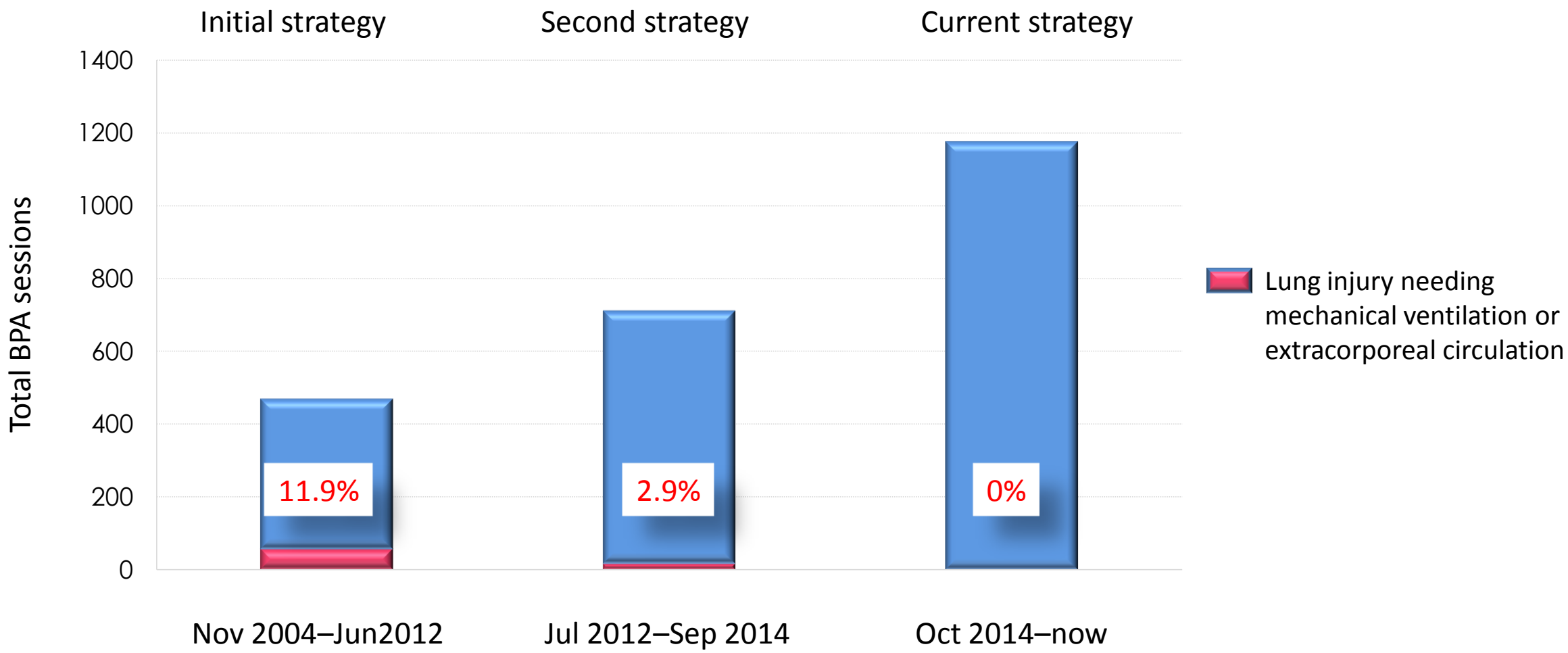
after





PAP 31/9 (18) mmHg
CO 3.01 L/min
CI 2.14 L/min/m^2
PVR 4.0 wood unit
SpO_2 95 % (room air)

Occurrence of severe lung injury during BPA



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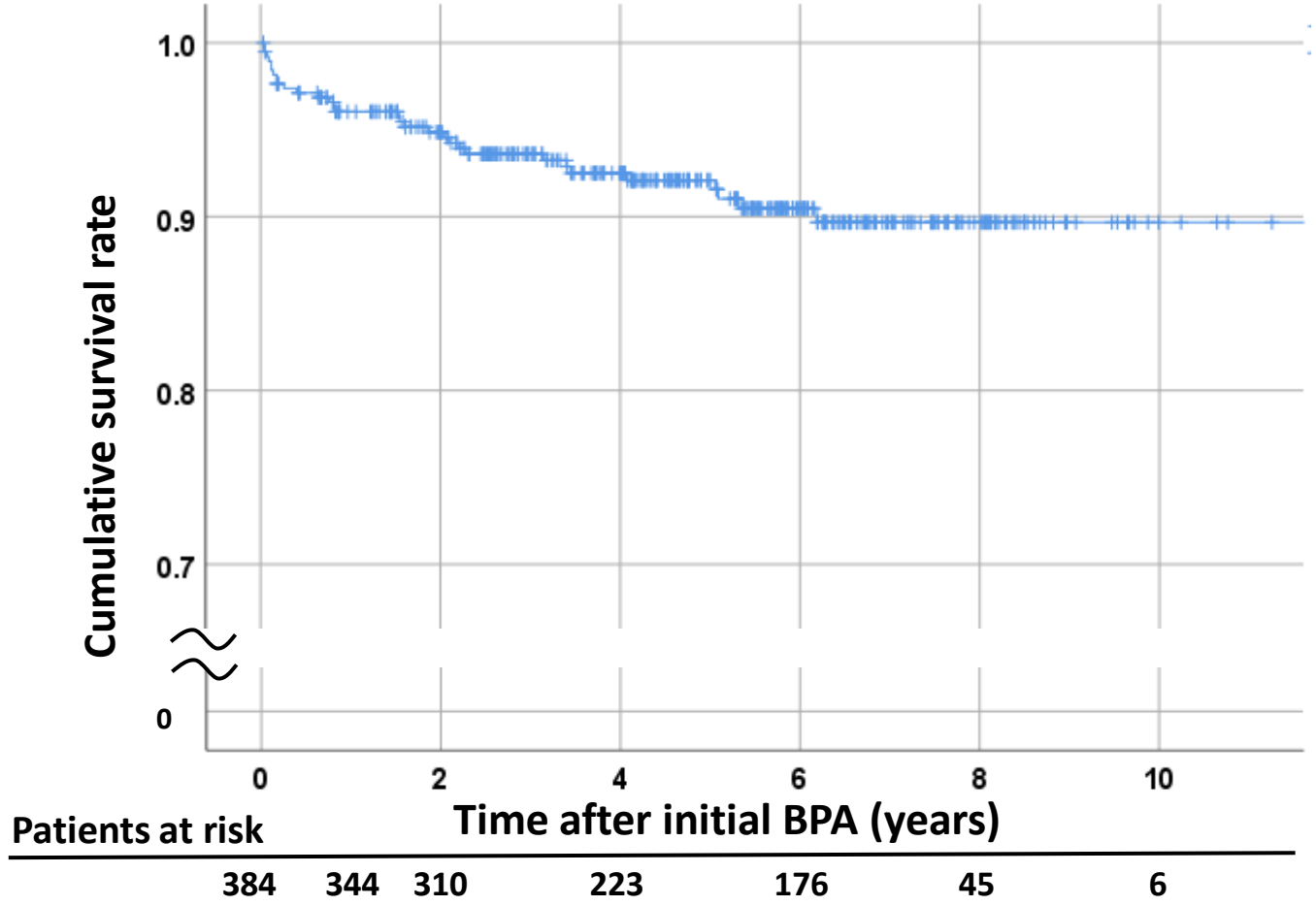
10-year survival after BPA (n=384)
Event: All cause death



Mean follow up period 4.4±2.6 years

1 year survival	96.0%
2 year survival	94.9%
3 year survival	93.6%
5 year survival	92.1%
10 year survival	89.7%

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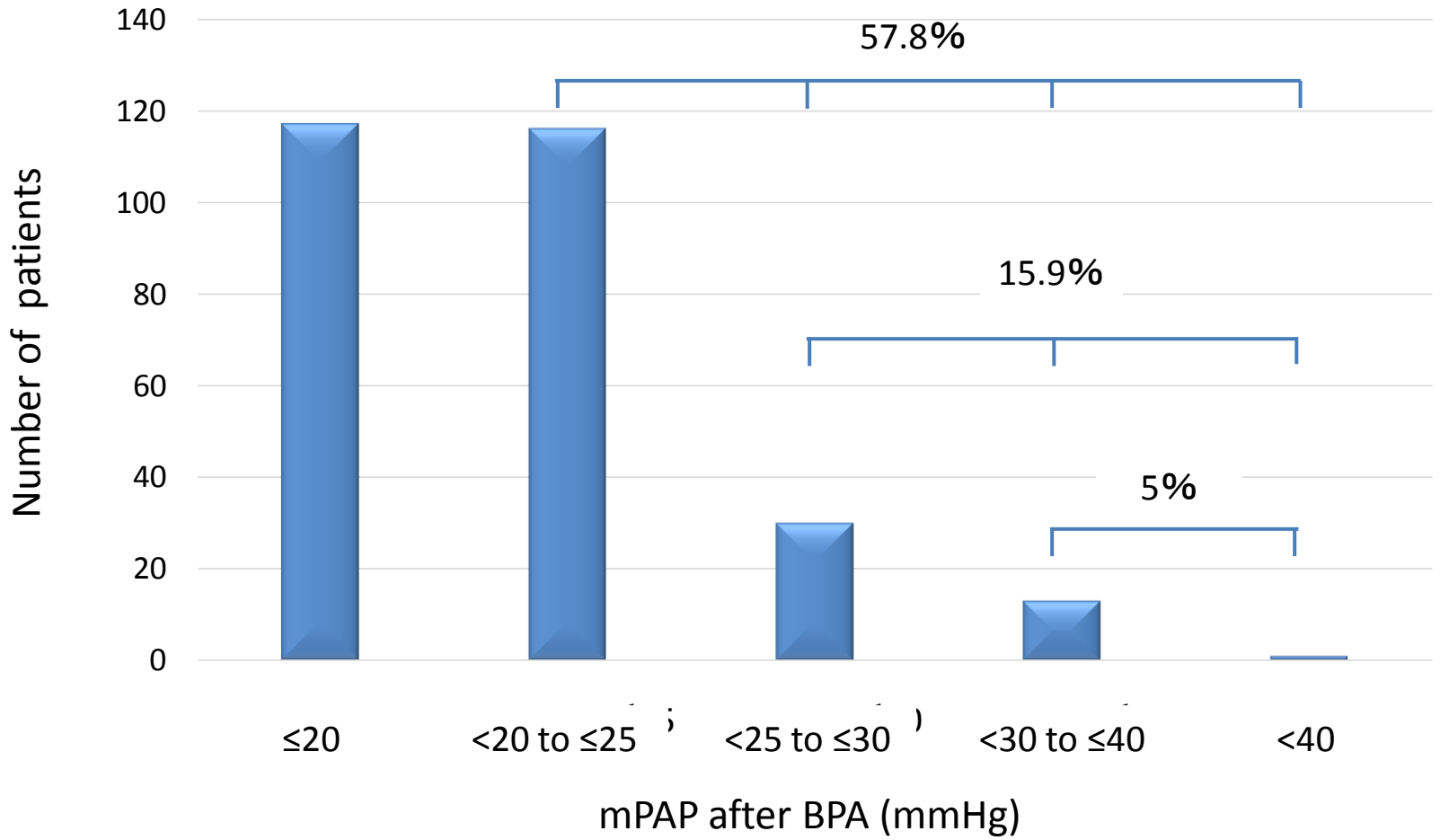
Decreases in mPAP achieved 6 months after the final BPA



n= 277 patients

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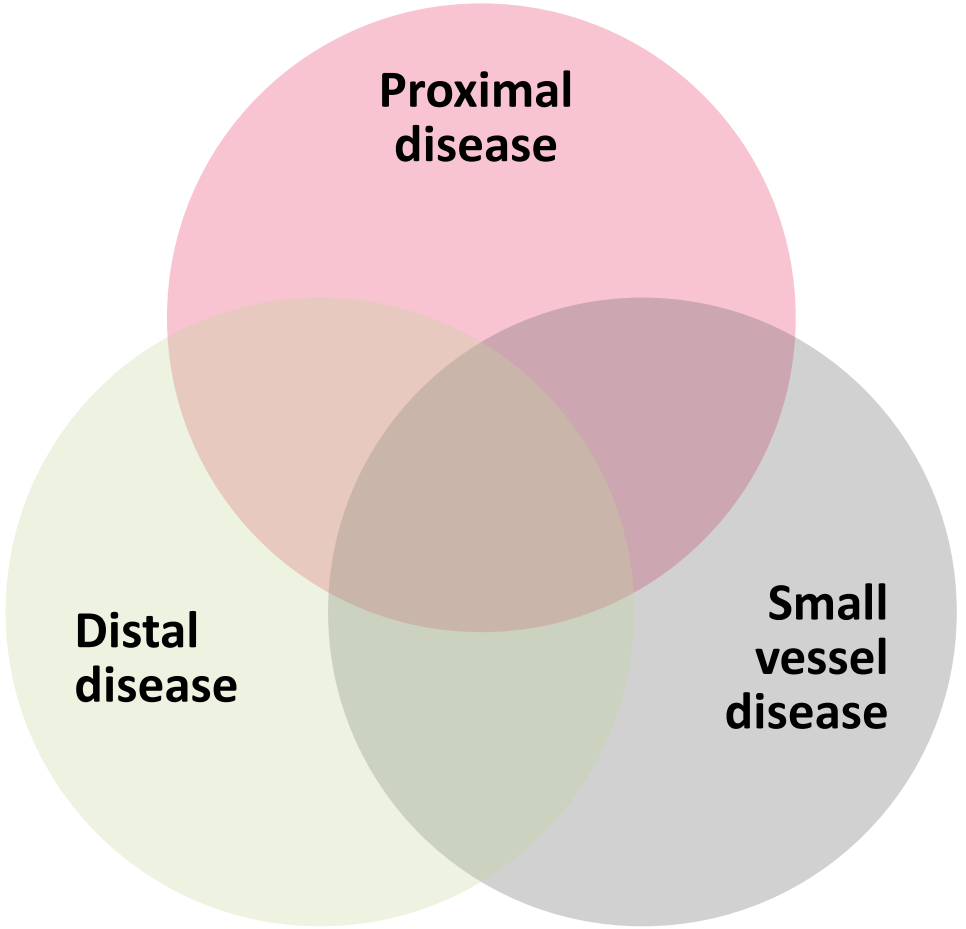
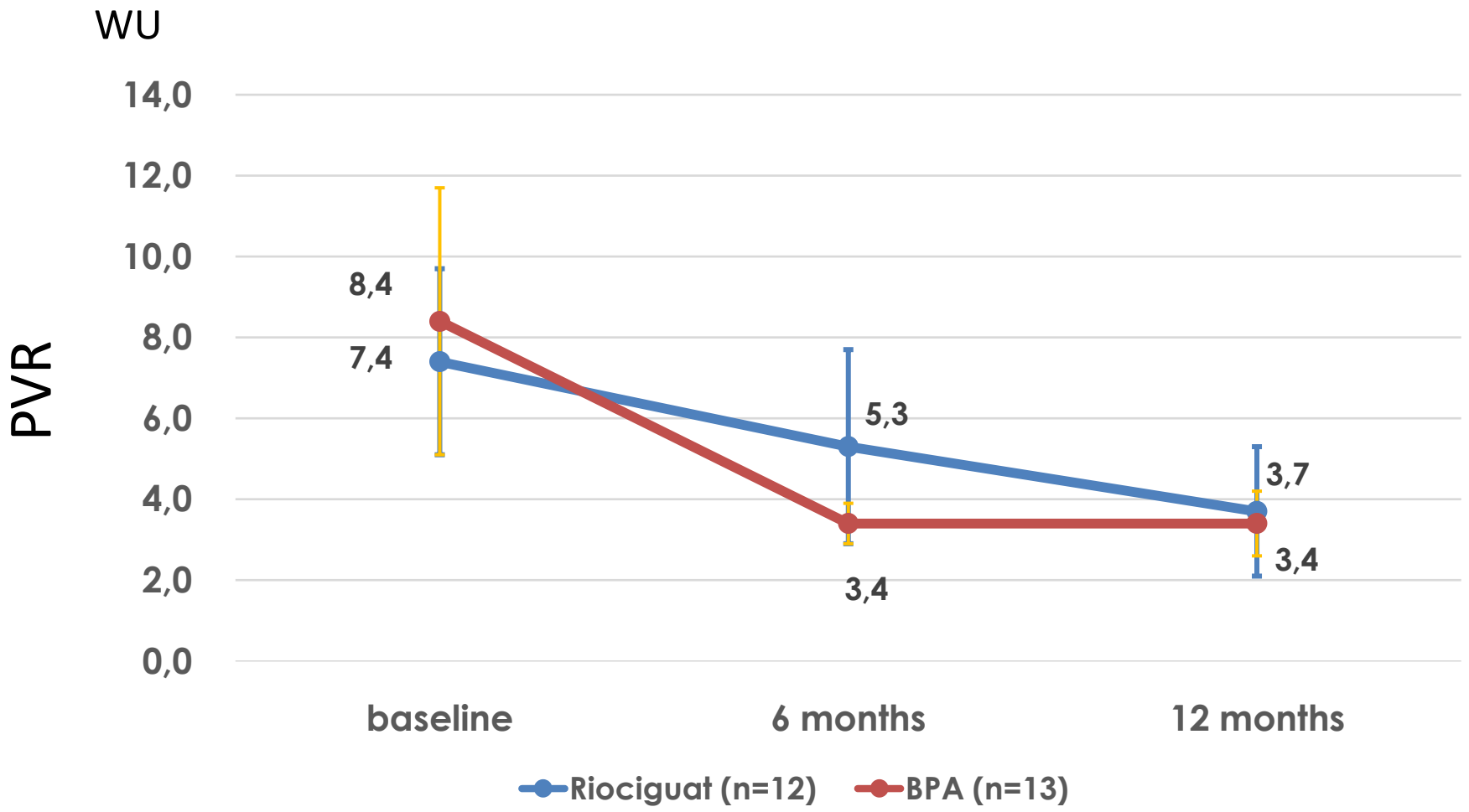
Is there rationale to combine treatment approaches for CTEPH?

- Some patients may benefit from more than one treatment approach to address different pathogenic manifestations of CTEPH that occur together[1]
- Combination treatment approaches may benefit patients with mixed disease[2,3]
- Is there potential to use multimodal strategies to benefit from the complementary actions of different treatments?[3,4]



1. Kim NH *et al. Eur Respir J.* 2019;53:1801915. 2. Wiedenroth CB *et al. J Heart Lung Transpl.* 2016;35:591–596. 3. Madani M *et al. Eur Respir Rev.* 2017;26:pii: 170105. 2. Wiedenroth CB *et al. J Heart Lung Transpl.* 2016;35:591–596. 4. Yanaka K *et al. J Am Heart Assoc.* 2018;7:e008838.

Effect of Riociguat and BPA on Japanese CTEPH patients



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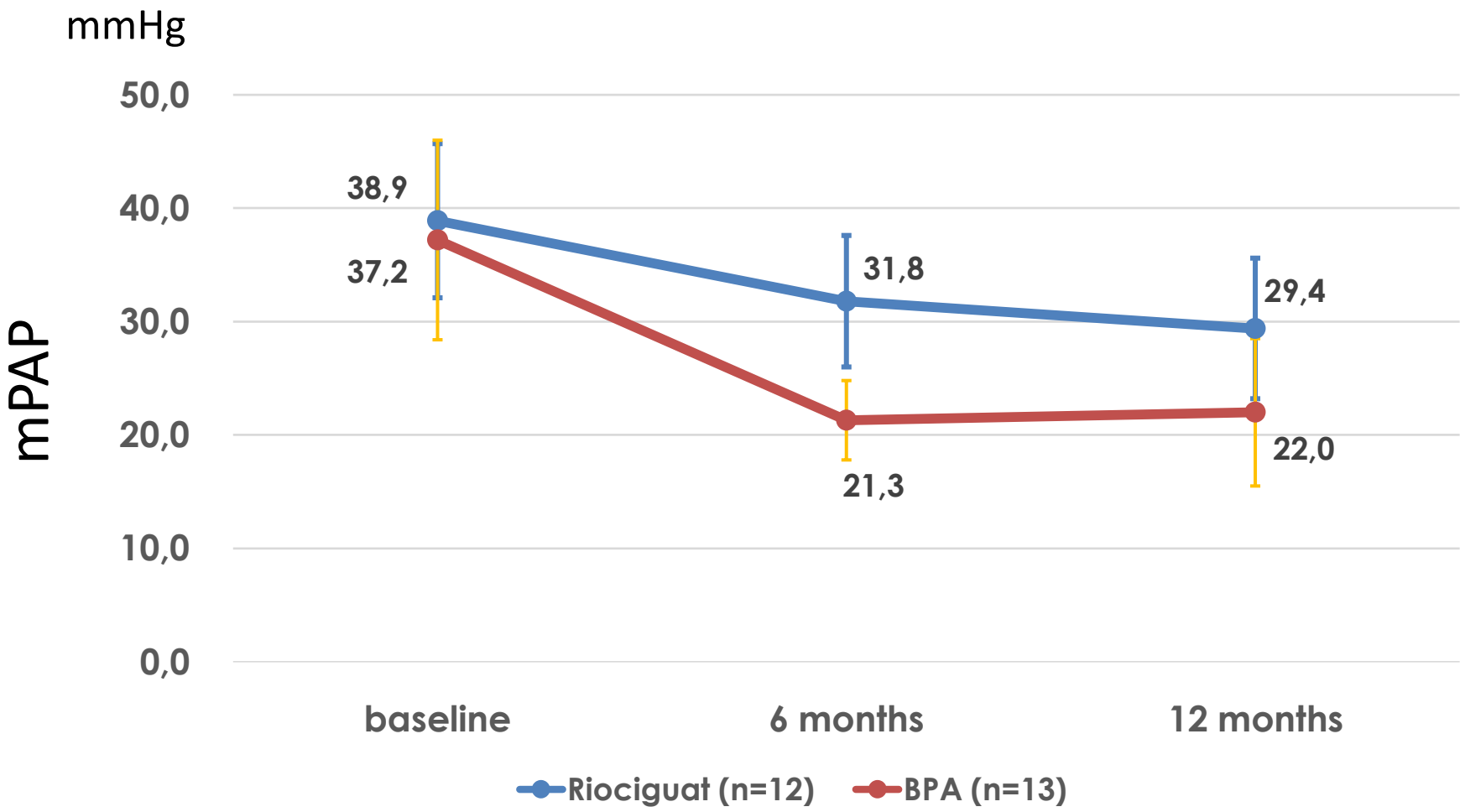
Effect of Riociguat and BPA on Japanese CTEPH patients



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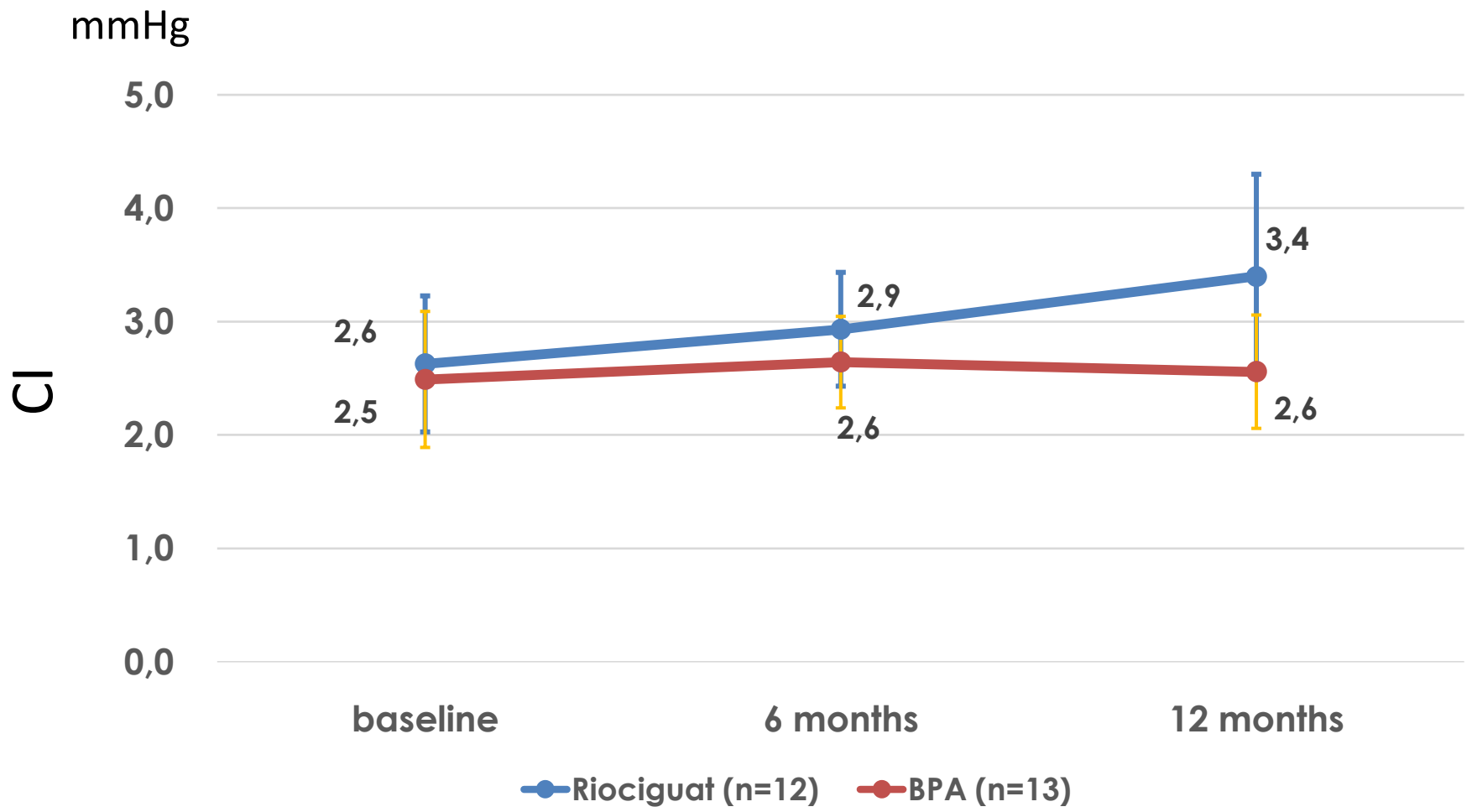
Effect of Riociguat and BPA on Japanese CTEPH patients



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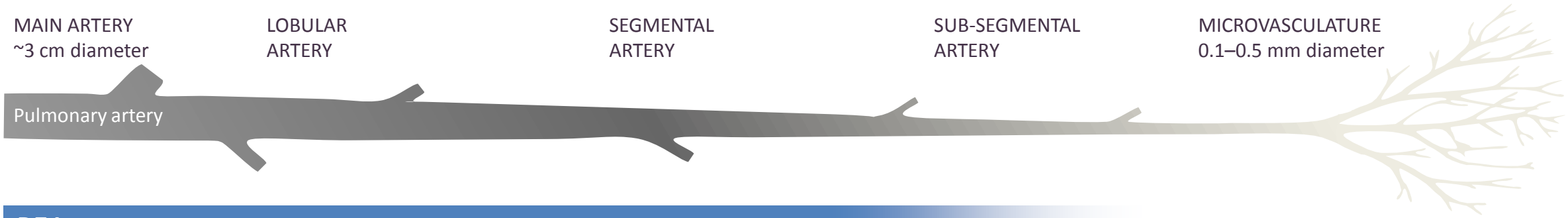
PEA and BPA target thromboembolic lesions in different parts of the pulmonary vascular bed[1]



PEA

Used to remove thromboembolic lesions primarily in the proximal main artery, and lobar and segmental arteries[1]

Surgical classification[2]	
Level 0	No evidence of thromboembolic disease in either lung
Level I (Level IC)	CTE starting in the main pulmonary arteries (Complete occlusion of one main pulmonary artery with CTE)
Level II	CTE starting at the level of lobar arteries or in main descending pulmonary arteries
Level III	CTE starting at the level of the segmental arteries
Level IV	CTE starting at the level of the sub-segmental arteries

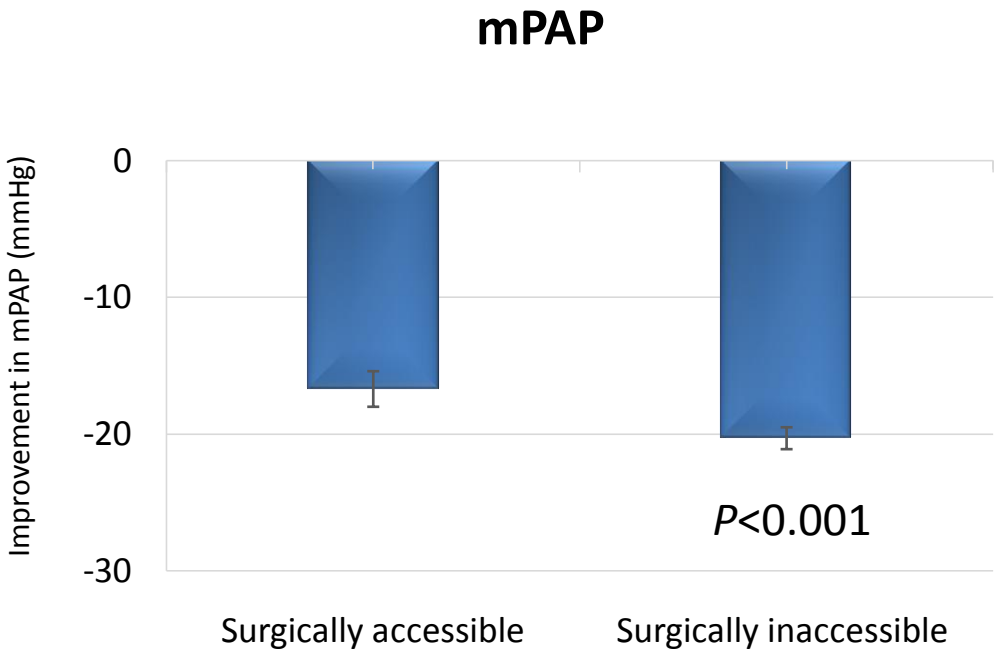
BPA

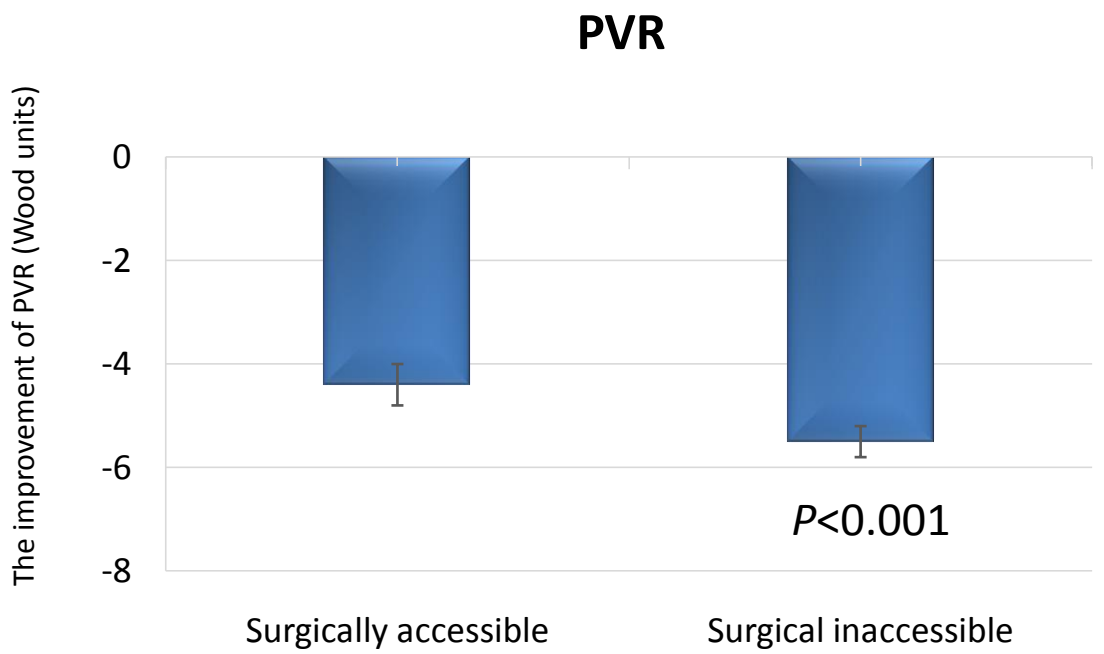
Mainly targets distal lesions in the segmental and sub-segmental vasculature, down to small pulmonary arteries 2–5 mm in diameter[1]

CTE, chronic thromboembolism.

1. Madani M *et al. Eur Respir Rev.* 2017;26:pii:170105. 2. Kim NH *et al. Eur Respir J.* 2019;53:pii.1801915.

Difference in therapeutic efficacy of BPA according to surgical accessibility





The reduction in mPAP and PVR in the surgically accessible group is inferior to those in the surgically inaccessible group

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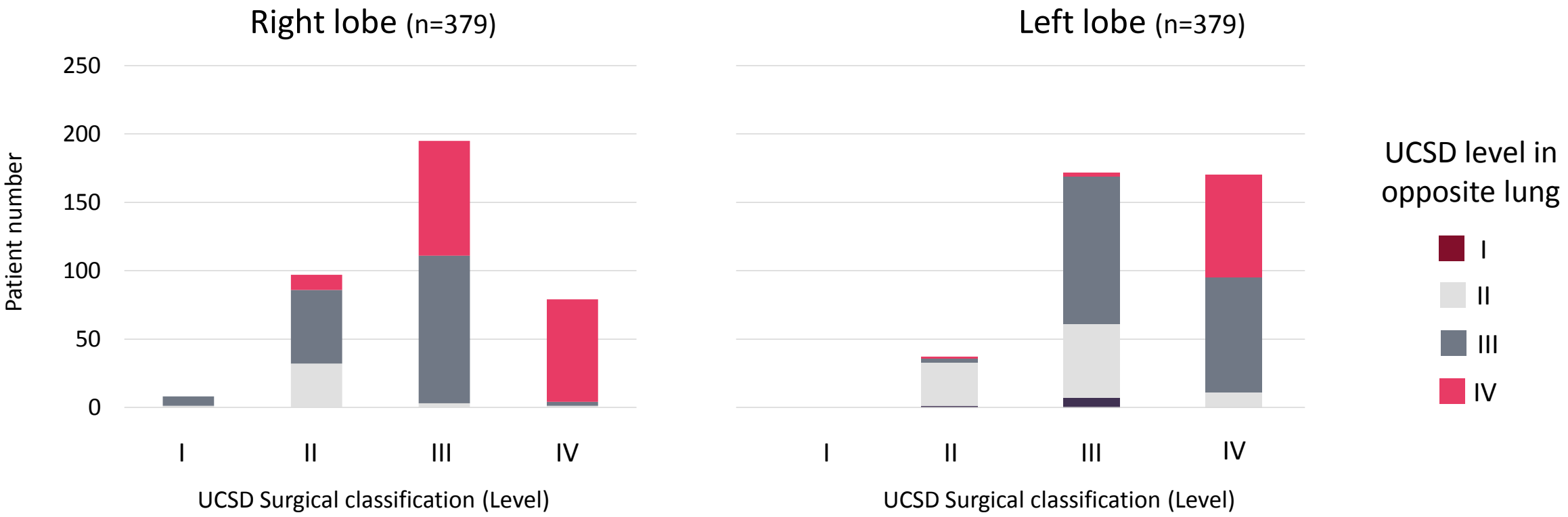
Distribution of lesions according to UCSD surgical classification



- The number of patients with Level 1 and 2 lesions (UCSD classification) is infrequent in our hospital
- Most of the patients with Level 2 lesions in right lobe have Level 3 or 4 lesions in left lobe
- Almost half of the patients with Level 3 lesions in right lobe have level 4 lesions in left lobe

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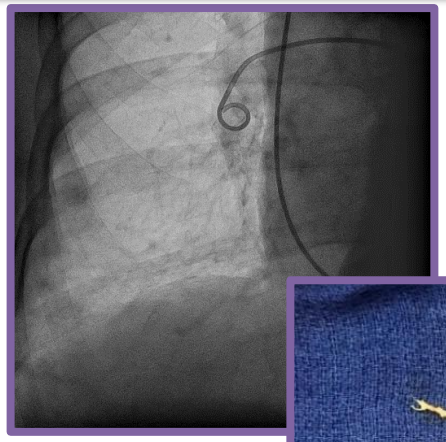
UCSD, University of California, San Diego.

Both proximal and distal lesions exist together

Lesions suitable for PEA



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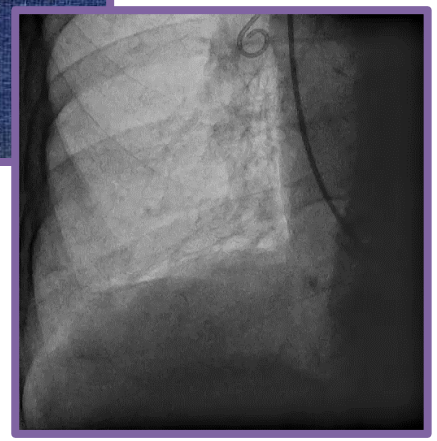
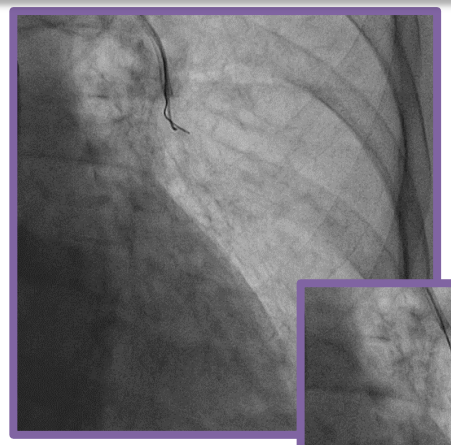


After

Lesions suitable for BPA



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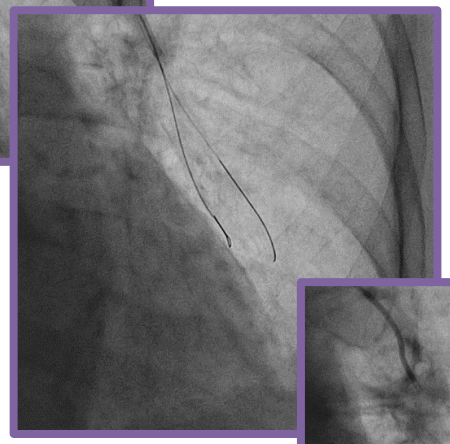

Immediately after

6 months later

Summary

Latest treatment algorithms provide clear recommendations on CTEPH management

- Operable CTEPH: Treatment of choice is PEA
- Inoperable and persistent/recurrent disease post-PEA: Medical therapy and/or BPA

BPA has evolved to be a promising and established treatment for inoperable CTEPH

- Requires extensive training and case experience; should be reserved for expert centers

Current treatment paradigm is evolving to include multimodal approaches; BPA would have a key role in such strategies in future CTEPH management