CTEPH Management in 2019:
Reflections and Prospects for Future Research

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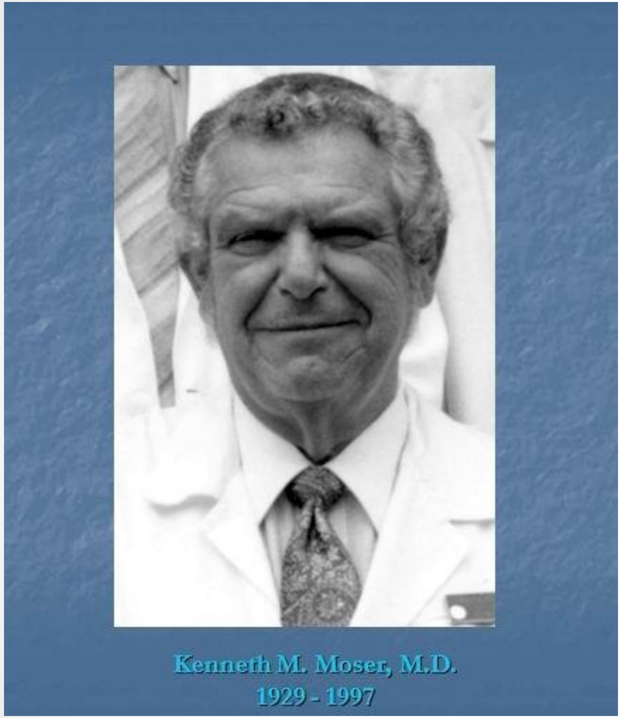
Disclosures

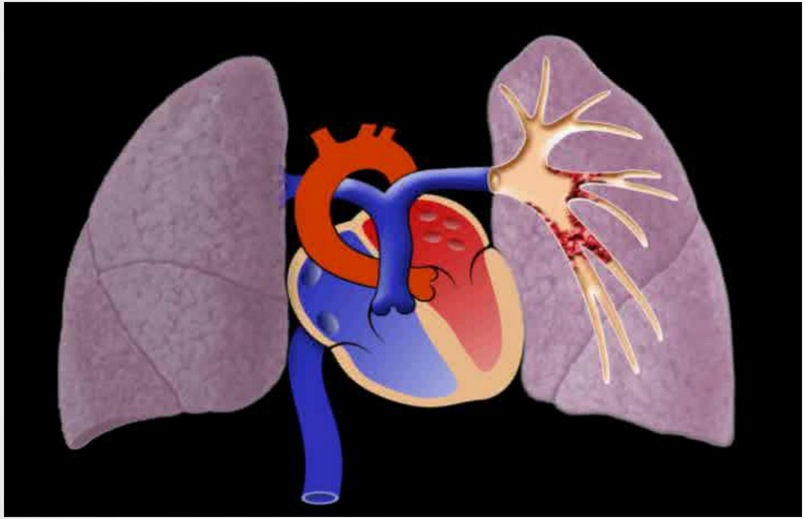
- Co-Investigator, National CTEPH Registry (Grant by Bayer)
- Advisory Board member, CTEPH Image Expert Panel (Bayer sponsored)



"The exploration of any new area inevitably produces as many questions as answers"

Kenneth M. Moser, MD 1965

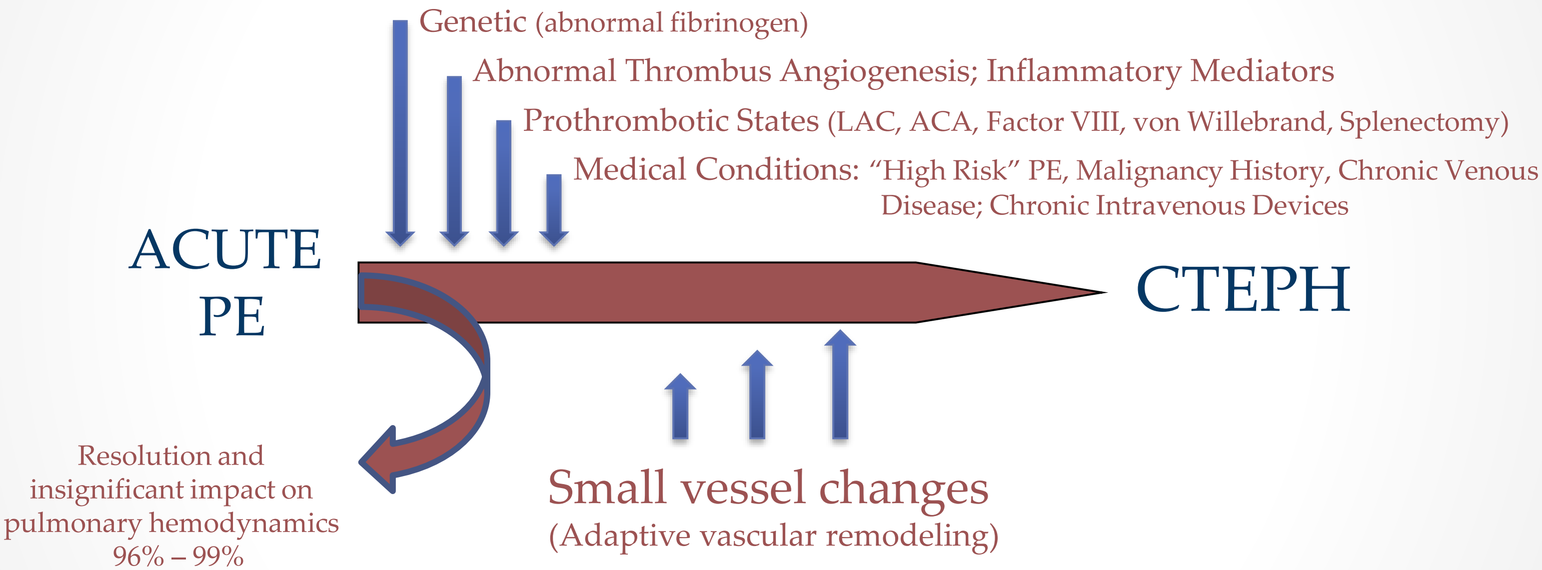
What is Chronic Thromboembolic Disease?



Video courtesy of Fabio Jatene MD

- Acute Pulmonary Embolus
- Incomplete resolution (>3 months AC)
- Loss of pulmonary vascular bed
- Progressive pulmonary hypertension (mean PA >25)
- Right heart failure

Natural history of CTEPH

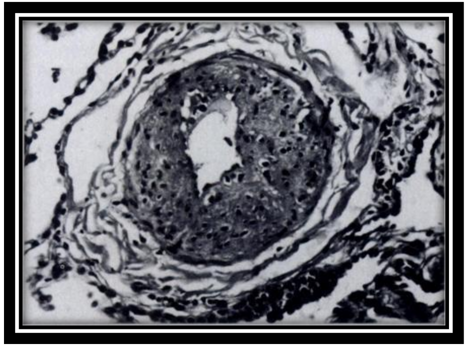


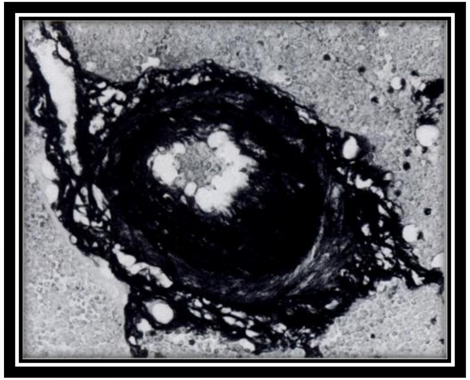
ACA, anticardiolipin antibodies; CTEPH, chronic thromboembolic pulmonary hypertension; LAC; lupus anticoagulant; PE, pulmonary embolism; TE, thromboembolic.

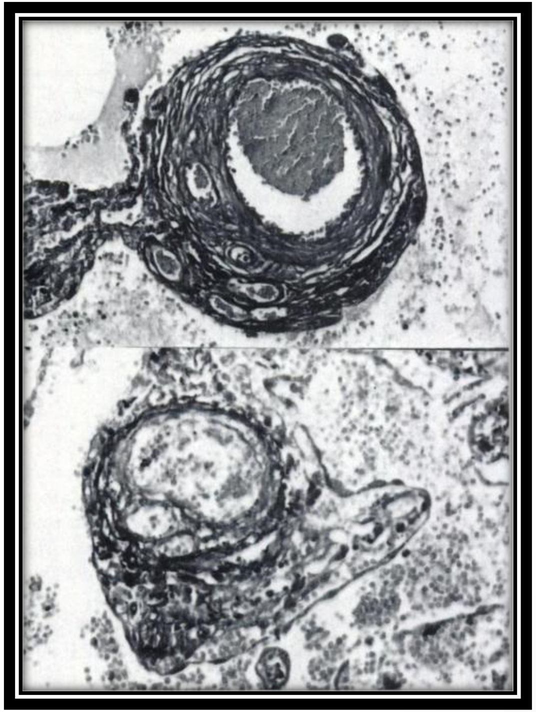
Lang IM et al. Eur Respir J 2013;41:462–8.

Small Vessel disease in CTEPH

Moser, Bloor *Chest* 1993; 103:685-692







Remaining Questions

- Transition to a “chronic clot”

  Genetic background, Inflammation, Thrombosis abnormalities

- The development of a small vessel disease

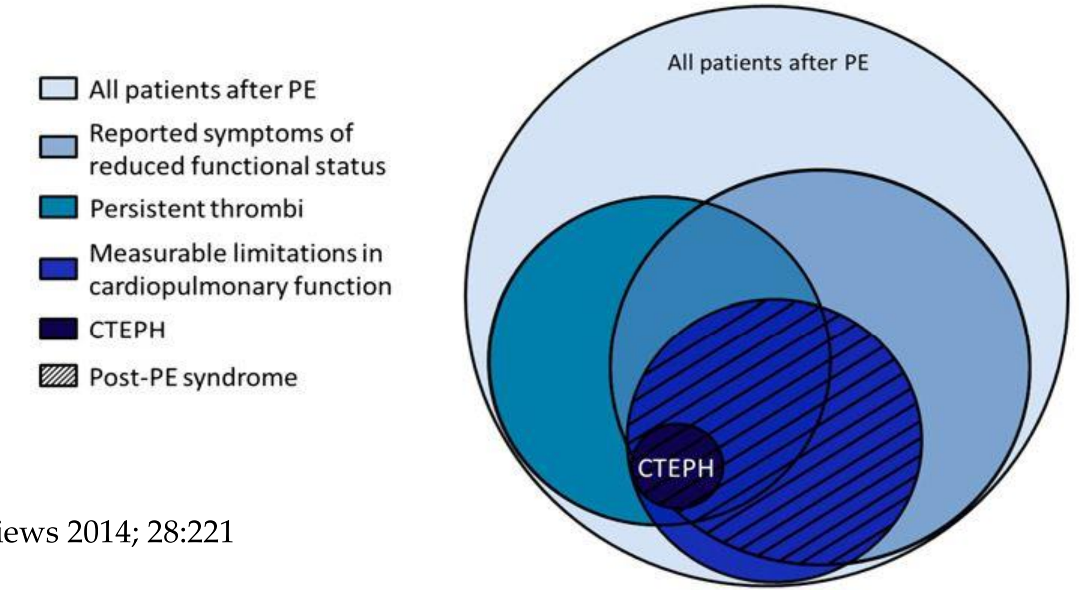
  Mediator or Hemodynamic driven

How common is CTEPH in China?

- Yang et al. J Thorac Dis 2015
  614 patients (median FU 3.3 years): 1.6% at 2 years, 1.7% at 3 years
- Xi et al. Chin Circ 2016
  214 patients (avg 31 months FU): 7.5%
- Xu et al. Chin J Geriatr 2016
  129 patients (median FU 26 months): 6.29%
- Yu et al. Clin Resp J 2018 (Xijing Hospital)
  239 patients (median FU 32.6 years): 9.4% following acute PE
- Zhang et al. J Thorac Dis 2018 (meta-analysis)
  Fifteen studies (3 from China): 4.46% in China compared to 2.82% from Europe
  (Previous/recurrent PE, previous VTE, idiopathic PE and Right heart dysfunction)

Post PE Syndrome

Spectrum of disease from Acute to Chronic



Klok et al. Blood Reviews 2014; 28:221

Remaining Questions

- Transition to a “chronic clot”
  - Genetic background, Inflammation, Thrombosis abnormalities
- The development of a small vessel disease
  - Mediator or Hemodynamic driven
- What is the true incidence of CTED and CTEPH?

Diagnosis of CTEPH

Evaluation for CTEPH

Disease Suspicion

1) Acute PE patients with persistent CP symptoms after 3 months of anticoagulation
2) ALL patients with pulmonary hypertension
3) Unexplained exertional dyspnea with or without history of thromboembolic event

Screening for CTEPH

Echocardiogram: detection of PH/RV size and function

+

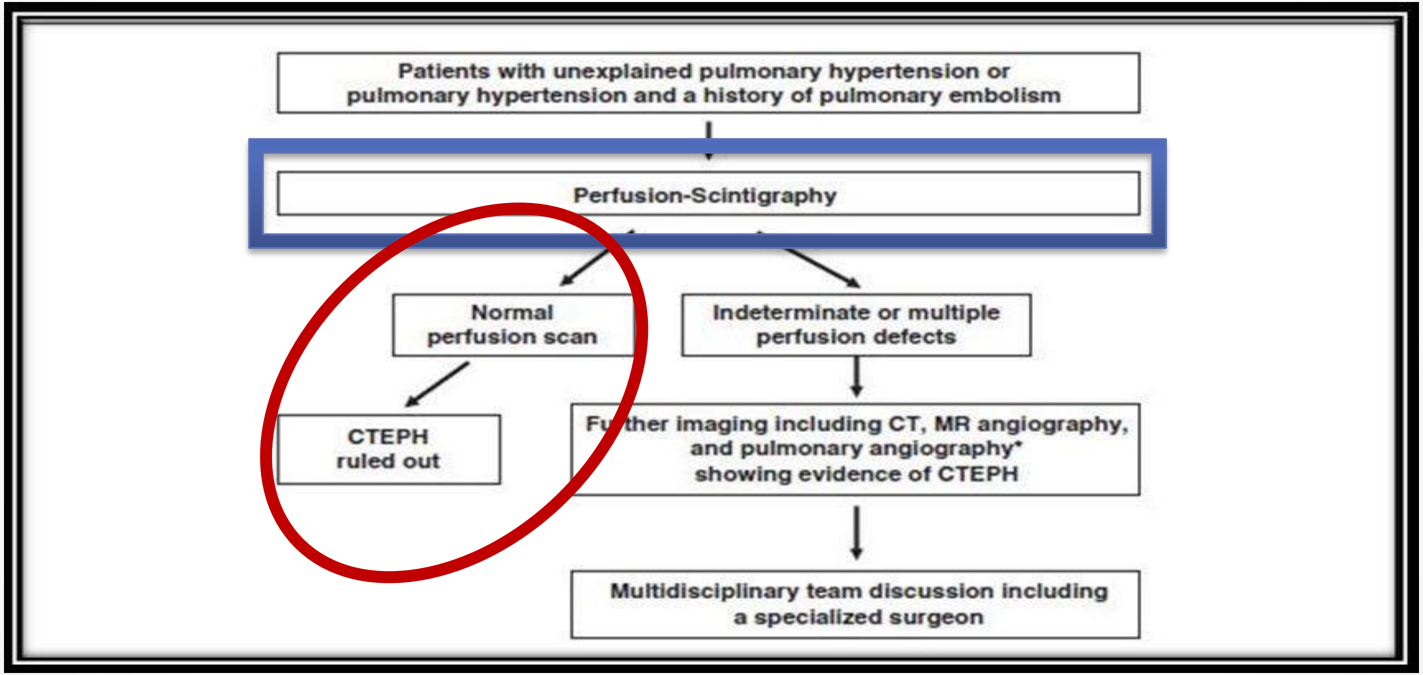
Lung V/Q Scan: detection of perfusion defects

Confirming CTEPH

CT Angiography
Pulmonary Angiography
MRA/CMR

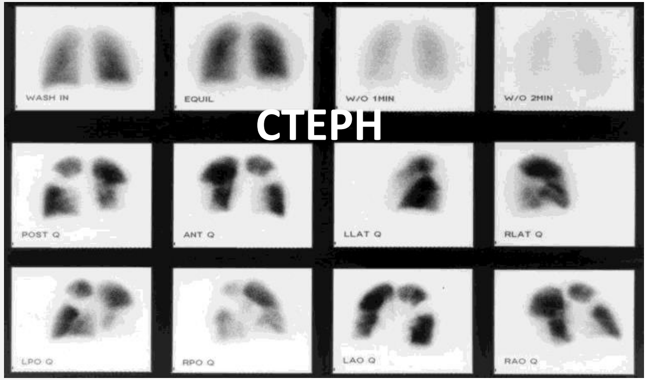
→ **CTEPH Diagnosis**
CTE Location

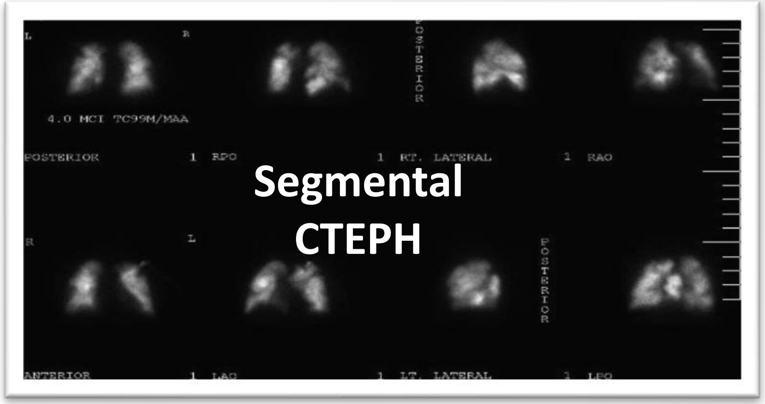
Diagnostic Approach to Patients with suspected CTE Disease

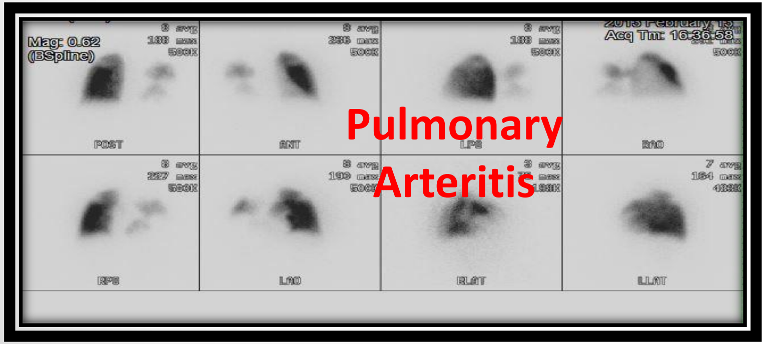


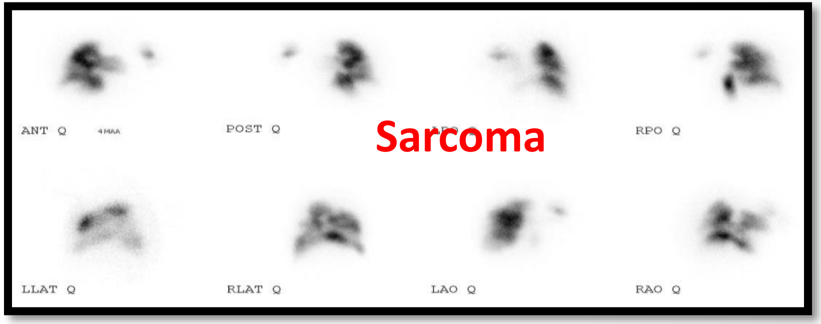
Hoeper et al. Am Coll Cardiol 2009; 54:S85-S96

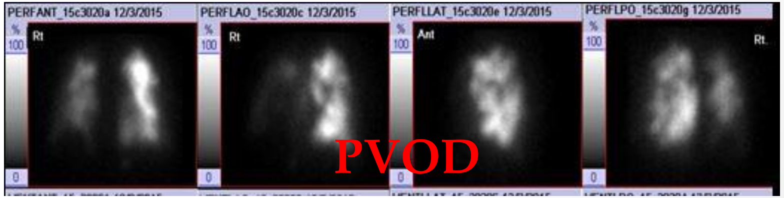
Perfusion Scans



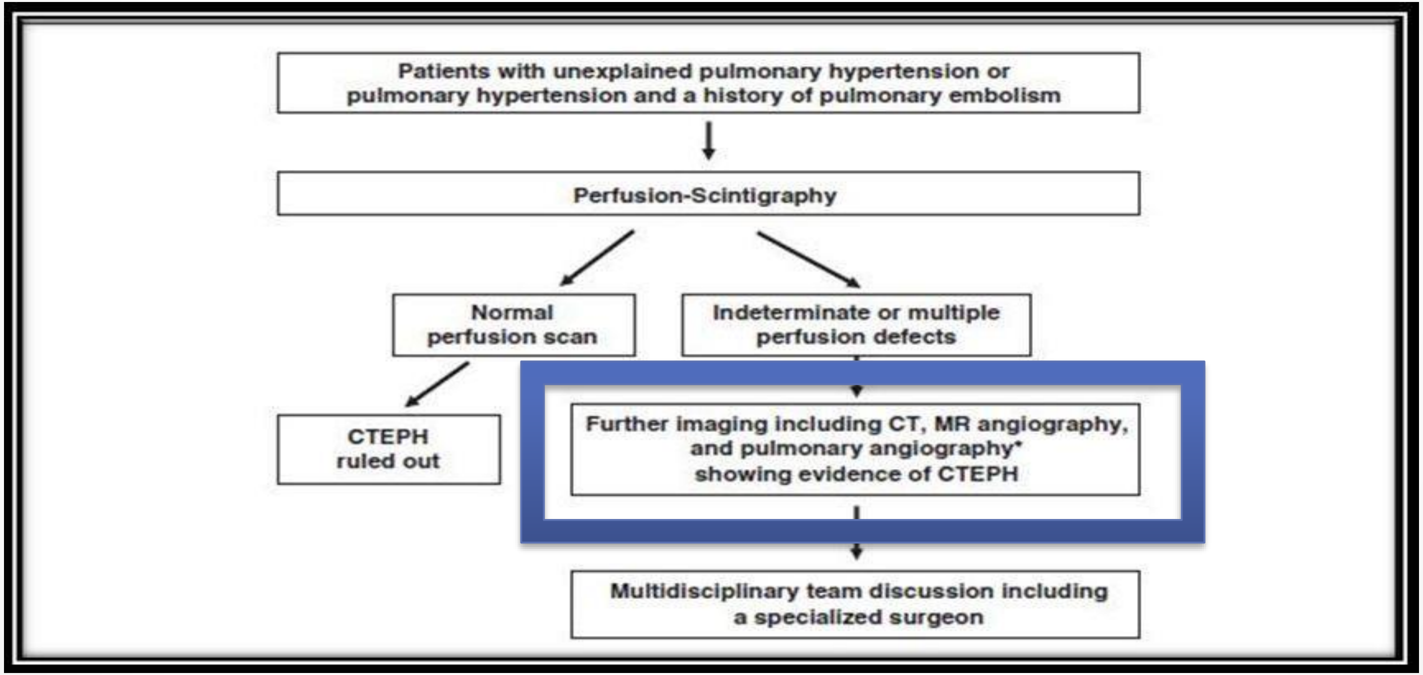








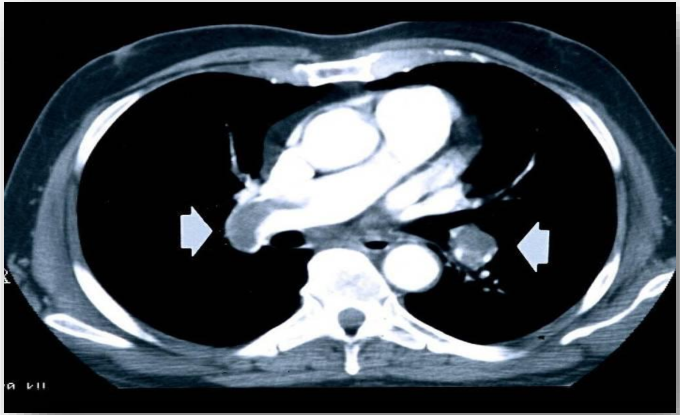
Diagnostic Approach to Patients with suspected CTE Disease



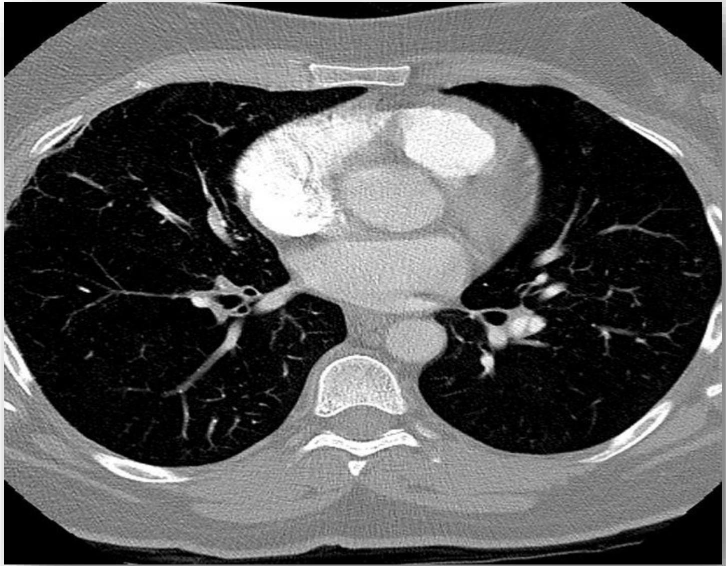
Hoeper et al. Am Coll Cardiol 2009; 54:S85-S96

CTEPH: CTA Findings

Eccentric thrombus



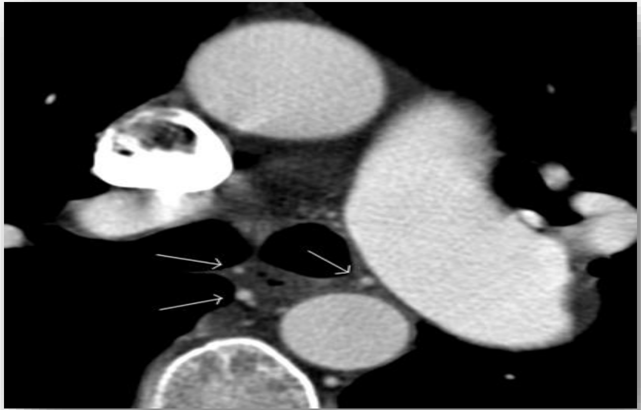
Vessel attentuation, web



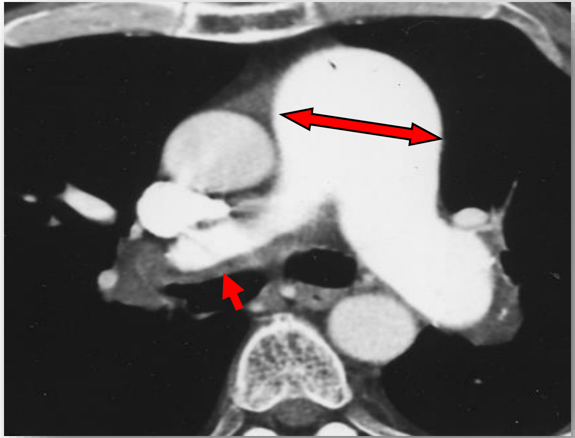
Lining thrombus and web

CTEPH: CTA Findings

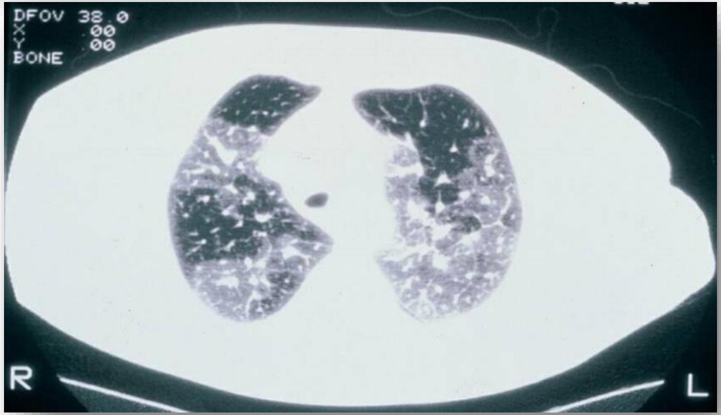
Bronchial arterial collateral vessels



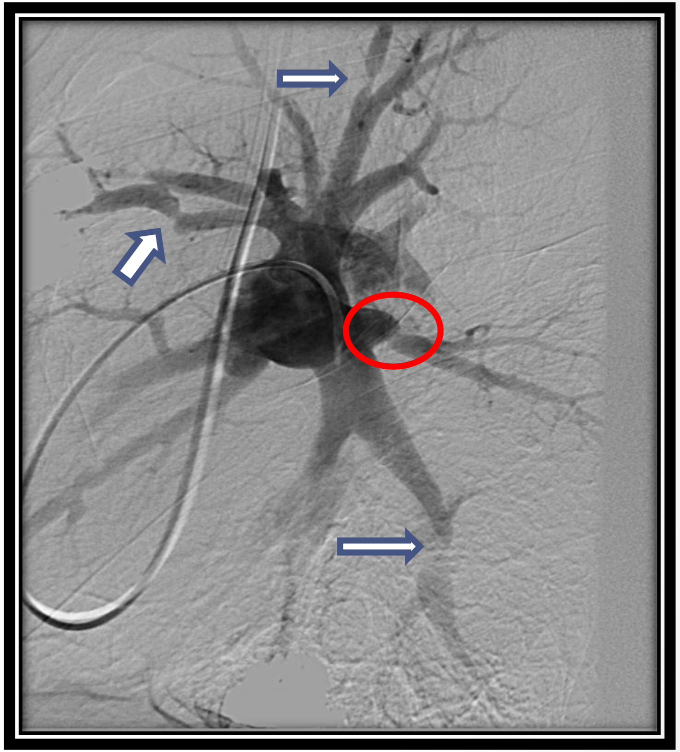
Lining thrombus, Enlarged main PA (PH)



Mosaic Perfusion



CTEPH: Pulmonary Angiogram



CTEPH Pulmonary Angiogram

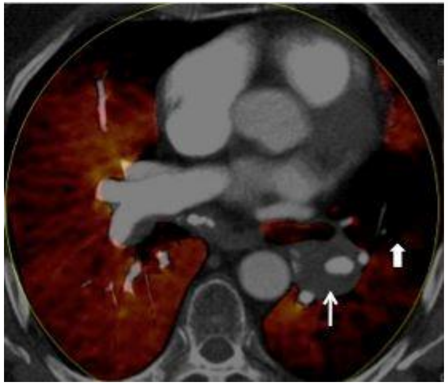
POST PTE:
CVP 7
PAp 37/12 (21)
CO 5.3 l/min
PVR 211 dyn-s/cm-5

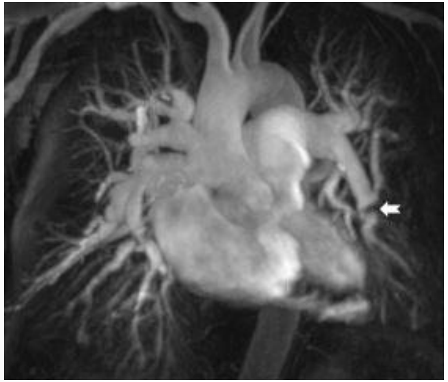
Preop PVR 1752 dyn-s/cm-5

Dual Energy CT & MRI

Dual Energy CT

➢ Same angiographic assessment as standard CT but also provides functional impact by assessing parenchymal perfusion





MRI /CMR

➢To evaluate hemodynamics/ RV function and response to therapy

➢To evaluate clot burden with MRA angiogram and assess functional significance by perfusion

Remaining Questions

- Transition to a “chronic clot”
  - Genetic background, Inflammation, Thrombosis abnormalities
- The development of a small vessel disease
  - Mediator or Hemodynamic driven
- What is the true incidence of CTED and CTEPH?
- Are there more accurate tests to detect the disease?

PH Medical Therapy for Inoperable/Non-surgical CTEPH

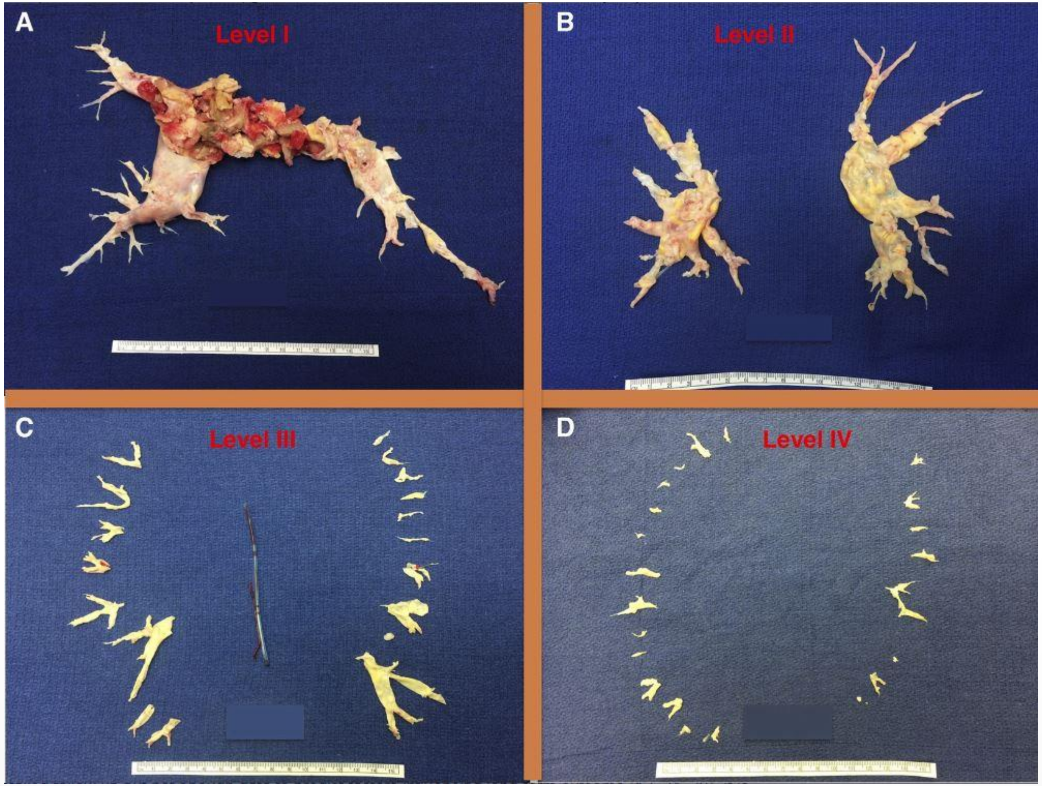
Pulmonary Thromboendarterectomy

Balloon Pulmonary Angioplasty

CTEPH: Surgical Approach

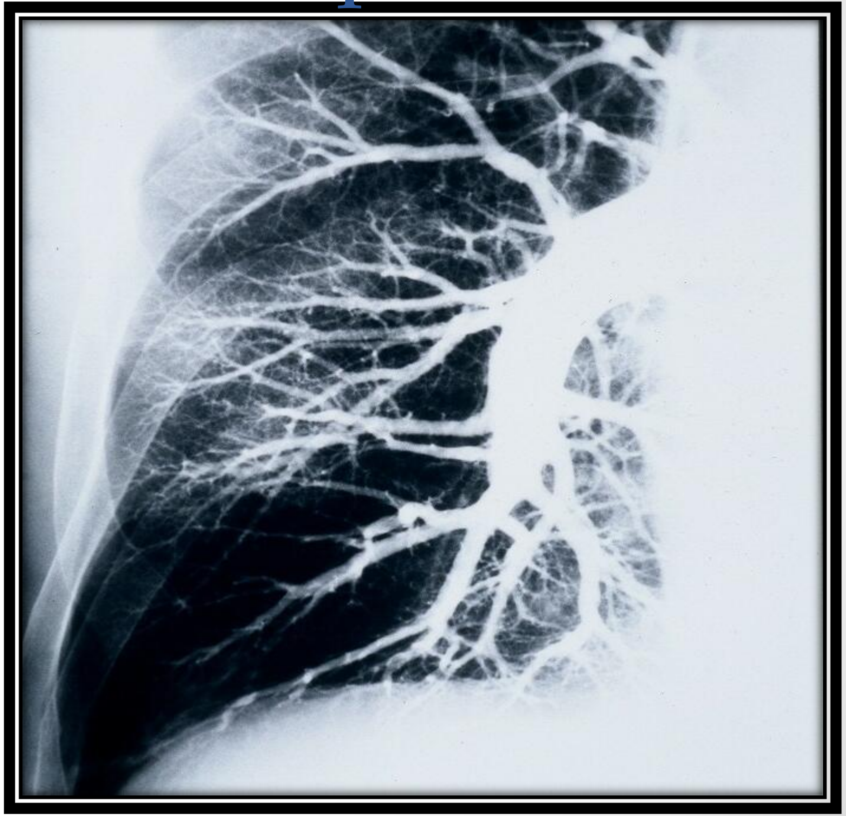
- Median Sternotomy (not thoracotomy)
- Cardiopulmonary bypass
- Deep hypothermia (18-20°) Circulatory arrest
- True endarterectomy Not embolectomy

UCSD Surgical Classification

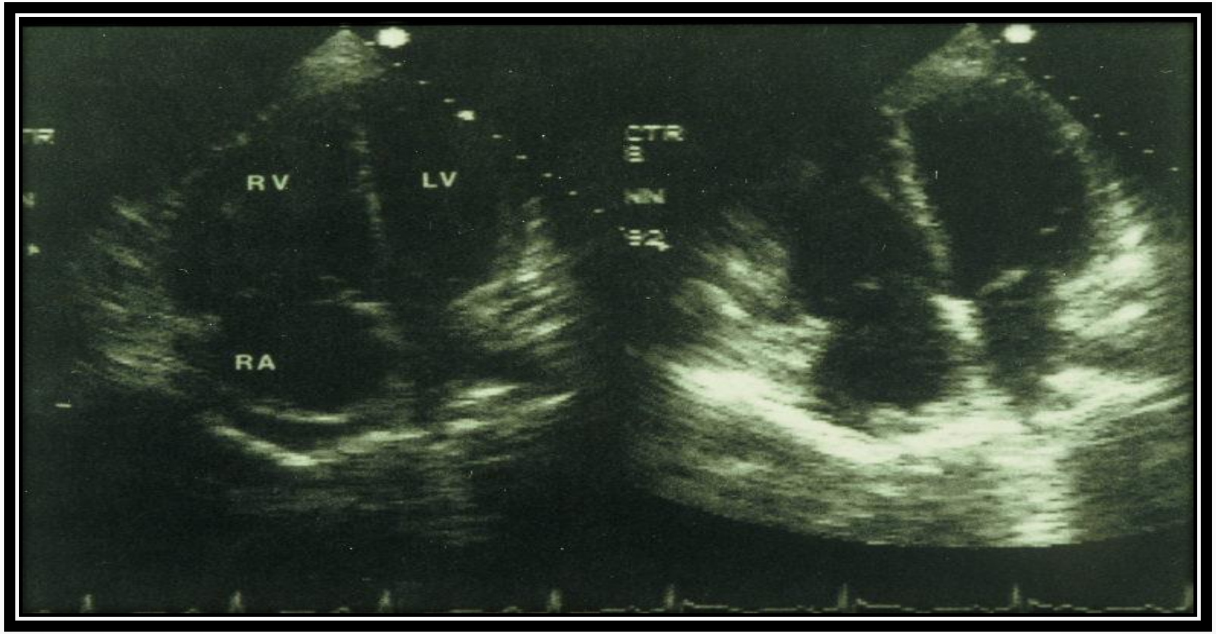


Preoperative

Postoperative



Perioperative Echocardiogram



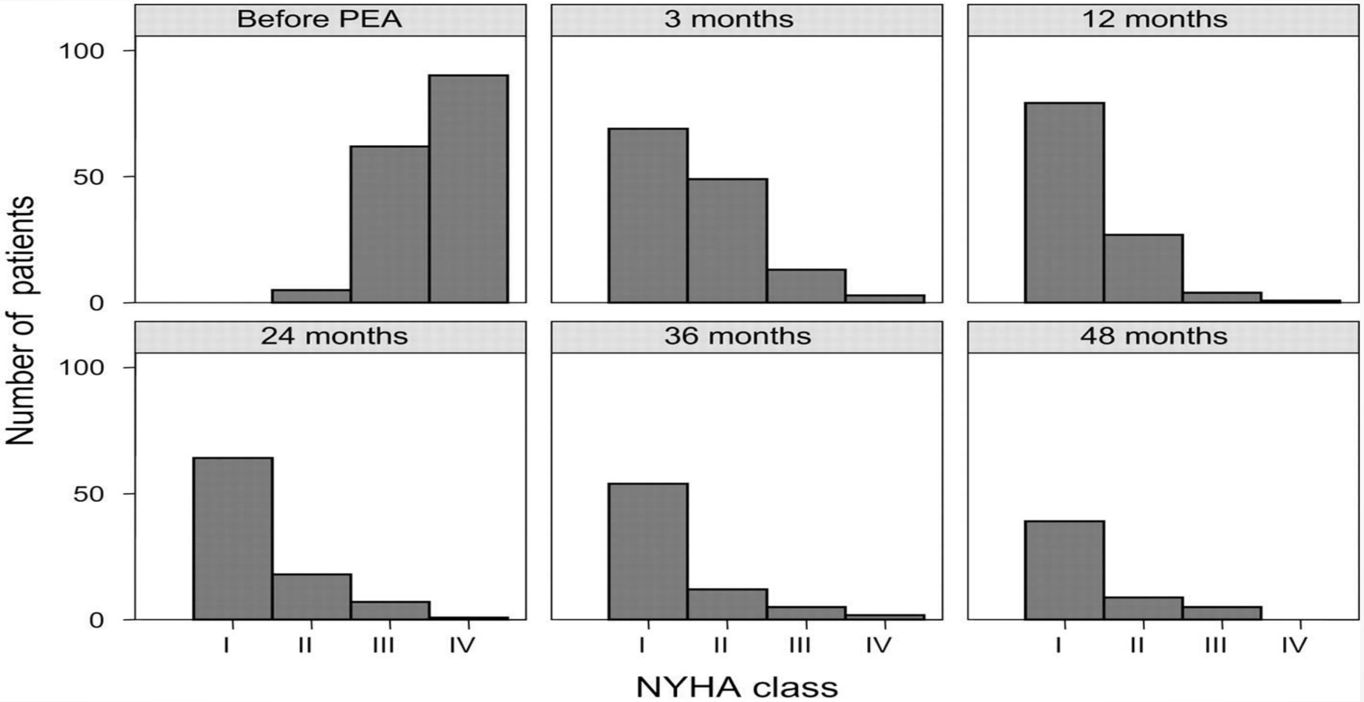
PTE: Postoperative Outcome

	In-hospital nonsurvivors (n = 18)	In-hospital survivors (n = 368)	1-y nonsurvivors (n = 27)	1-y survivors (n = 359)
Time until PEA (y)				
From symptoms	1.1 (0.7–15.6) n = 15	1.6 (0.1–36.7) n = 357	1.2 (0.7–15.6) n = 24	1.5 (0.1–36.7) n = 348
From last pulmonary embolism	5.0 (0.2–29.2) n = 8	1.2 (0.0–33.8) n = 257	3.0 (0.2–29.2) n = 14	1.2 (0.0–33.8) n = 251
Diagnosis characteristics				
6MWD (m)	290 (110–500) n = 15	350 (20–700) n = 321	280 (50–500) n = 23	351 (20–700) n = 313
mPAP (mm Hg)*	52 (46–75) n = 18	48 (17–80) n = 364	51 (31–75) n =27	48 (17–80) n = 355
PVR (dyn.s.cm^{-5})†	1091 (416–2682) n = 15	712 (97–2880) n = 325	905 (320–2682) n = 24	715 (97–2880) n = 316
Peri/postoperative characteristics				
Duration of circulatory arrest (min)	42 (10–87) n = 18	35 (0–146) n = 360	41 (10–87) n = 25	35 (0–146) n = 353
PVR at the end of intensive care (dyn.s.cm^{-5})	400 (191–1432) n = 11	245 (32–1440) n = 269	260 (164–1432) n = 19	245 (32–1440) n = 261

6MWD, 6-minute walk distance; *mPAP*, mean pulmonary artery pressure; *PEA*, pulmonary endarterectomy; *PVR*, pulmonary vascular resistance. Values are expressed as median with range, n. See text for ORs. *mPAP: 9 values < 25 mm Hg; 3 values > 75 mm Hg. †PVR: 13 values < 200 dyn.s.cm^{-5}

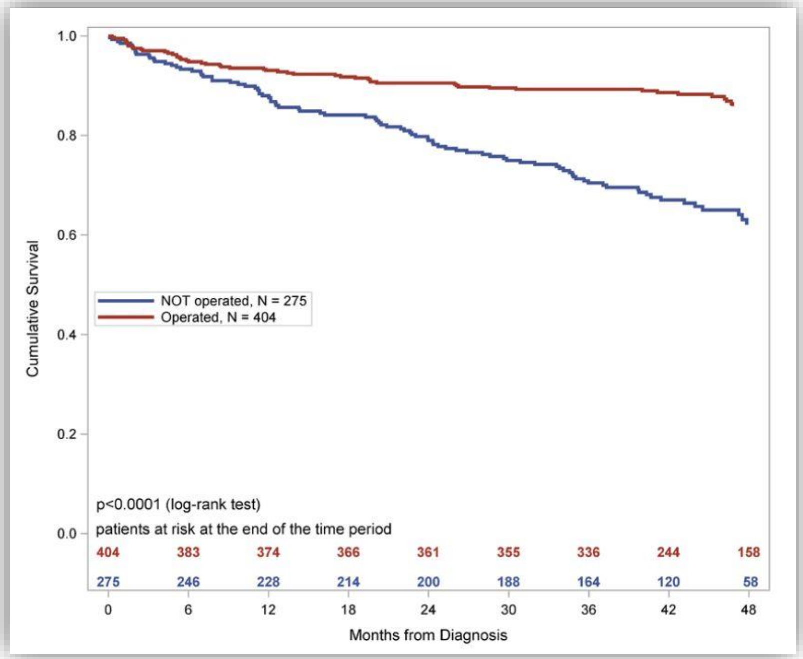
Mayer et al. J Thorac Cardiovasc Surg 2011; 141:702

NYHA FUNCTIONAL STATUS
157 PATIENTS UNDERGOING PTE: PAVIA



Corsic AG, et al. Am J Resp Crit Care Med 2008;178:419-424

PTE: Survival Benefit



Delcroix et al. Circulation 2016; 133:859

World Symposium Recommendations

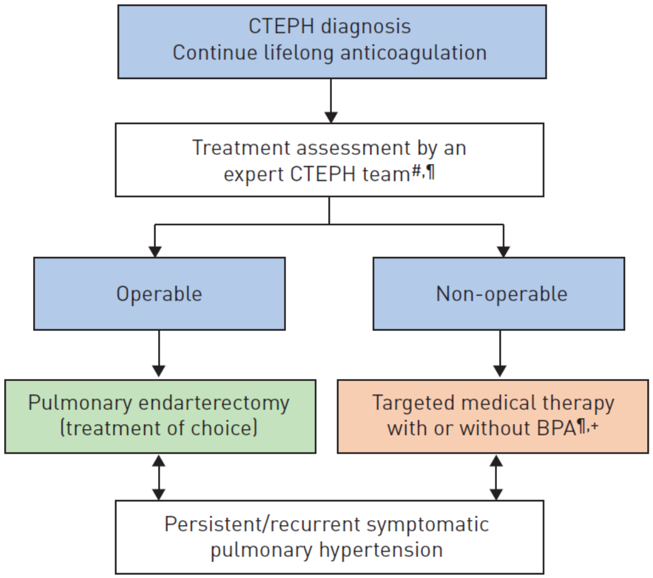


FIGURE 1 Chronic thromboembolic pulmonary hypertension (CTEPH): revised treatment algorithm. BPA: balloon pulmonary angioplasty. #: multidisciplinary: pulmonary endarterectomy surgeon, PH expert, BPA interventionist and radiologist; ¶: treatment assessment may differ depending on the level of expertise; +: BPA without medical therapy can be considered in selected cases.

Kim NH et al. Chronic thromboembolic pulmonary hypertension. Eur Resp J 2019; 53: 1801915

Non Surgical Treatments

Obstructive Component

Small Vessel Disease

CTEPH: RCTs of PH Targeted Medical Therapy

TABLE 5 Pulmonary hypertension-targeted medical therapy randomised controlled trials in chronic thromboembolic pulmonary hypertension

Trial [ref.]	Study drug	Duration weeks	Subjects n	NYHA FC	6MWD m	6MWD effect m	PVR baseline dyn·s·cm^{-5}	PVR effect %
BENEFIT [73]	Bosentan	16	157	II–IV	342±84	+2^{NS}	783 (95% CI 703–861)	−24
CHEST-1 [55]	Riociguat	16	261	II–IV	347±80	+46	787±422	−31
MERIT-1 [74]	Macitentan	16 (24#)	80	II–IV	352±81	+34	957±435	−16

Data are presented as n or mean±SD, unless otherwise stated. NYHA FC: New York Heart Association Functional Class; 6MWD: 6-min walk distance; PVR: pulmonary vascular resistance; NS: non-significant. All three trials had an adjudication process for operability. #: 6MWD measured at 24 weeks.

Kim NH et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2019; 53: 1801915.

The NEW ENGLAND JOURNAL of MEDICINE

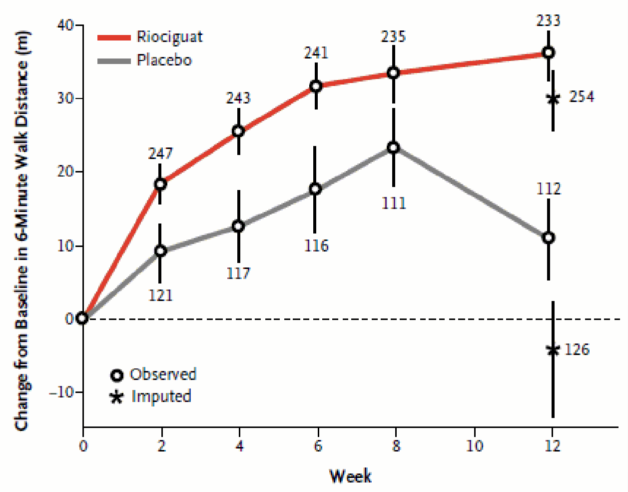
ORIGINAL ARTICLE

Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

Hossein-Ardeschir Ghofrani, M.D., Andrea M. D'Armini, M.D., Friedrich Grimminger, M.D., Marius M. Hoeper, M.D., Pavel Jansa, M.D., Nick H. Kim, M.D., Eckhard Mayer, M.D., Gerald Simonneau, M.D., Martin R. Wilkins, M.D., Arno Fritsch, Ph.D., Dieter Neuser, M.D., Gerrit Weimann, M.D., and Chen Wang, M.D., for the CHEST-1 Study Group*

- **Randomized, placebo-controlled study**
- **261 patients, 173 receiving drug**
- **16 weeks**

- Increase in 6 minute walk distance (mean difference 46 m)
- Reduction in PVR (mean difference -246 dyn-sec-cm-5)
- Improvements in WHO functional class, NT-proBNP



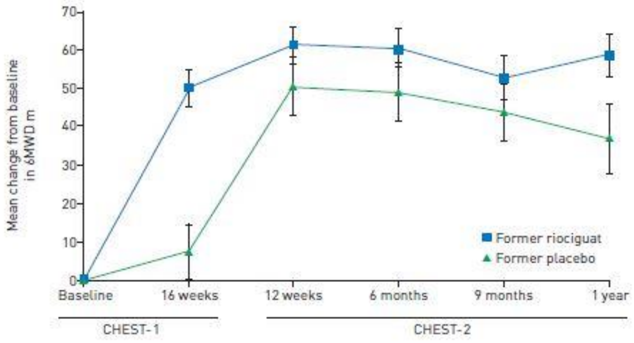
Ghofrani HA at al. N Engl J Med 2013; 369:319

Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2)

Gérald Simonneau[1], Andrea M. D'Armini[2], Hossein-Ardeschir Ghofrani[3,4], Friedrich Grimminger[3], Marius M. Hoeper[5], Pavel Jansa[6], Nick H. Kim[7], Chen Wang[8], Martin Wilkins[9], Arno Fritsch[10], Neil Davie[10], Pablo Colorado[11] and Eckhard Mayer[12]

Improvements in 6MWD and FC observed in CHEST-1 persisted at a year in this extension study (237 enrolled patients)

- **6MWD** changed by +51 ± 61 m (N=172) vs CHEST-1 baseline
- **Functional class**: (improved/stable/worse) in 47/50/3% of patients (N=176) vs CHEST-1 baseline
- **Safety profile** similar to CHEST-1



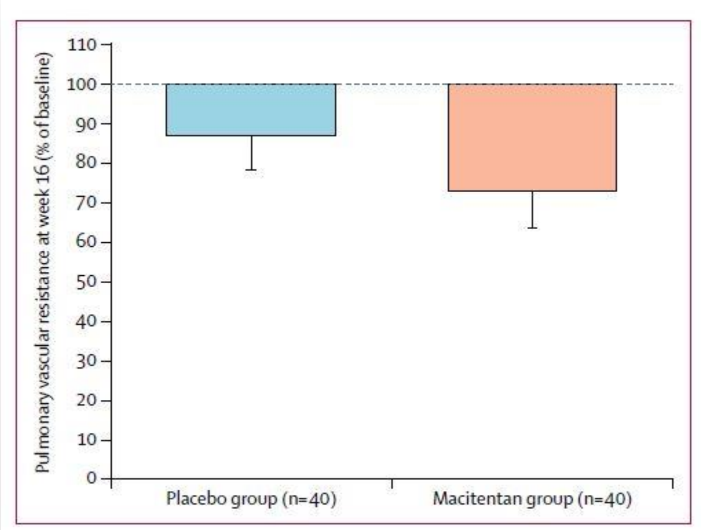
	Baseline	16 weeks	12 weeks	6 months	9 months	1 year
Mean 6MWD absolute values m						
Former riociguat	345	396	406	406	400	411
Placebo	360	368	414	411	408	405
Patients n						
Former riociguat	155	154	145	143	143	114
Placebo	82	81	75	75	72	58

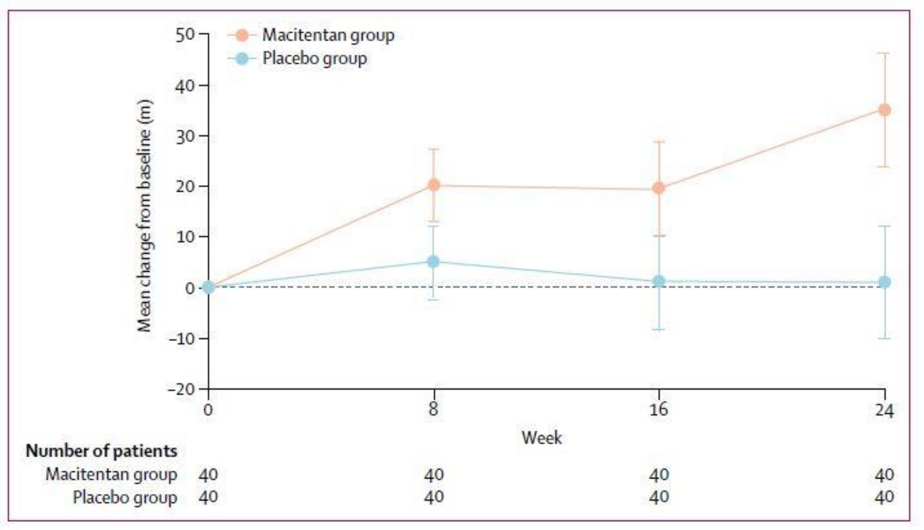
Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study

Prof Hossein-Ardeschir Ghofrani, MD, Prof Gérald Simonneau, MD, Prof Andrea M D'Armini, MD, Prof Peter Fedullo, MD, Luke S Howard, DPhil, Xavier Jaïs, MD, David P Jenkins, MD, Prof Zhi-Cheng Jing, MD, Prof Michael M Madani, MD, Nicolas Martin, MSc, Prof Eckhard Mayer, MD, Kelly Papadakis, MD, Dominik Richard, DVM, Prof Nick H Kim, MD on behalf of the MERIT study investigators†

Lancet Respir Med 2017 Sep 8

N=80 (40 per arm, 40%/38% treatment naïve); 16 weeks





Treatment: PVR 929 to 723 d.s.cm^{-5}
Control: PVR 984 to 899 d.s.cm^{-5}

Treatment: 6MWD 355 vs 388 m
Control: 6MWD 351 vs 352 m

CTEPH: *Balloon Pulmonary Angioplasty*

Percutaneous Transluminal Pulmonary Angioplasty Markedly Improves Pulmonary Hemodynamics and Long-Term Prognosis in Patients With Chronic Thromboembolic Pulmonary Hypertension

Koichiro Sugimura, MD, PhD; Yoshihiro Fukumoto, MD, PhD; Kimio Satoh, MD, PhD;

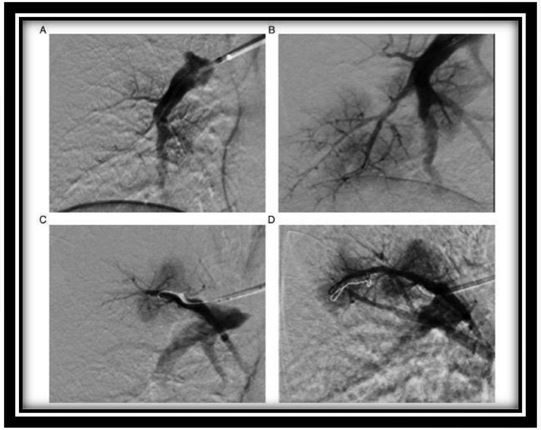
Pulmonary Vascular Disease

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

Original Article

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



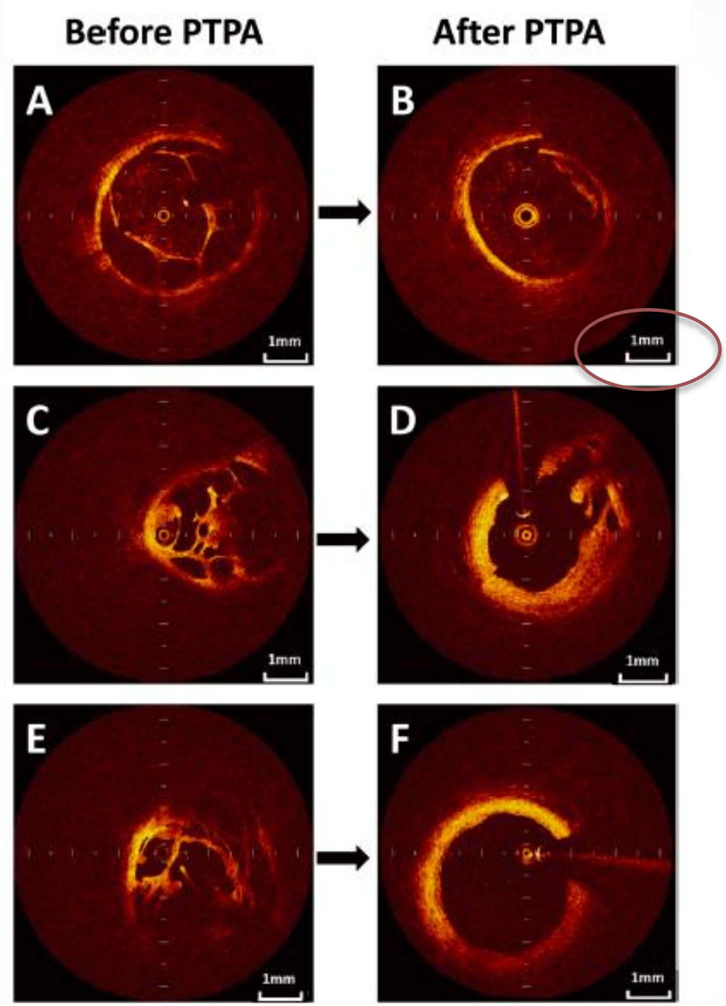
Heart 2013; 99:1415

ORIGINAL ARTICLE

Balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension

Arne K Andreassen,[1] Asgrimur Ragnarsson,[1] Einar Gude,[1] Odd Geiran,[2] Rune Andersen[3]

Optical Coherence Tomography (OCT)



Sugimura K, et al. *Circ J.* 2012

BPA: Angiographic Lesions

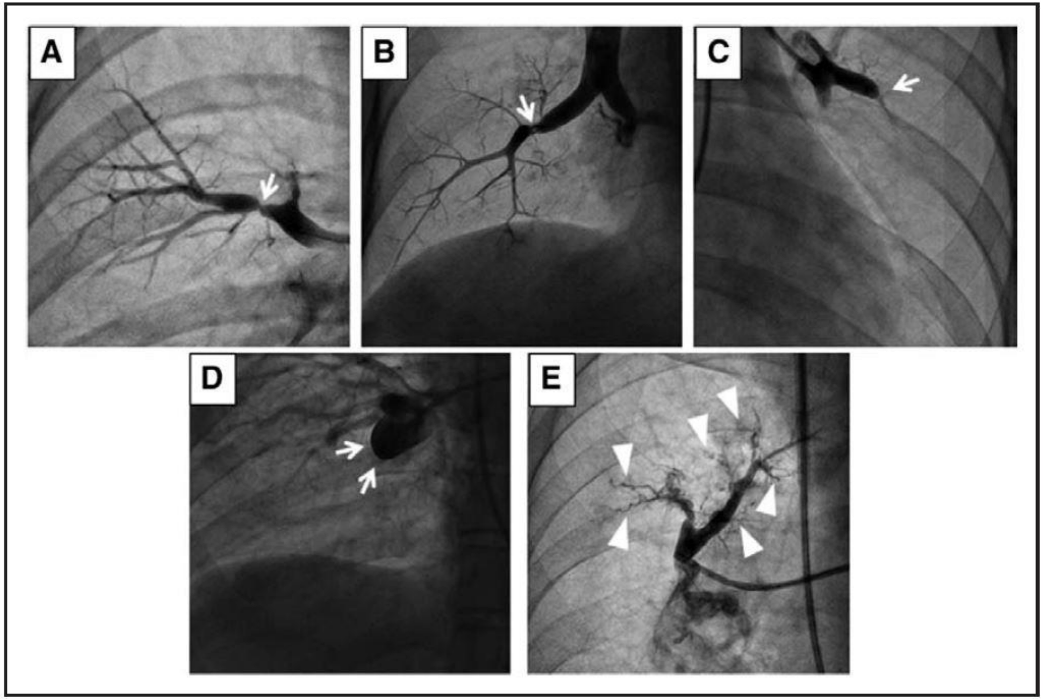


Figure 1. Angiographic classification of lesion morphology based on the lesion opacity and the blood flow distal to the lesion. **A**, Ring-like stenosis lesion. **B**, Web lesion. **C**, Subtotal lesion. **D**, Total occlusion lesion. **E**, Tortuous lesion. Type A–D lesions are located proximal to the subsegmental pulmonary artery, namely, the segmental and subsegmental arteries. Type E lesions are located distal to the subsegmental artery.

Kawakami et al. Circ Cardiovasc Interv 2016;9:e003318

BPA Studies

Table 1. Recent studies of balloon pulmonary angioplasty

	Sugimura *et al.* [10]	Kataoka *et al.* [11]	Mizoguchi *et al.* [12]	Andreassen *et al.* [13]	Fukui *et al.* [14■]	Inami *et al.* [15■]	Taniguchi *et al.* [16]
Publication year	2012	2012	2012	2013	2014	2014	2014
N	12	29	68	20	20	68	29
Follow-up, years	1	0.5	2.2	4	4	2	1
Severe reperfusion oedema, %	0	2	6	0	0	7	3.5
Pulmonary artery perforation, %	0	3.4	7	0	0	0.9	Not stated
Peri-procedural mortality, %	0	3.4	1.5	10	0	1.5	3.4

Table 2. Recent haemodynamic results from balloon pulmonary angioplasty

		PVR, $dyn/s/cm^{-5}$		
	n	**Before BPA**	**After BPA**	**BPA effect in PVR**
Sugimura *et al.* [10]	12	627 ± 236	310 ± 73	−54%
Mizoguchi *et al.* [12]	68	942 ± 367	327 ± 151	−65%
Andreassen *et al.* [13]	20	704 ± 320	472 ± 288	−33%
Fukui *et al.* [14■]	20	889 ± 365	490 ± 201	−45%
Taniguchi *et al.* [16]	29	763 ± 308	284 ± 128	−63%

Data are presented as mean ± standard deviation unless otherwise noted. BPA, balloon pulmonary angioplasty; PVR, pulmonary vascular resistance.

Ogo; Curr Opin Pulm Med 2015; 21:425

Balloon Pulmonary Angioplasty: Brenot et al Eur Resp J 2019; 53: 1802095

TABLE 2 Clinical and haemodynamic data before and after balloon pulmonary angioplasty

Variables	Total (n=154)			Initial period (n=75)			Recent period (n=79)			p-value#
	Before	p-value	After	Before	p-value	After	Before	p-value	After	
Characteristics										
NYHA FC % (I,II/III,IV)	35.3/64.7	<0.001	78.7/21.3	25.3/74.7	<0.001	65.3/34.7	44.9/55.1	<0.001	92.0/8.0	<0.001
6MWD m	396±120	<0.001	441±104	383±137	<0.001	434±119	407±103	<0.001	449±86	0.411
P_{aO_2} mmHg	65.0±9.0	<0.001	73.3±12.0	65.0±9.9	0.001	73.2±12.9	65.1±7.9	0.008	73.6±10.5	0.901
Haemodynamics										
Systolic PAP mmHg	75.7±17.0	<0.001	53.0±16.9	75.4±16.9	<0.001	57.4±18.2	75.9±17.2	<0.001	48.9±14.7	0.002
Diastolic PAP mmHg	24.2±7.0	<0.001	18.4±6.4	24.6±7.4	<0.001	20.0±6.8	23.9±6.6	<0.001	17.0±5.6	0.003
Mean PAP mmHg	43.9±9.5	<0.001	31.6±9.0	44.3±9.8	<0.001	33.8±9.8	43.6±9.1	<0.001	29.5±7.7	0.003
Mean RAP mmHg	8.1±3.8	<0.001	6.3±2.8	8.0±3.7	0.010	6.6±2.9	8.2±3.8	<0.001	6.0±2.7	0.149
PAWP mmHg	9.6±3.4	0.050	10.3±3.5	9.8±3.5	0.176	10.4±3.8	9.4±3.2	0.160	10.1±3.3	0.524
Cardiac output $L \cdot min^{-1}$	4.86±1.22	<0.001	5.56±1.35	4.88±1.27	<0.001	5.47±1.47	4.85±1.18	<0.001	5.65±1.23	0.400
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	2.68±0.60	<0.001	3.07±0.75	2.62±0.58	<0.001	2.96±0.80	2.73±0.62	<0.001	3.18±0.68	0.062
PVR $dyn \cdot s \cdot cm^{-5}$	604±226	<0.001	329±177	607±218	<0.001	371±188	601±236	<0.001	289±157	0.004
S_{vO_2} %	62.6±7.4	<0.001	67.9±7.3	62.9±7.5	<0.001	67.3±8.1	62.4±7.3	<0.001	68.5±6.4	0.353
Absolute change of mean PAP mmHg			−12.4±10.6			−10.5±10.4			−14.1±10.5	0.038
Decrease of mean PAP %			−26.1±21.3			−21.9±21.5			−30.1±20.4	0.017
Decrease of PVR %			−42.7±27.4			−36.5±29.1			−48.6±24.5	0.006

Data are presented as mean±SD, unless otherwise stated. NYHA FC: New York Heart Association functional class; 6MWD: 6-min walk distance; P_{aO_2}: arterial partial pressure of oxygen; PAP: pulmonary artery pressure; RAP: right atrial pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; S_{vO_2}: mixed venous oxygen saturation. #: comparison between initial and recent periods.

Long-term BPA Results: Aoki et al. Eur Heart J 2017; 38:3152

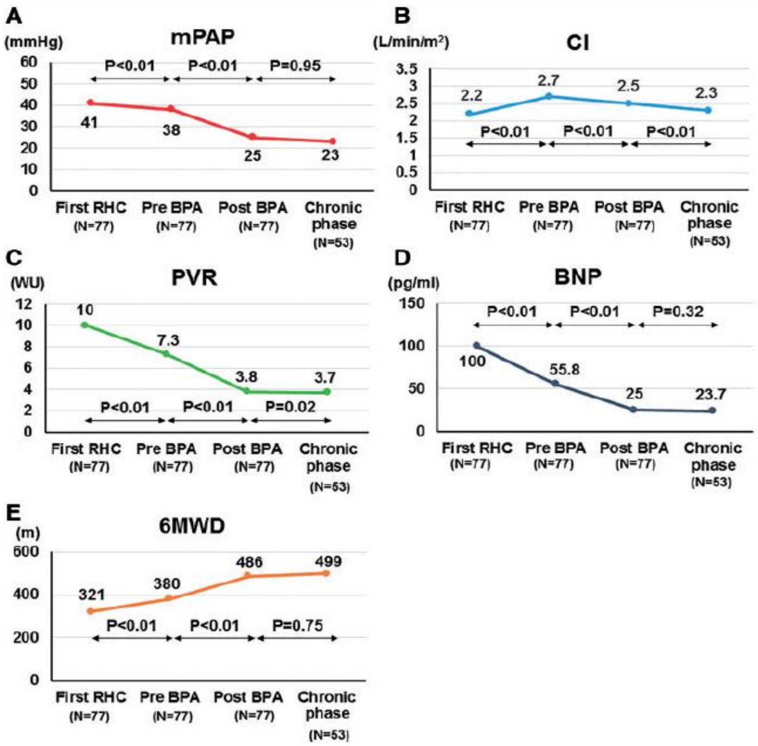


Figure 3 Changes in haemodynamics, exercise capacity, and BNP before and after balloon pulmonary angioplasty (BPA) therapy. (*A*) Mean pulmonary arterial pressure (mPAP). (*B*) Cardiac index (CI). (*C*) Pulmonary vascular resistance (PVR). (*D*) Brain natriuretic peptide (BNP). (*E*) 6-minute walk distance (6MWD). Haemodynamics, exercise capacity, and serum BNP levels were examined at the following four points; at first right heart catheterization (RHC) ($N = 77$), just before first BPA after medication ($N = 77$), at 6 months after last BPA ($N = 77$), and in the chronic phase (at the time of > 12 months after last BPA sessions, $N = 53$).

CTEPH: ***Balloon Pulmonary Angioplasty***

- Role in Rx CTEPH patients evolving
- Center experience
- Technically demanding
- Multiple sessions required
- Complication risks: reperfusion lung injury
  vessel injury/bleeding
- Long-term outcomes poorly defined
- Comparative studies unavailable

Remaining Questions

- Transition to a “chronic clot”
  - Genetic background, Inflammation, Thrombosis abnormalities
- The development of a small vessel disease
  - Mediator or Hemodynamic driven
- What is the true incidence of CTED and CTEPH?
- Are there more accurate tests to detect the disease?
- What is the optimal approach for those patients with inoperable disease?

Riociguat and BPA in Inoperable CTEPH: Wiedenroth et al. Pulm Circ 2018; 8:1

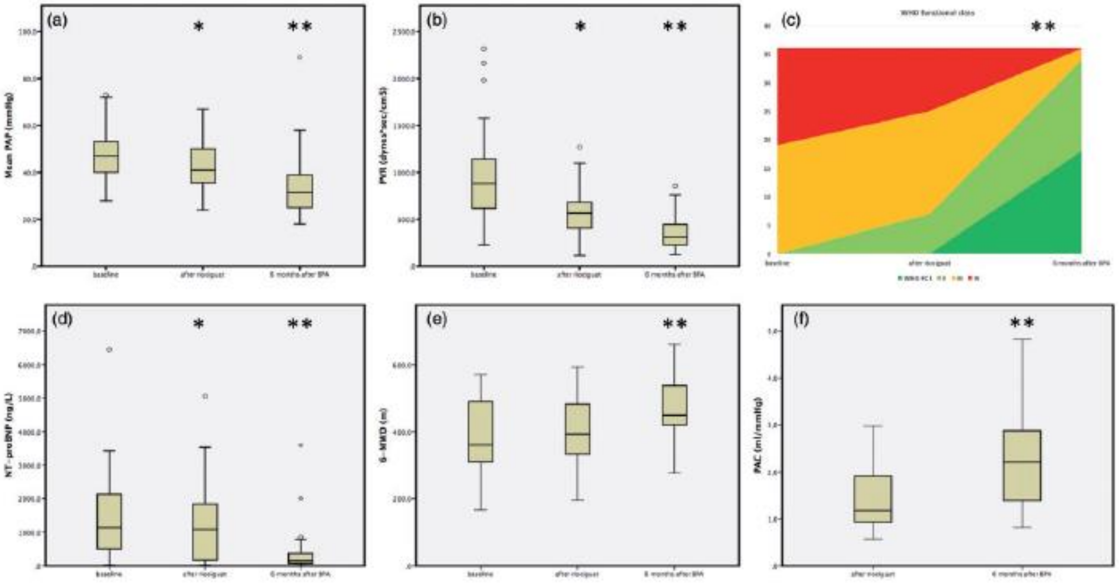


Fig. 3. Effects of riociguat and BPA on (a) mPAP, (b) PVR, (c) WHO FC given in mean values, (d) NT-proBNP, (e) 6MWD, and (f) PAC. The asterisk indicates the significance level (*P < 0.05; **P < 0.001).

Thank you for your kind attention

谢谢