New Era of Interventional Treatment in Pulmonary Hypertension:

Balloon pulmonary angioplasty for CTEPH

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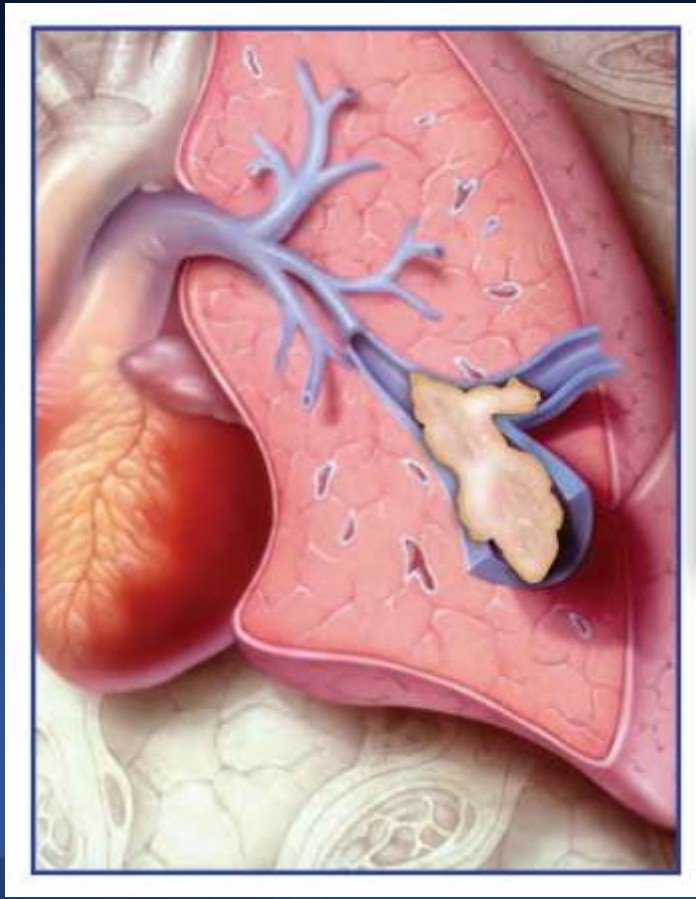
Definition of CTEPH

CTEPH (chronic thromboembolic pulmonary hypertension) is often a sequel of venous thromboembolism with fatal natural history



After 3 months of therapeutic anticoagulation

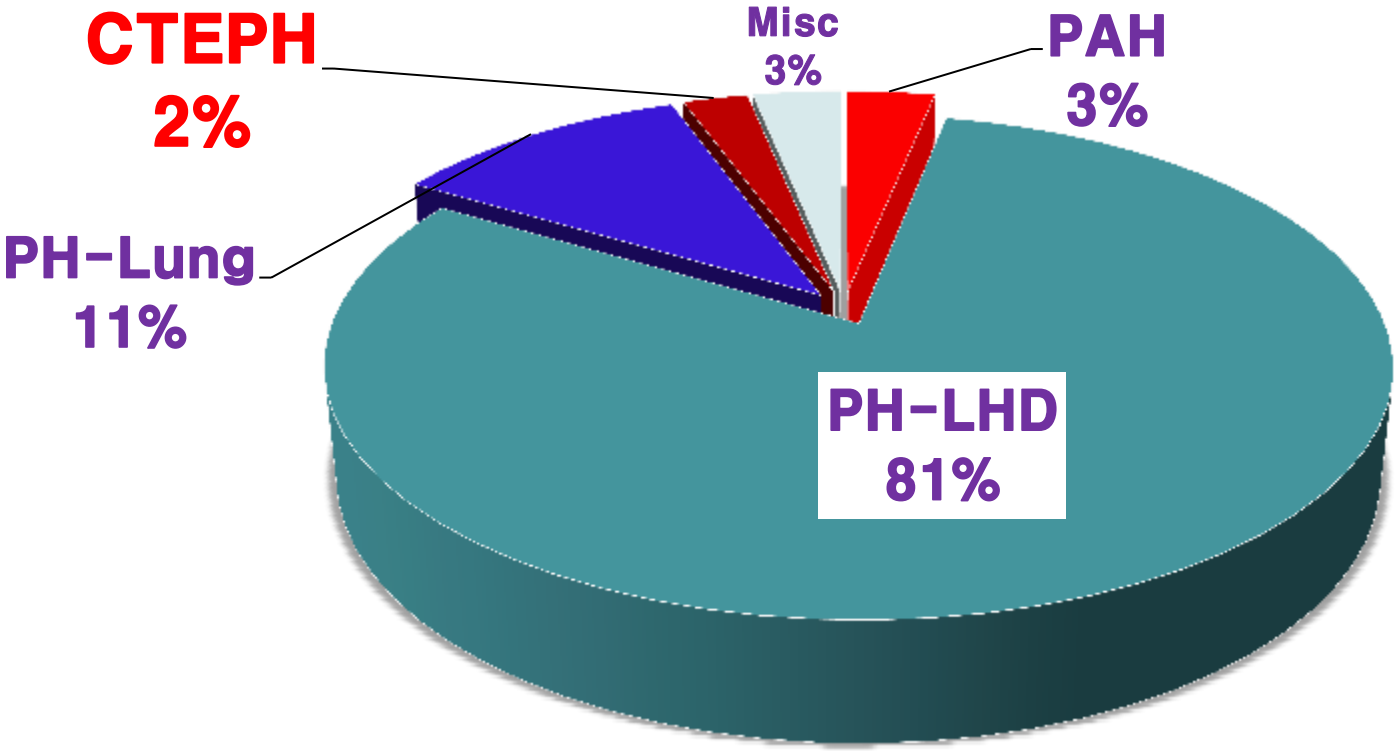
- mPAP ≥25 mmHg
- PCWP ≤15 mmHg
- Chronic/organized occlusive thrombi/emboli

Overall Prevalence of CTEPH

- CTEPH has been reported with a cumulative incidence of 0.1–9.1% within the first 2 years after a symptomatic PE event

- Some data suggest that CTEP may occur in approximately 5 individuals per million population per year

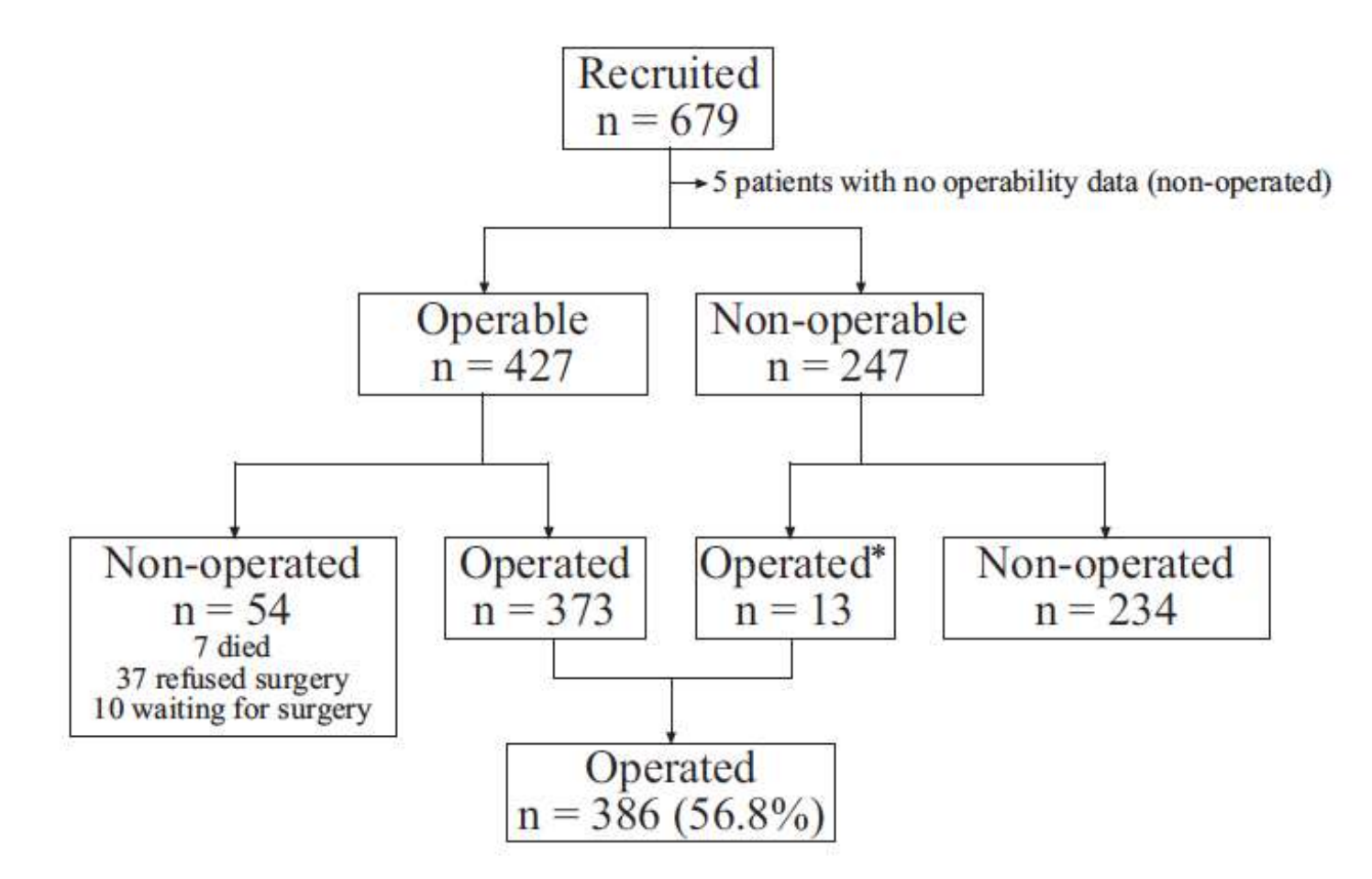
Prevalence of CTEPH in PH Patients



Strange G,et al. Heart 2012

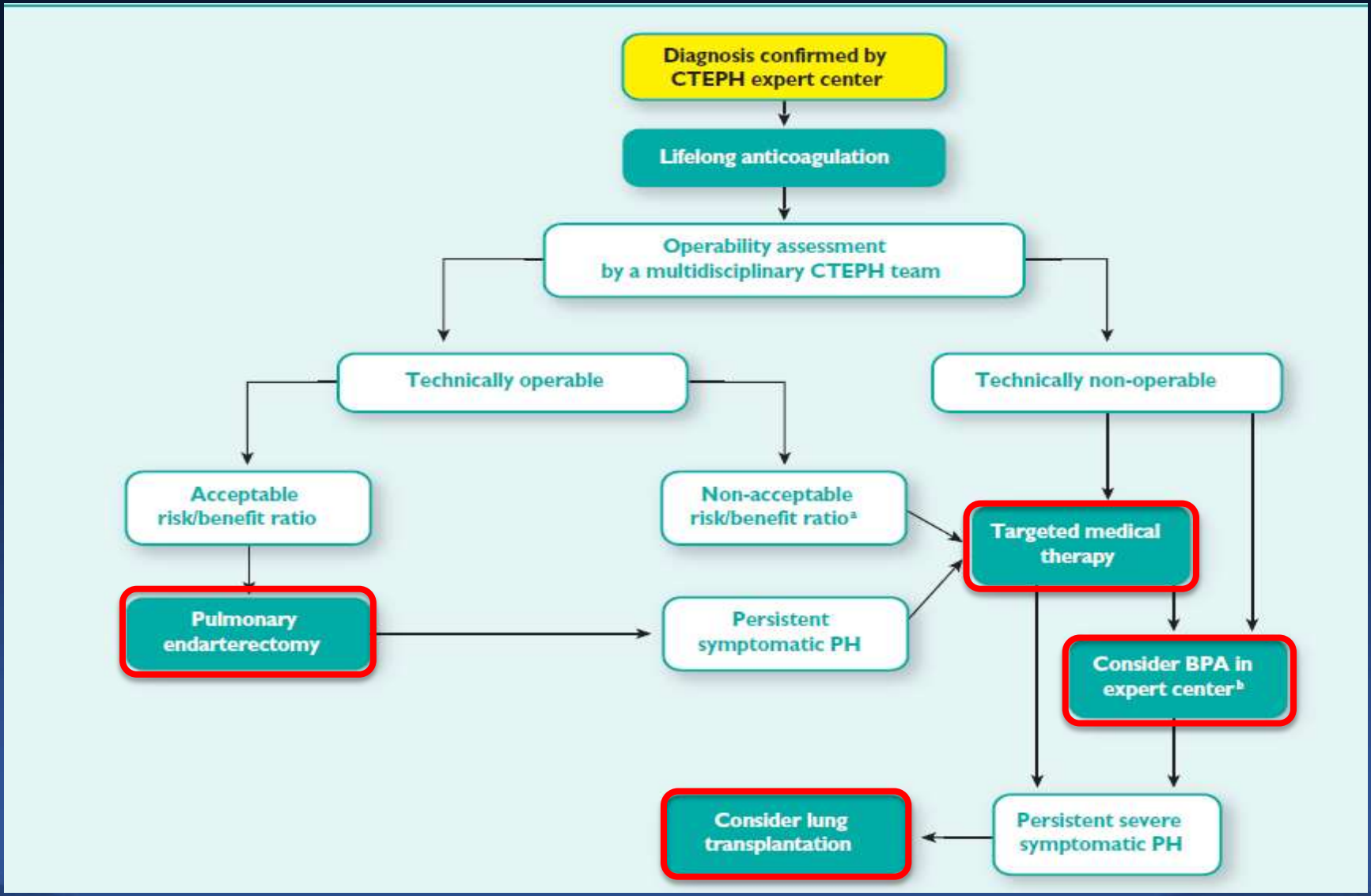
Pattern of CTEPH

679 CTEPH patients from an International Prospective Registry



Circulation 2011;124:1973-1981

Guideline of CTEPH Treatment

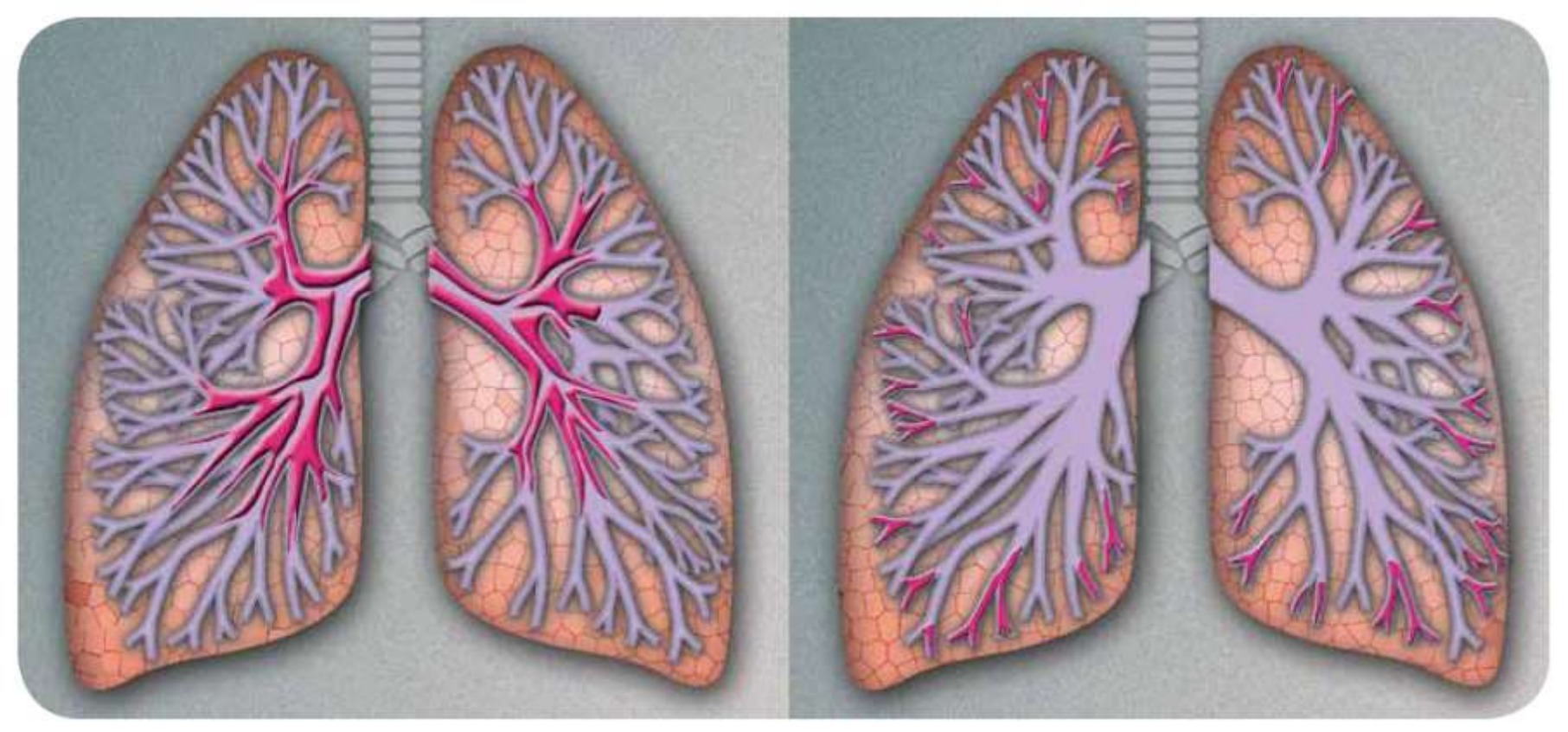


2015 ESC/ERS guidelines for PH

Guideline of CTEPH Tx

Recommendations	Class[a]	Level[b]	Ref.[c]
Interventional BPA may be considered in patients who are technically non-operable or carry an unfavourable risk:benefit ratio for PEA	IIb	C	57, 444–446, 448
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended	III	C	417

OPERABILITY ASSESSMENT



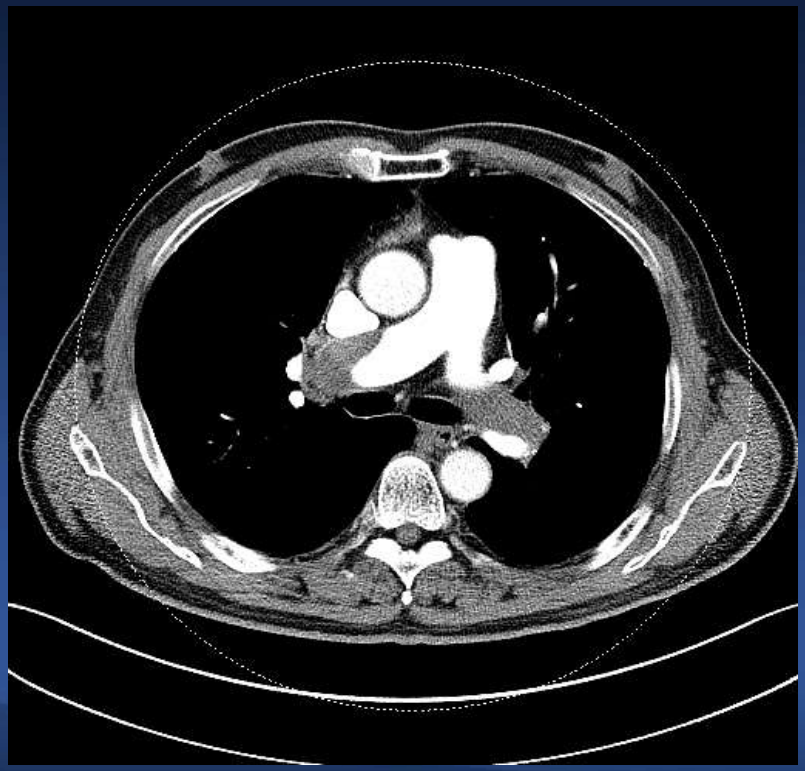
Case: 64 male patient with CTEPH Eligible for Endarterectomy

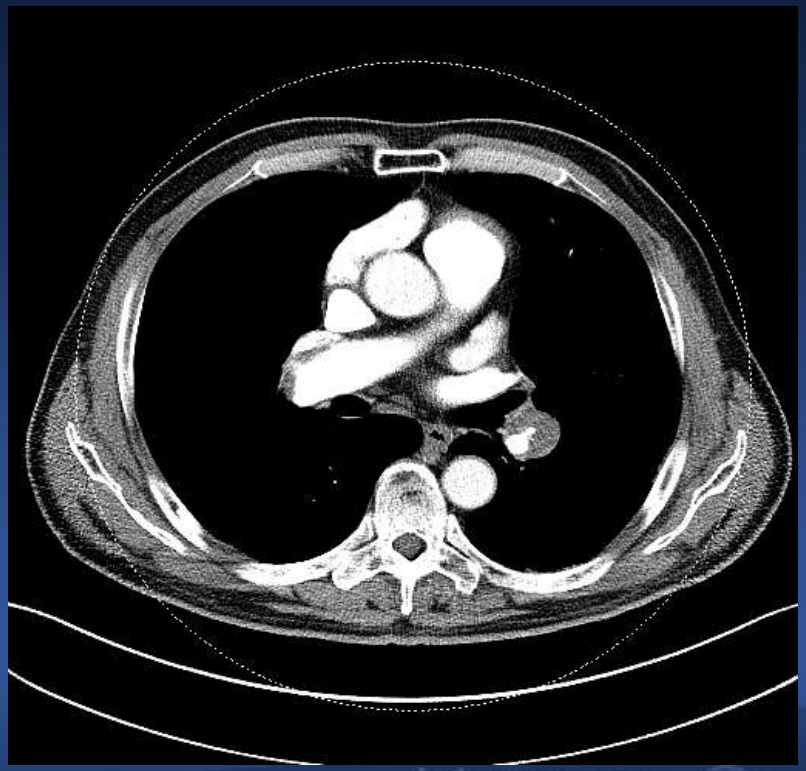
9YA acute PE with DVT -> thrombolysis and anticoagulation

2YA CTEPH -> sildenafil

Echo: TR Vmax 4.4 m/s PG 77mmHG RV dysfunction (+)

referred for stomach cancer operation





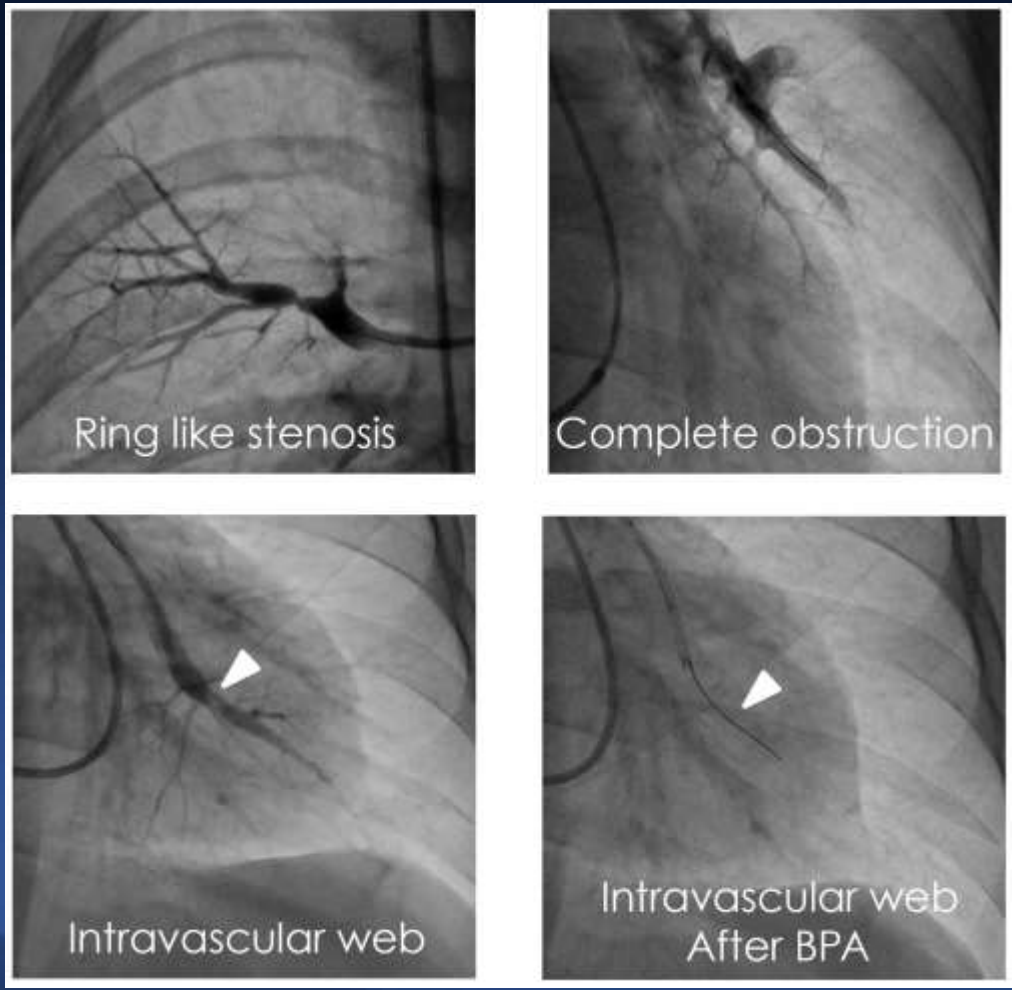
Preoperative RHC and PEA

		max	min	mean
Assumed VO2 (ml/min/m²)			227.5	
Hemoglobin (g/dL)			16.9	
Aorta	Pressure	98	57	74
Aorta(PV)	Saturation		97	
Aorta(PV)	PaO2		85	
SVC	Saturation		62	
IVC	Saturation		63	
MV O2			62.25	
RA	Pressure	14	9	9
RV	Pressure	82	6	14
MPA	Pressure	88	22	42
	Saturation		59	
	PaO2		25	
PCW(LA)	Pressure	12	11	10

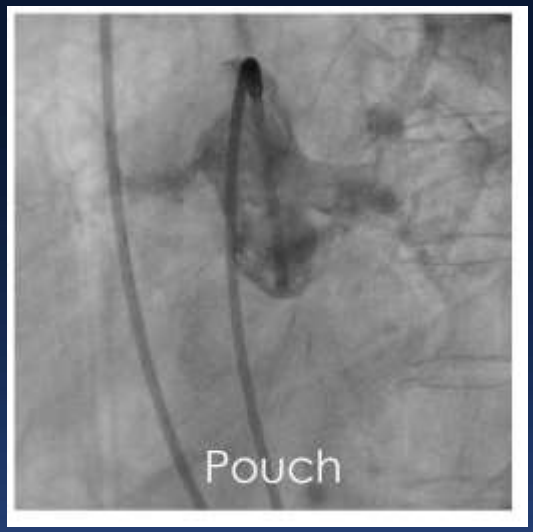
PBF(Qp) (L/min)	2.55
SBF(Qs) (L/min)	2.79
Qp/Qs	0.92
Total PVR (Wood units)	12.54

Angiographic Findings of CTEPH Lesions

Suitable for intervention



Not suitable for intervention



Evolution of BPA Strategy

	Initial Strategy 2004~2012.Oct	Previous Strategy 2012.Nov~2013.Nov	Current Strategy 2013.Dec~
			
Balloon size	As large as possible	Under sized corresponding to lesion type and mPAP	Under sized corresponding to lesion type and mPAP
Treated vessels	2 vessels	2 vessels	As many as possible

JAPAN - Kyorin University School

Percutaneous Transluminal Pulmonary Angioplasty for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

Masaharu Kataoka, MD; Takumi Inami, MD; Kentaro Hayashida, MD; Nobuhiko Shimura, MD; Haruhisa Ishiguro, MD; Takayuki Abe, PhD; Yuichi Tamura, MD; Motomi Ando, MD; Keiichi Fukuda, MD; Hideaki Yoshino, MD; Toru Satoh, MD

Background—Chronic thromboembolic pulmonary hypertension leads to pulmonary hypertension and right-sided heart failure. The purpose of this study was to investigate the efficacy of percutaneous transluminal pulmonary angioplasty (PTPA) for the treatment of chronic thromboembolic pulmonary hypertension.

Methods and Results—Twenty-nine patients with chronic thromboembolic pulmonary hypertension underwent PTPA. One patient had a wiring perforation as a complication of PTPA and died 2 days after the procedure. In the remaining 28 patients, PTPA did not produce immediate hemodynamic improvement at the time of the procedure. However, after follow-up (6.0±6.9 months), New York Heart Association functional classifications and levels of plasma B-type natriuretic peptide significantly improved (both $P<0.01$). Hemodynamic parameters also significantly improved (mean pulmonary arterial pressure, 45.3±9.8 versus 31.8±10.0 mm Hg; cardiac output, 3.6±1.2 versus 4.6±1.7 L/min, baseline versus follow-up, respectively; both $P<0.01$). Twenty-seven of 51 procedures in total (53%), and 19 of 28 first procedures (68%), had reperfusion pulmonary edema as the chief complication. Patients with severe clinical signs and/or severe hemodynamics at baseline had a high risk of reperfusion pulmonary edema.

Conclusions—PTPA improved subjective symptoms and objective variables, including pulmonary hemodynamics. PTPA may be a promising therapeutic strategy for the treatment of chronic thromboembolic pulmonary hypertension.

Clinical Trial Registration—URL: http://www.umin.ac.jp. Unique identifier: UMIN000001572. **(*Circ Cardiovasc Interv*. 2012;5:756-762.)**

Key Words: chronic thromboembolic pulmonary hypertension ■ hypertension ■ pulmonary ■ percutaneous transluminal pulmonary angioplasty ■ reperfusion pulmonary edema

Immediate effect of BPA was minimal

Table 2. Acute Hemodynamic Effects of PTPA

	Just Before PTPA LS mean±SE	Just After PTPA LS mean±SE	*P*-value
Mean RAP, mm Hg	5.2±0.6	5.0±0.6	0.82
Mean PAP, mm Hg	41.8±1.7	40.8±1.7	0.42
CO, L/min	3.8±0.2	3.9±0.2	0.55

Mid-term (median 6.0 month) effect of BPA was excellent

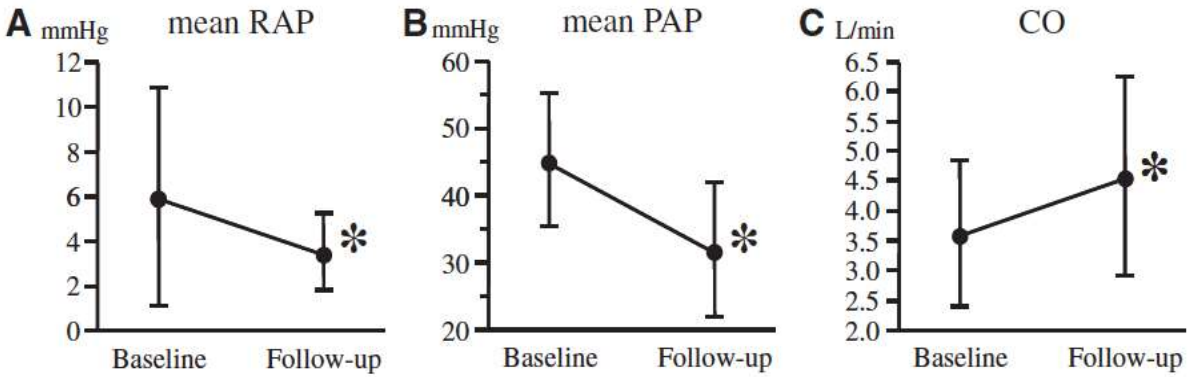
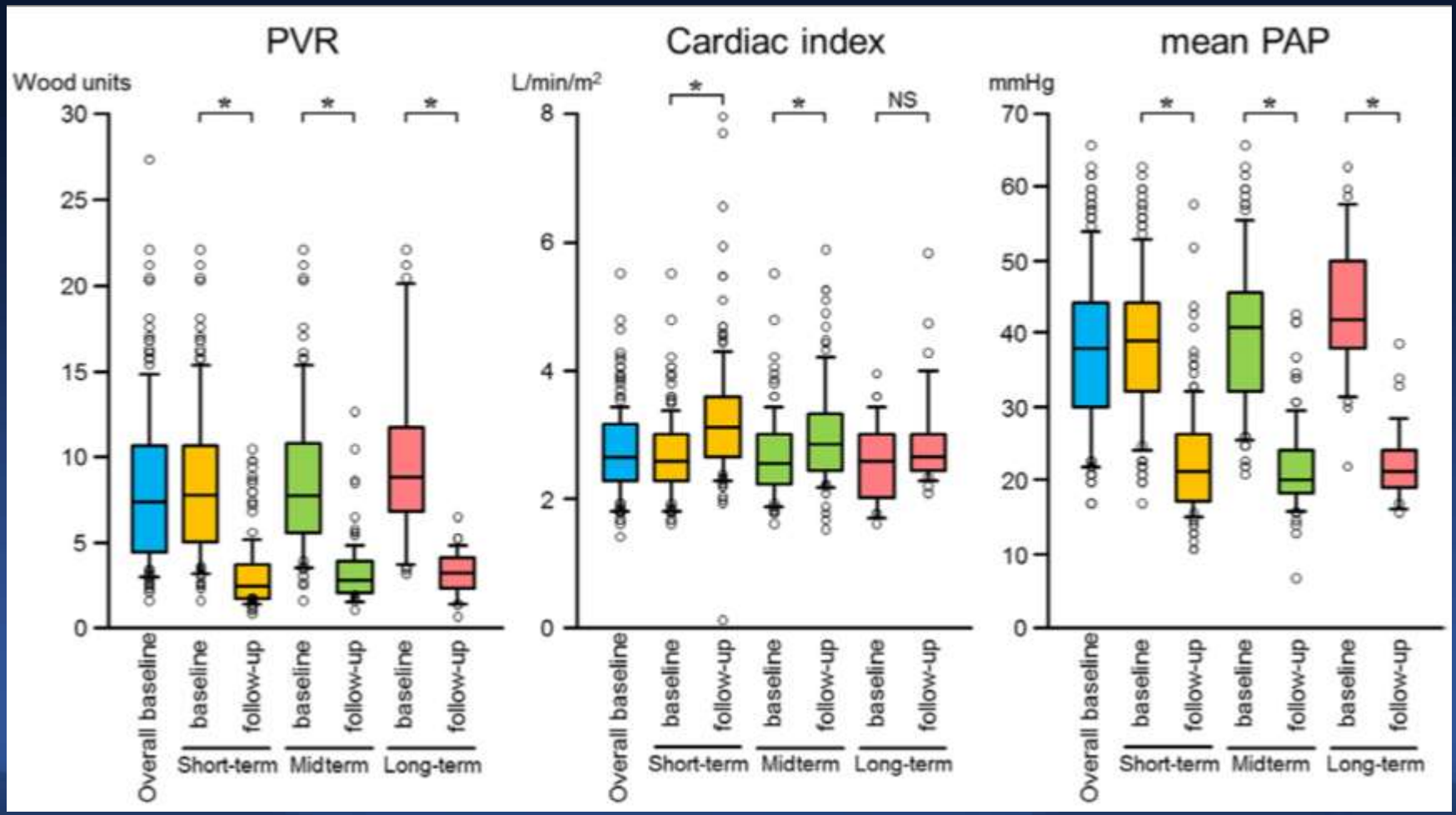


Figure 3. Hemodynamic changes at follow-up after percutaneous transluminal pulmonary angioplasty. Mean RAP (**A**), mean PAP (**B**), and CO (**C**) improved significantly at follow-up. **P*<0.01 vs baseline. RAP indicates right atrial pressure; PAP, pulmonary arterial pressure; and CO, cardiac output.

Long-Term Outcomes After BPA

649 consecutive BPA in 170 CTEPH patients
median 2.8 years (IQR; 1.2-4.1 years)



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JAPAN – Okayama Medical Center

Refined Balloon Pulmonary Angioplasty for Inoperable Patients with Chronic Thromboembolic Pulmonary Hypertension

Hiroki Mizoguchi, MD; Aiko Ogawa, MD, PhD; Mitsuru Munemasa, MD, PhD; Hiroshi Mikouchi, MD, PhD; Hiroshi Ito, MD, PhD; Hiromi Matsubara, MD, PhD

Background—Although balloon pulmonary angioplasty (BPA) for inoperable patients with chronic thromboembolic pulmonary hypertension was first reported over a decade ago, its clinical application has been restricted because of limited efficacy and complications. We have refined the procedure of BPA to maximize its clinical efficacy.

Methods and Results—Sixty-eight consecutive patients with inoperable chronic thromboembolic pulmonary hypertension underwent BPA. We evaluated pulmonary artery diameters and determined the appropriate balloon size by using intravascular ultrasound. We performed BPA in a staged fashion over multiple, separate procedures to maximize efficacy and reduce the risk of reperfusion pulmonary injury. A total of 4 (2–8) sessions were performed in each patient, and the number of vessels dilated per session was 3 (1–14). The World Health Organization functional class improved from 3 to 2 ($P<0.01$), and mean pulmonary arterial pressure was decreased from 45.4±9.6 to 24.0±6.4 mm Hg ($P<0.01$). One patient died because of right heart failure 28 days after BPA. During follow-up for 2.2±1.4 years after the final BPA, another patient died of pneumonia, and the remaining 66 patients are alive. In 57 patients who underwent right heart catheterization at follow-up, improvement of mean pulmonary arterial pressure was maintained (24.0±5.8 mm Hg at 1.0±0.9 years). Forty-one patients (60%) developed reperfusion pulmonary injury after BPA, but mechanical ventilation was required in only 4 patients.

Conclusions—Our refined BPA procedure improves clinical status and hemodynamics of inoperable patients with chronic thromboembolic pulmonary hypertension, with a low mortality. A refined BPA procedure could be considered as a therapeutic approach for patients with inoperable chronic thromboembolic pulmonary hypertension. (***Circ Cardiovasc Interv.* 2012;5:748-755.**)

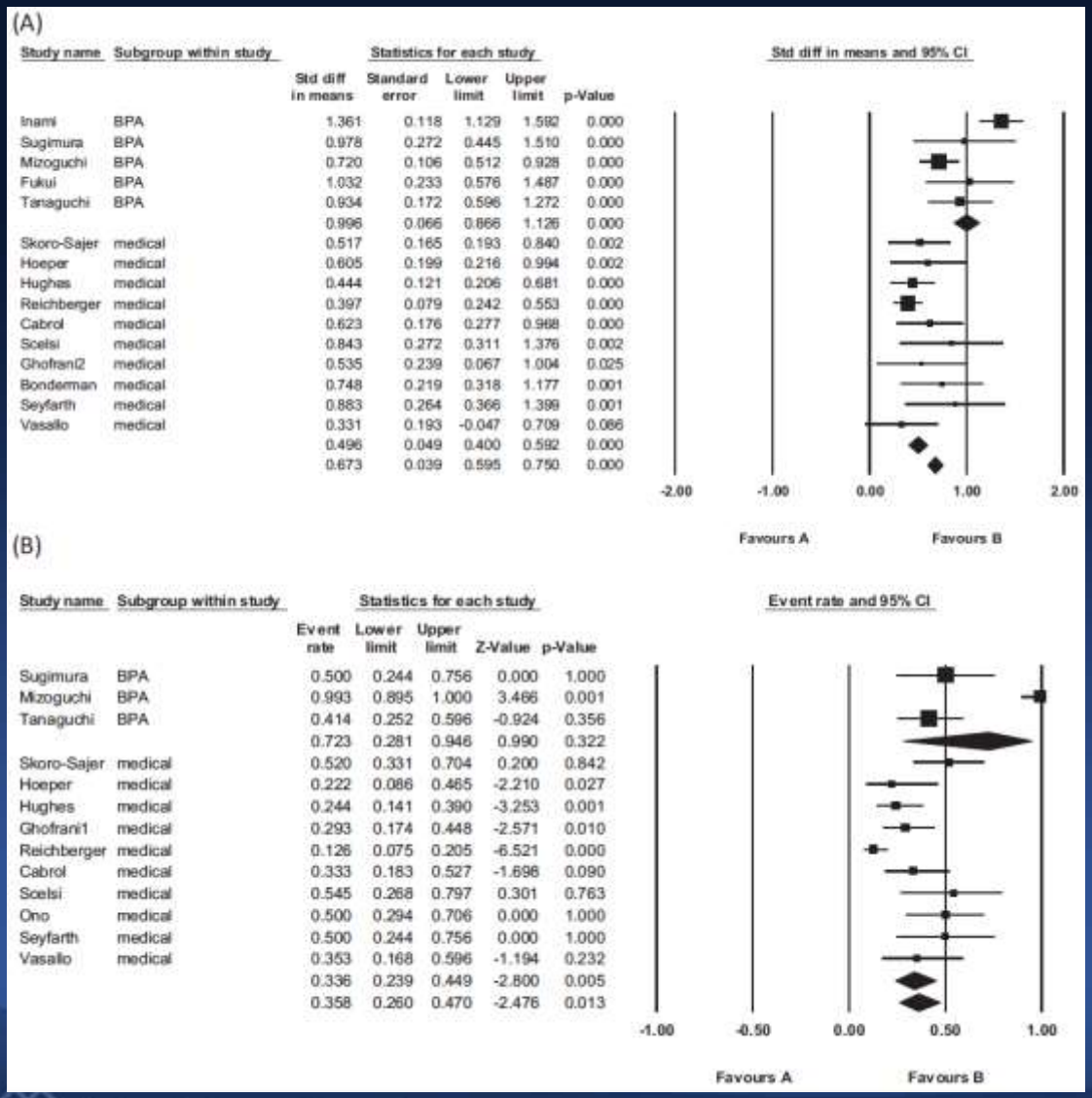
Key Words: peripheral vascular disease ■ pulmonary hypertension ■ reperfusion ■ revascularization

FU; median 2.2 year

Table 1. Clinical and Hemodynamic Data Before and After BPA

	Before BPA (n=68)	After BPA (n=67)	*P* Value
WHO functional class (I/II/III/IV)	3 (0/0/49/19)	2 (11/53/3/0)	<0.01
Oxygen inhalation (L/min)	3.0±1.4	1.3±1.0	<0.01
6MWD, m	296±108	368±83	<0.01
BNP, pg/mL	330±444	35±55	<0.01
sPAP, mm Hg	81.3±16.9	42.3±11.9	<0.01
dPAP, mm Hg	24.3±7.1	13.4±4.8	<0.01
mPAP, mm Hg	45.4±9.6	24.0±6.4	<0.01
RAP, mm Hg	8.1±4.4	1.9±1.5	<0.01
CI, L/min/m^2	2.2±0.7	3.2±0.6	<0.01
PVR, dyne sec/cm^5	942±367	327±151	<0.01

Medical Tx vs. BPA for CTEPH: Systemic Review and Meta-Analysis

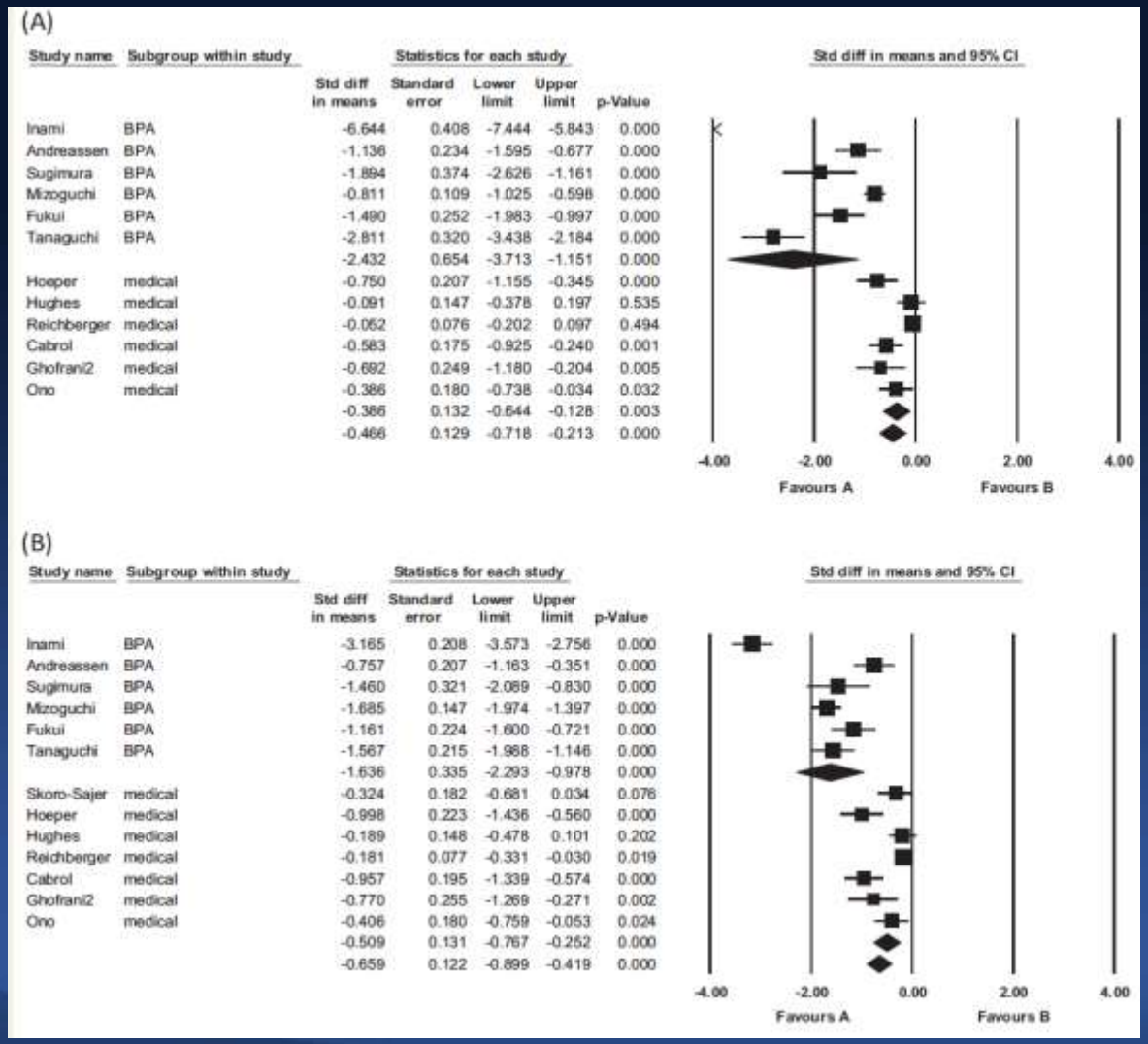


6-min Walk Distance

NYHA Functional Class

Heart Lung Circ. 2017 Mar 1

Medical Tx vs. BPA for CTEPH:
Systemic Review and Meta-Analysis



(A)

Study name	Subgroup within study	Std diff in means	Standard error	Lower limit	Upper limit	p-Value
Inami	BPA	-6.644	0.408	-7.444	-5.843	0.000
Andreassen	BPA	-1.136	0.234	-1.595	-0.677	0.000
Sugimura	BPA	-1.894	0.374	-2.626	-1.161	0.000
Mizoguchi	BPA	-0.811	0.109	-1.025	-0.598	0.000
Fukui	BPA	-1.490	0.252	-1.983	-0.997	0.000
Tanaguchi	BPA	-2.811	0.320	-3.438	-2.184	0.000
		-2.432	0.654	-3.713	-1.151	0.000
Hoeper	medical	-0.750	0.207	-1.155	-0.345	0.000
Hughes	medical	-0.091	0.147	-0.378	0.197	0.535
Reichberger	medical	-0.052	0.076	-0.202	0.097	0.494
Cabrol	medical	-0.583	0.175	-0.925	-0.240	0.001
Ghofrani2	medical	-0.692	0.249	-1.180	-0.204	0.005
Ono	medical	-0.386	0.180	-0.738	-0.034	0.032
		-0.386	0.132	-0.644	-0.128	0.003
		-0.466	0.129	-0.718	-0.213	0.000

(B)

Study name	Subgroup within study	Std diff in means	Standard error	Lower limit	Upper limit	p-Value
Inami	BPA	-3.165	0.208	-3.573	-2.756	0.000
Andreassen	BPA	-0.757	0.207	-1.163	-0.351	0.000
Sugimura	BPA	-1.460	0.321	-2.089	-0.830	0.000
Mizoguchi	BPA	-1.685	0.147	-1.974	-1.397	0.000
Fukui	BPA	-1.161	0.224	-1.600	-0.721	0.000
Tanaguchi	BPA	-1.567	0.215	-1.988	-1.146	0.000
		-1.636	0.335	-2.293	-0.978	0.000
Skoro-Sajer	medical	-0.324	0.182	-0.681	0.034	0.076
Hoeper	medical	-0.998	0.223	-1.436	-0.560	0.000
Hughes	medical	-0.189	0.148	-0.478	0.101	0.202
Reichberger	medical	-0.181	0.077	-0.331	-0.030	0.019
Cabrol	medical	-0.957	0.195	-1.339	-0.574	0.000
Ghofrani2	medical	-0.770	0.255	-1.269	-0.271	0.002
Ono	medical	-0.406	0.180	-0.759	-0.053	0.024
		-0.509	0.131	-0.767	-0.252	0.000
		-0.659	0.122	-0.899	-0.419	0.000

mPAP

PVR

Case #1

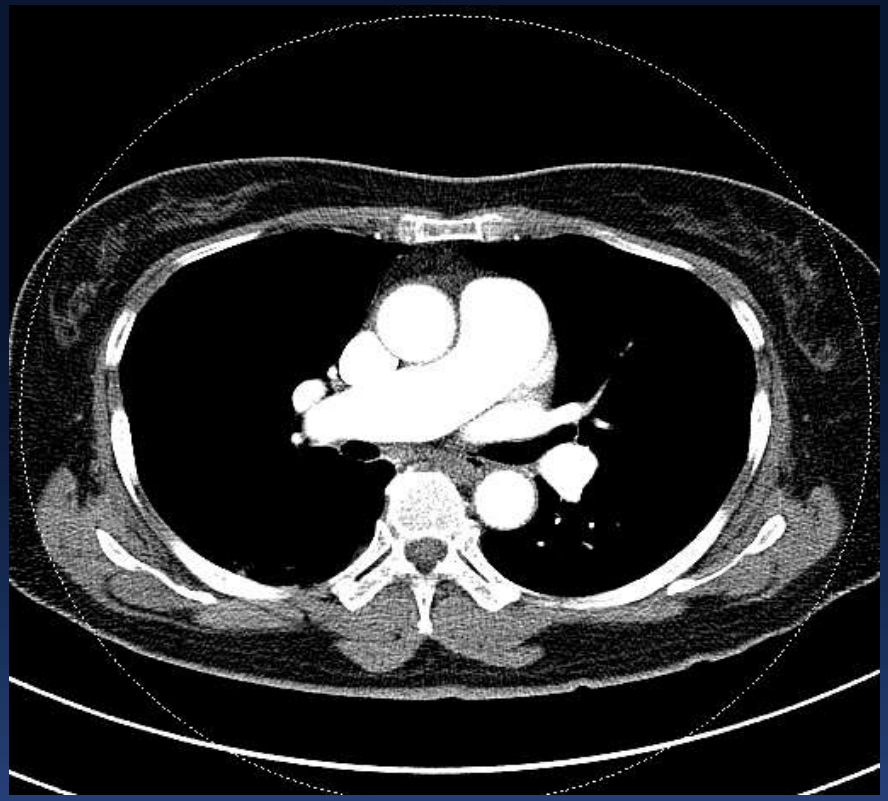
- 60/F, HTN/hyperlipidemia

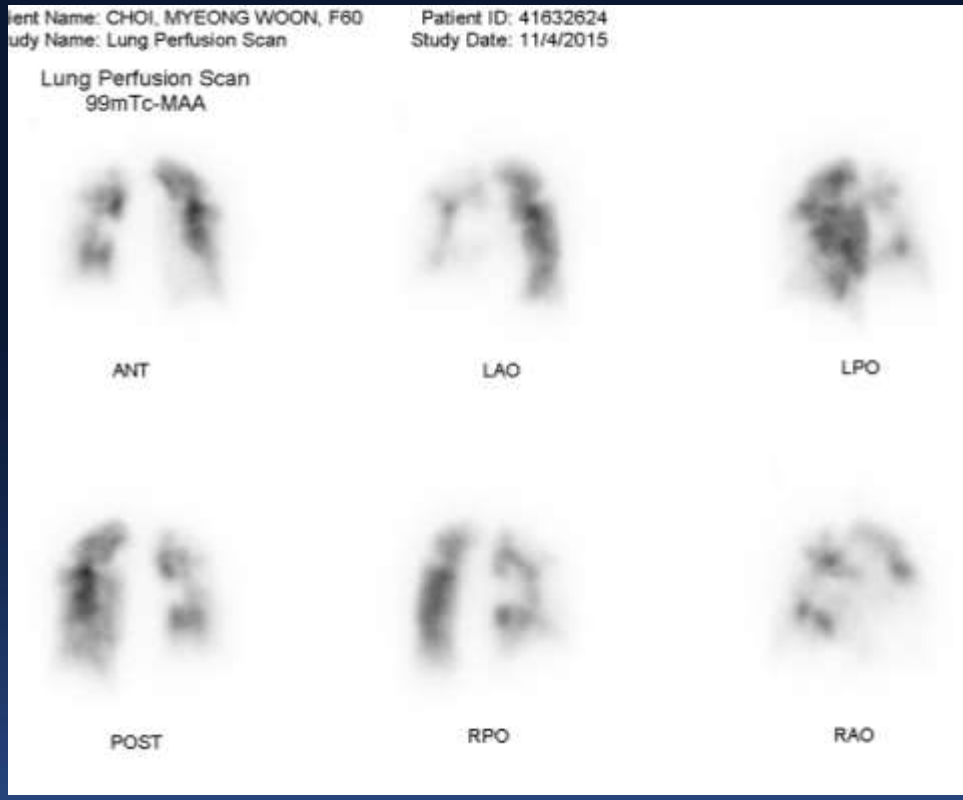
- 1st time refer; 2015/04 DOE Fc I-II
- Echo; normal, TR-Vmax; 2.5, trace,
- EKG; NSR, CXR; normal

- 2nd time refer: 2015/11 DOE Fc III, clinic oxygen sat. 85%
- ABGA; 7.4-29.6-66.9-93.9 (room air)
- Echo; severe RV dysfunction, TR-Vmax 4.3 (PG=74)

Echo


AMC ROOM 7
M5S
MI 1.1
11/03/2015 14:45:57
USR
CardiacV
TIS:0.8
V
5
10
71
HR



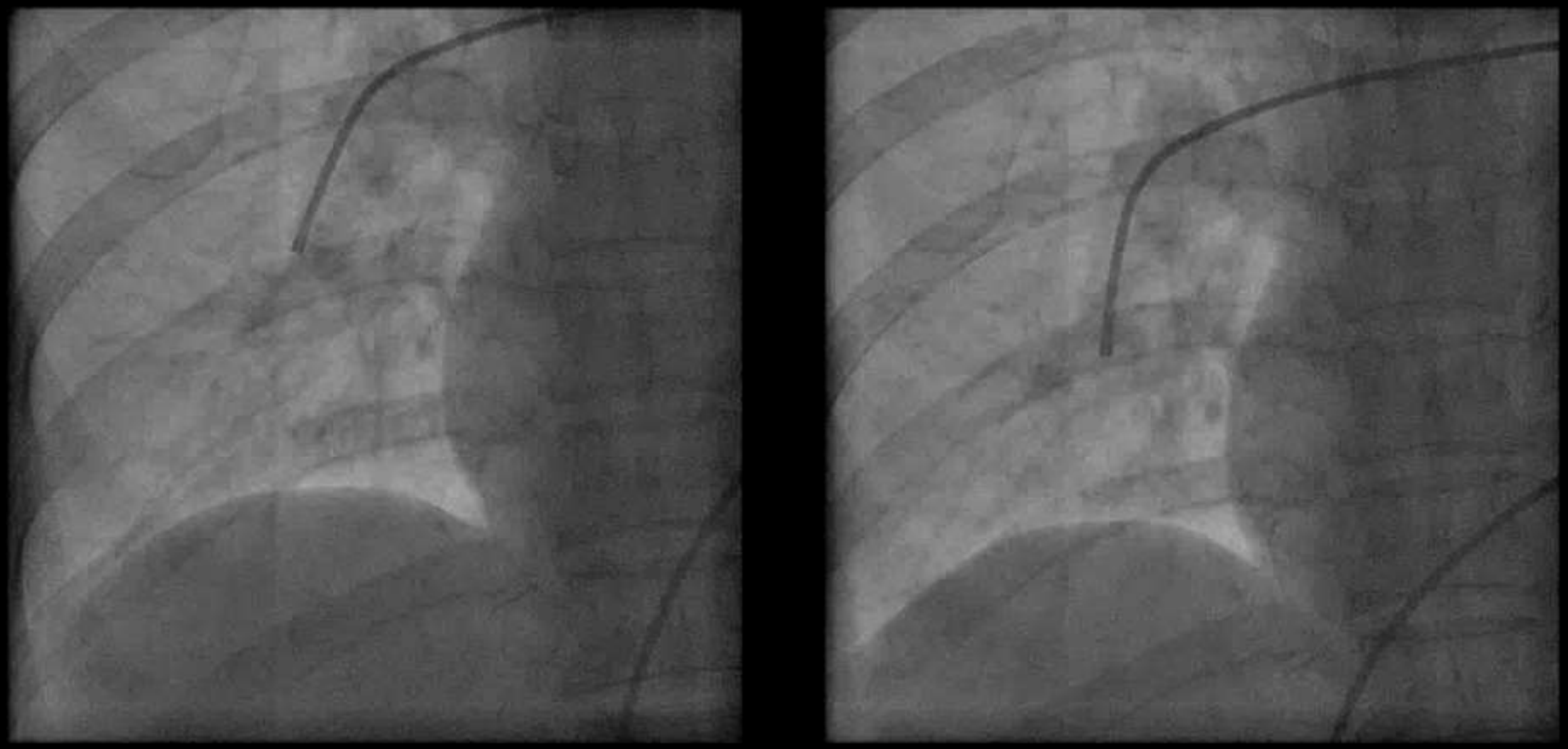


1. No pulmonary thromboembolism.
2. Mosaic pattern of lung attenuation.
3. Enlarged pulmonary trunk and right heart dysfunction.

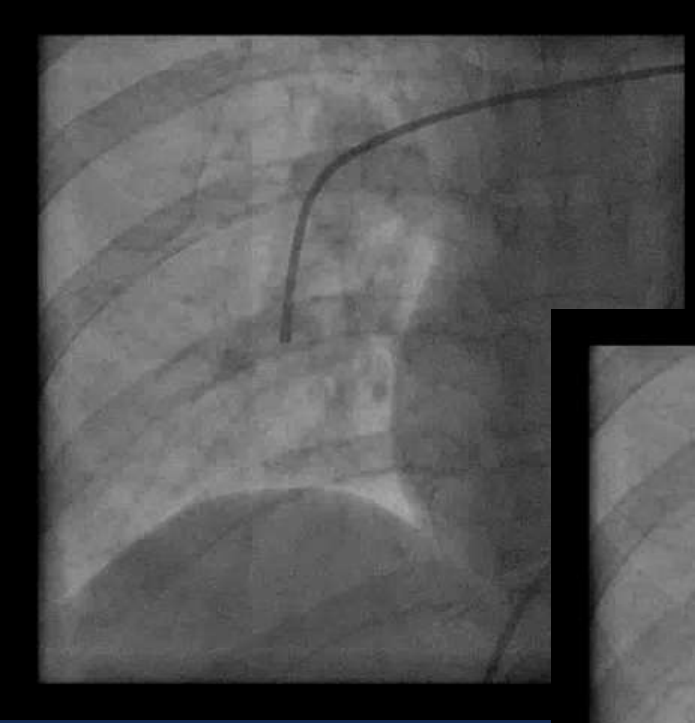
r/o pulmonary artery hypertension.

Large V/Q mismatch;
High probability of pulmonary embolism

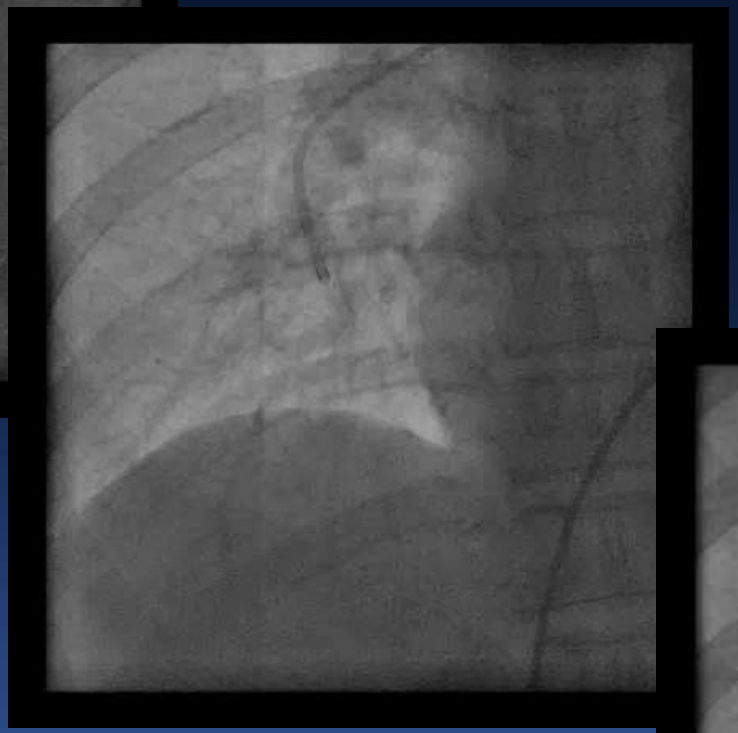
Baseline Pul. Angio



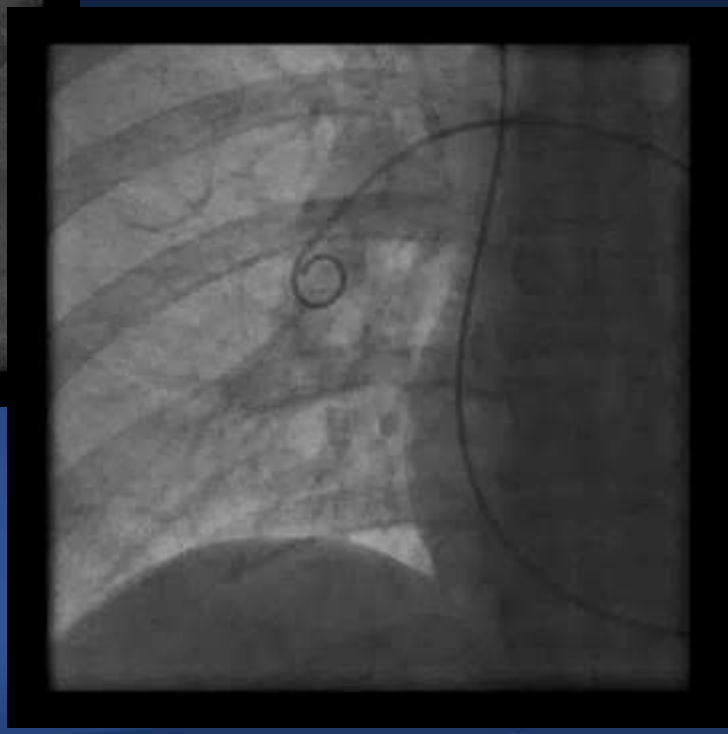
BPA



PRE



POST



1 MONTH

Echo FU at 1 Mo after BPA

PRE

POST

Case #2

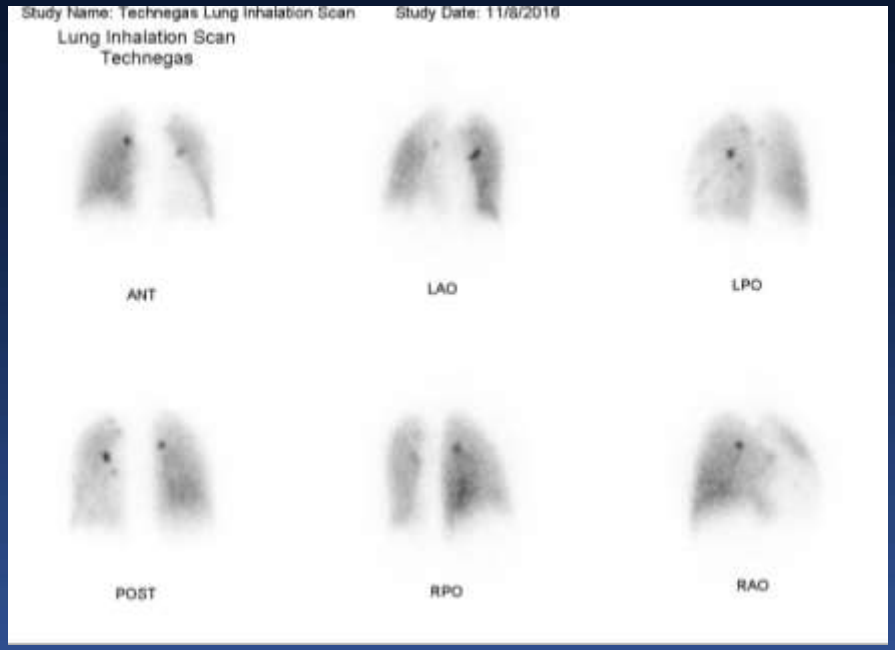
- 37Yr, Female,
- 2015 fever, cough, dyspnea

➔ Diagnosis of Takayasu's arteritis with aorta and pulmonary involvement

- Sildenafil, Bosentan medication ➔ dyspnea aggravation
- 6min walk test; 486m, HR 120, SaO2 91
- ESR 16 mm/hr (0-20), CRP 0.3 mg/dl (0-0.6)

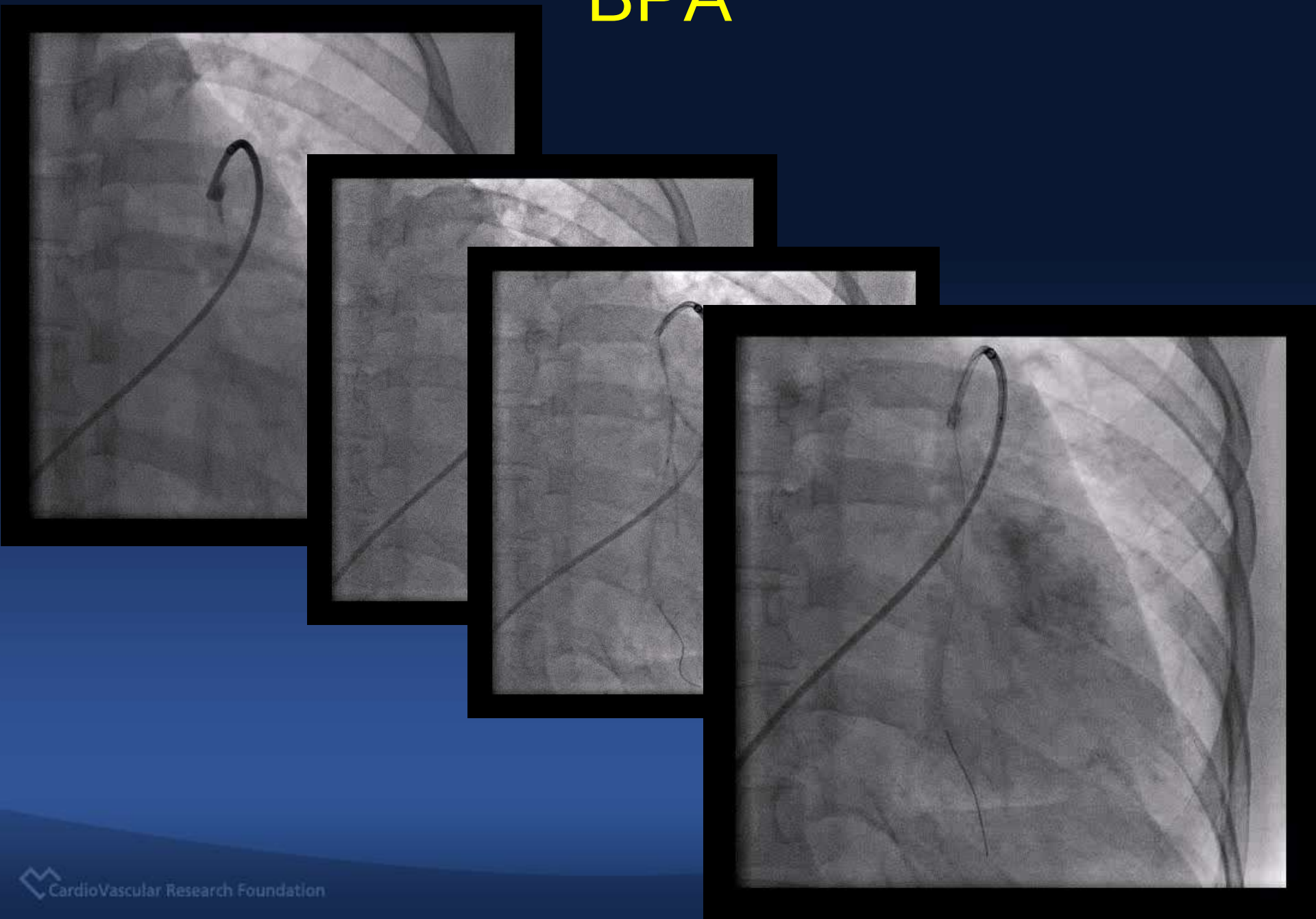
Large V/Q Mismatch

Lung inhalation scan



Lung perfusion scan

BPA



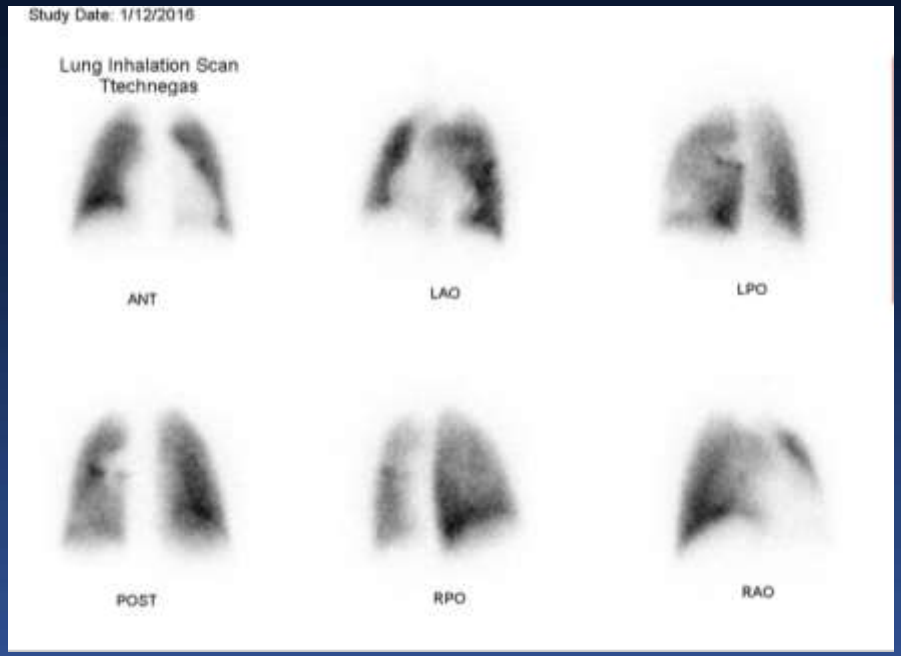
1Mo FU

Case #3

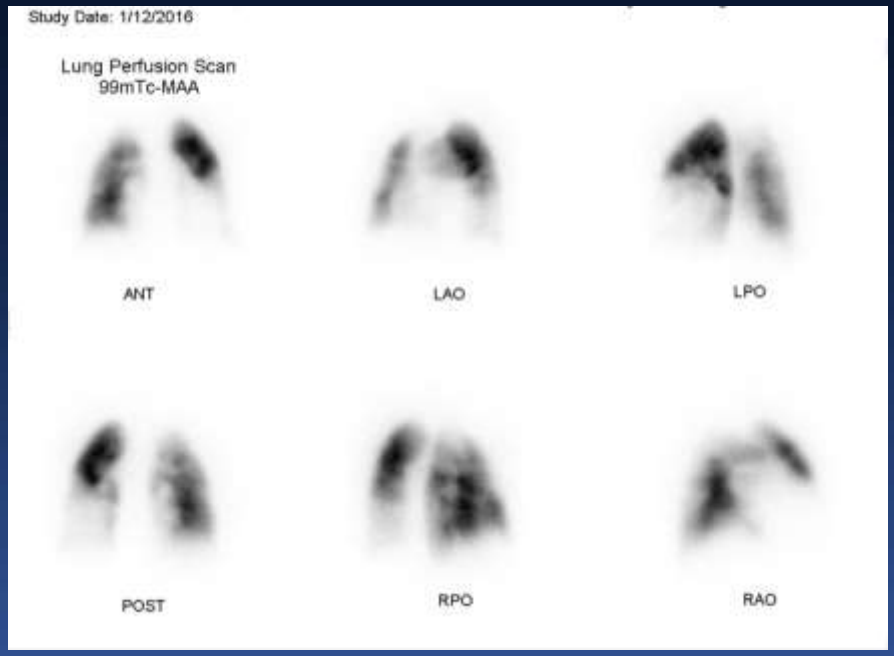
- 36Yr, Male
- Mar/2015; diagnosis of DVT, warfarin therapy start
- Sep/2015; sudden dyspnea after stopping of warfarin 2Mo
- ➔ Cardiac arrest, CPR, ECMO/hypothermia
- ➔ Pul. Thromboembolectomy, IVC embolectomy and ASD creation
- May/2016; ASD device closure
- DOE Fc III, remained large lung perfusion defect

Large V/Q Mismatch

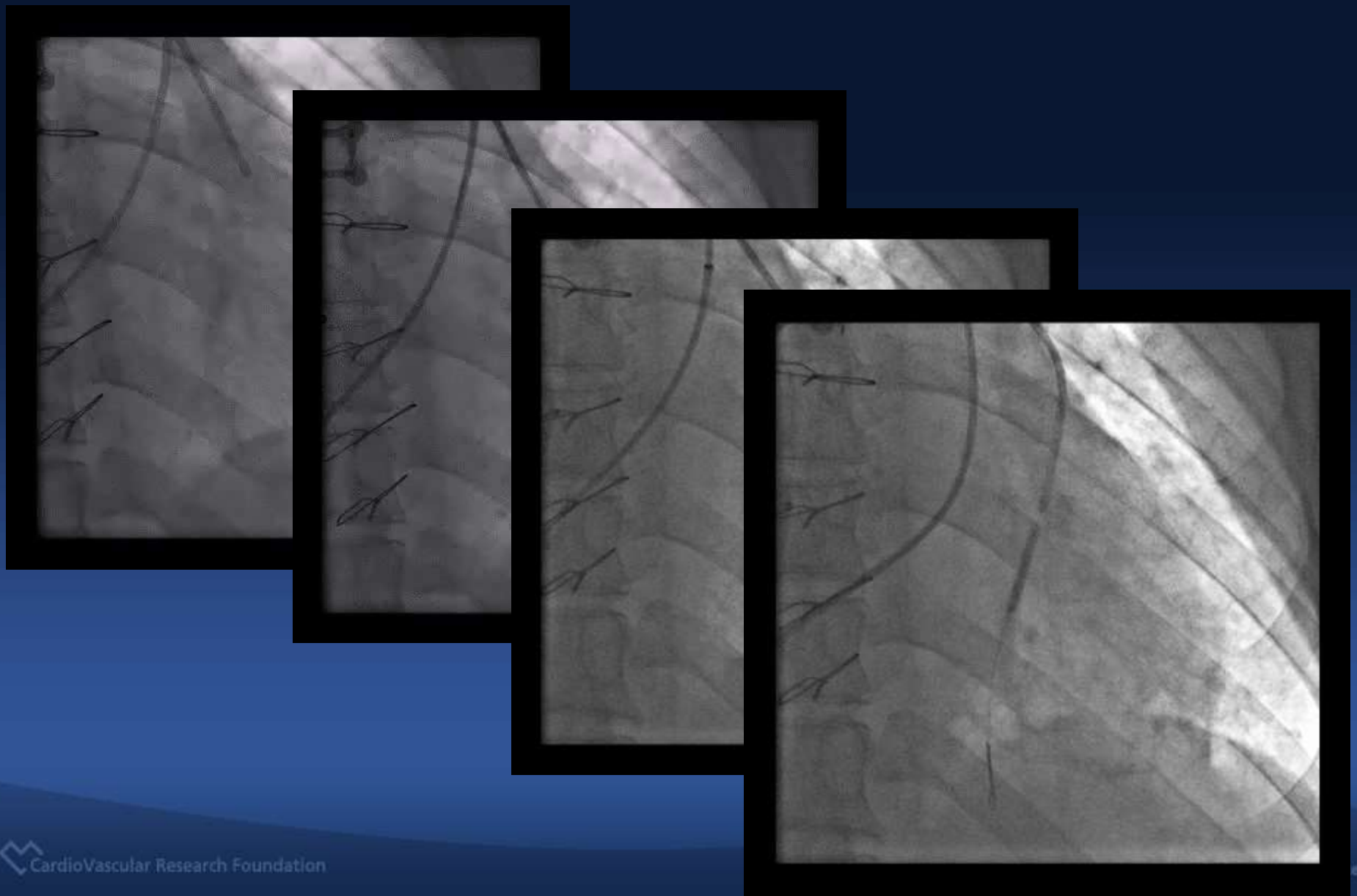
Lung inhalation scan



Lung perfusion scan



BPA



BPA - final

In Summary

- There is only low-/moderate-quality evidence from observational studies supporting the efficacy of BPA in improving both hemodynamics and exercise capacity.
- It is still unclear whether targeted medical therapy or BPA should be offered as first-line treatment for patients with inoperable CTEPH, since direct comparative studies are lacking.
- Further RCTs and prospective observational studies are needed in well-defined patients with inoperable CTEPH.