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Multimodal Therapy for High-Risk CTEPH Patients

The Marie Lannelongue Hospital Experience

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Disclosures

No relevant conflicts of interest to disclose

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CTEPH: Disease Overview

Pathophysiology

Chronic thrombotic obstruction of pulmonary arteries

→ ↑ PVR → RV pressure overload → RV failure

Distinct from acute PE — fibrotic organized thrombus

VQ Scan: screening test to exclude CTEPH

CTPA: confirm CTEPH if +

RHC: confirm diag and assess severity

Treatment

- PEA – surgical gold standard (CPB + deep hypothermic circulatory arrest)

- BPA – percutaneous, distal/inoperable disease

- PHSP – pharmacotherapy (riociguat, bosentan…)

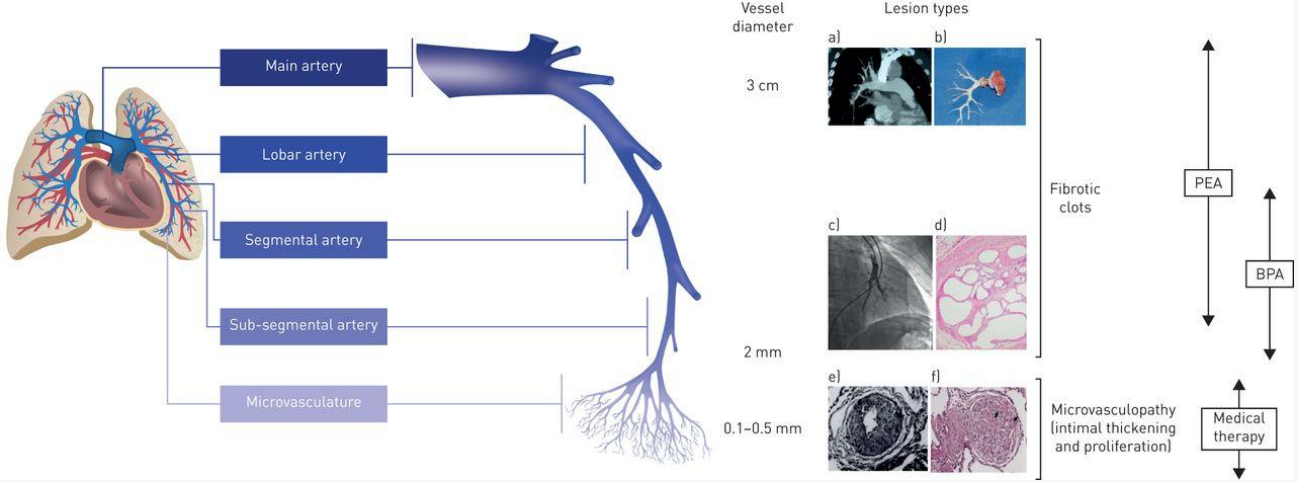
PEA: Outcomes & Limits

✔ Curative when complete
✔ ~2% mortality at expert centers
✔ Residual disease is common

⚠ Mortality ↑ with high PVR
⚠ Distal disease → worse outcomes
⚠ Asymmetric disease → challenging

⚠ **Mortality & morbidity after PEA are significantly higher in patients with severe hemodynamics, distal disease, and comorbidities**

CTEPH Treatments

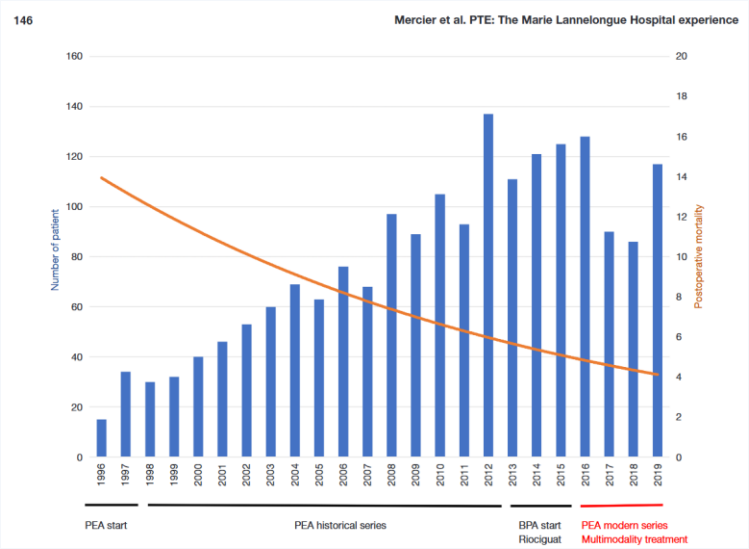




Madani MM et al, ERS 2017

⚠ **Disease level and patient background drives the treatment strategy**

PEA

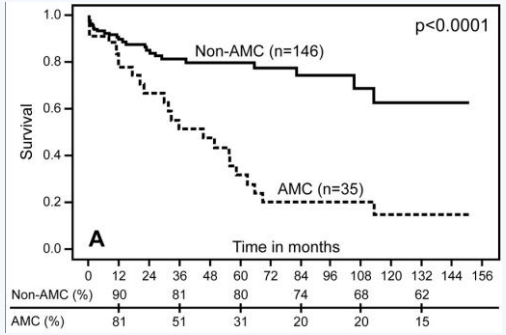


PEA Standard of care

- Expert center: >50case/years, mortality<5%
- 5 year OS >70%
- Post-operative mortality:
  - Hemodynamic impairment (↑ PVR)
  - Comorbidities
- Distal disease associated with longer DHCA time, and longer ICU Stay

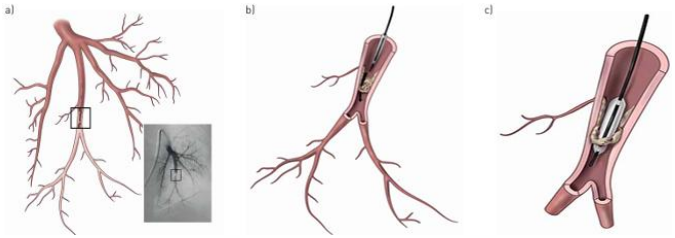
TABLE 3. Impact of specific parameters on in-hospital death and death at 1 year

		In-hospital deaths n (%)	Deaths at 1 year n (%)
PVR (dyn.s.cm^{-5}), n = 340			
<400	n = 48	0 (0%)*	1 (2.1%) NS
400–800	n = 141	4 (2.8%)*	8 (5.7%) NS
800–1200	n = 104	6 (5.8%) NS	9 (8.7%) NS
> 1200	n = 47	5 (10.6%)†	6 (12. 8%)†



Mercier, Annals Cardiothorac Surg 2020, D'Armini, JTCVS 2014, Mayer JTCVS 2011, Lang Circulation 2011, Fernandes JHLT 2023

BPA



BPA

- Approved for Surgically inaccessible patients/ Recurrent PH
- Good long term outcomes
- Less efficient with patient with proximal disease and comorbidities

	Distal disease $n = 378$			Proximal disease, ineligible for PEA[a] $n = 36$		
	Baseline	Last follow-up	*p* Value	Baseline	Last follow-up	*p* Value
NYHA, mean	3 ± 0.6	2 ± 0.7	<0.001	3 ± 0.6	2 ± 0.7	0.005
6MWD, m, mean	397 ± 117	441 ± 109	0.002	321 ± 127	388 ± 131	0.11
mPAP, mmHg, mean	44 ± 10	31 ± 9	<0.001	39 ± 9	31 ± 8	<0.001
PAOP, mmHg, mean	10 ± 3	11 ± 4	0.007	9 ± 5	12 ± 4	0.18
CO, L/min, mean	4.9 ± 1	5.7 ± 1	<0.001	5 ± 1	5.4 ± 2	0.27
CI, L/min/m^2, mean	2.7 ± 0.6	3 ± 0.6	<0.001	2.7 ± 0.4	2.9 ± 0.5	0.45
PVR, WU, mean	7.6 ± 3	3.8 ± 1	<0.001	6.5 ± 3	4.0 ± 3	<0.001
PTR, WU, mean	9.7 ± 4	5.8 ± 2	<0.001	8.4 ± 3	6.5 ± 4	<0.001
NT pro-BNP, ng/L, mean	619 ± 86	268 ± 63	<0.001	371 ± 88	289 ± 124	0.17

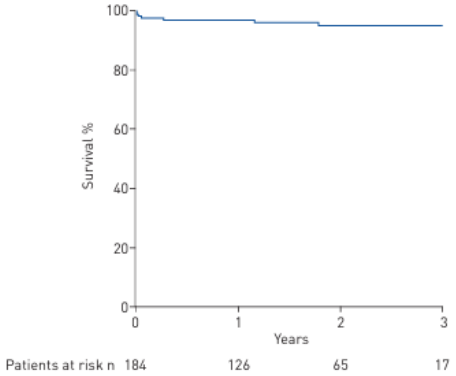
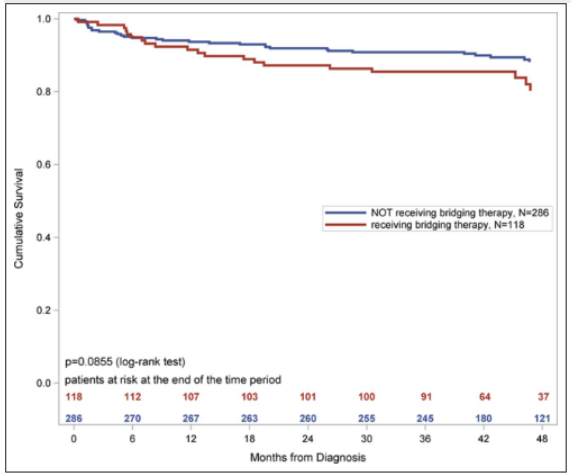


FIGURE 2 Survival from first balloon pulmonary angioplasty session (n=184).

Lang et al, ERR 2017, Brenot et al ERJ 2019, Issard et al Pulm Circ 2024

PHSP

	Bosentan (Δ), n = 8	No Bosentan (Δ), n = 7	*P* Value[a]
Hemodynamics			
mPAP, mm Hg	−11 (−17–11)[b]	5 (−6–21)	0.011
CI, L/min^{-1}/m^{-2}	0.18 (−0.7–0.6)	0.16 (−0.8–0.4)	0.418
TPR, dynes/s/cm^{-5}	−191 (−598–181)	46 (−316–698)	0.132
mRAP, mm Hg	−8 (−12–3)	0 (−8–6)	0.091
Functional capacity			
6MWD, m	20 (3–88)[b]	−4 (−40–40)	0.008



PHSP

- Patient not candidate for PEA
- Recurrent/residual PH
- role of PH therapy before PEA is debated
  - Decrease preoperative hemodynamic
  - Does not improve post-operative hemodynamic
  - Increase postoperative morbi-mortality
- PH therapy before BPA decrease post-procedural outcomes
- RACE Study Riociguat + BPA vs Riociguat alone (PVR -40% from baseline and Treatment related event 42% to 9%)

Jais et al, Lancet 2022, Surie et al Clin Cardiol 2013, Delcroix et al Circulation 2016

The High-Risk Patient: A Surgical Challenge

High Operative Risk Criteria

- PVR > 6 Wood Units (WU)
- Age > 75 years
- Severe comorbidities
- Proximal obstruction one side
  + Distal obstruction contralateral

Clinical Impact

→ ↑ post-PEA mortality with high PVR (multiple registries)

→ Longer circulatory arrest for distal disease → ↑ complications

→ PEA for distal disease: challenging even at high-volume centers

→ Optimal strategy undefined across international expert centers

CTEPH Patient Selection Criteria

- Upfront PEA: CTEPH patients (including segmental and subsegmental disease) without severely impaired hemodynamic (PVR <6 WU)
- PHSP / PEA (specific pharmacotherapy followed by PEA): CTEPH patients with severely impaired hemodynamic (PVR >6 WU)
- Multimodal Group (PH specific pharmacotherapy followed by BPA and PEA): CTEPH patients with mixed proximal and distal lesions, severely impaired hemodynamic (minimum threshold of elevated PVR >6 WU) and an age older than 75 years or severe comorbidities. **We targeted patients usually considered ineligible or at very high risk for upfront surgery**

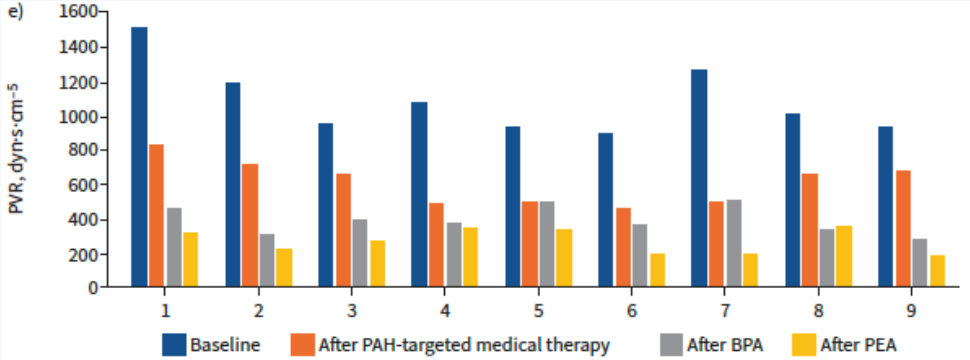
CTEPH expert team meeting





Combined Multimodal Strategy

e)



f)

	Baseline	After sequential multimodal treatment	p-value
NYHA FC I,II/III,IV, n	0,0/9,0	1,7/1,0	0.001
6MWD, m	299 (272–350)	403 (376–427)	0.005
RAP, mmHg	10 (8–19)	5 (3–5)	0.001
mPAP, mmHg	54 (48–61)	29 (21–33)	0.0001
PAWP, mmHg	8 (6–10)	6 (5–8)	0.74
CO, L·min^{-1}	3.3 (3–4)	4.9 (4.2–6.8)	0.0001
PVR, dyn·s·cm^{-5}	1018 (938–1188)	271 (191–328)	0.0001
NT-proBNP, ng·L^{-1}	3349 (1607–4335)	168 (120–236)	0.001

Proof of concept

- Association of 3 treatments
- Sequential
  - PHSP
  - BPA
  - PEA
- 9 first case: Improve pre-op hemodynamic data

Jevnikar et al, ERJ 2023

Rationale: Sequential Multimodal Strategy (SMS)

Step 1: PHSP

Riociguat ± Bosentan

↓ PVR · Improve hemodynamics
before BPA
3–6 months

→

Step 2: BPA

Distal lung (contralateral)

Treat all accessible distal lesions
2–6 sessions at 4–6 week intervals
on the side with distal disease

→

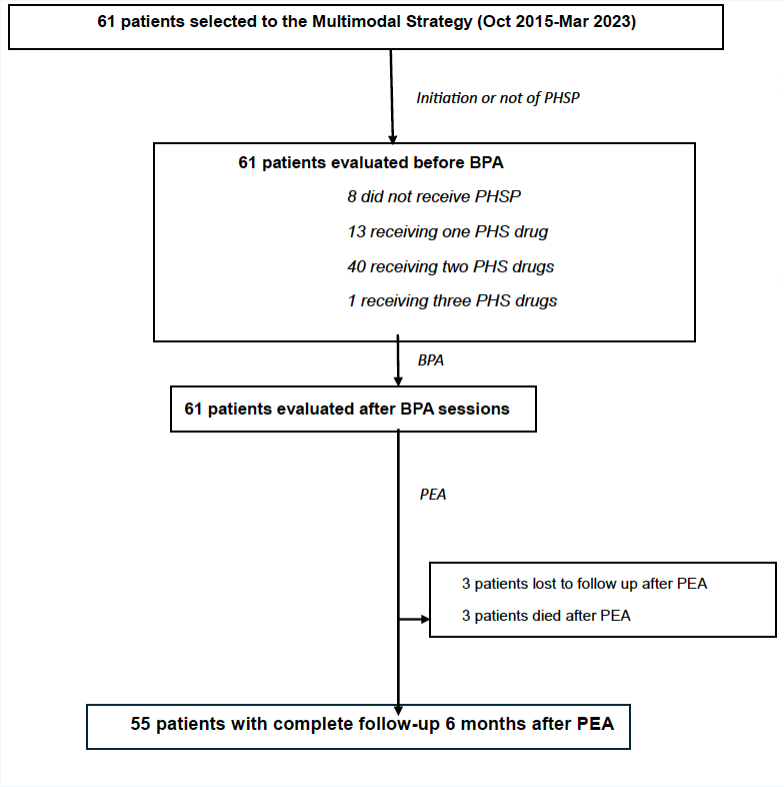
Step 3: PEA

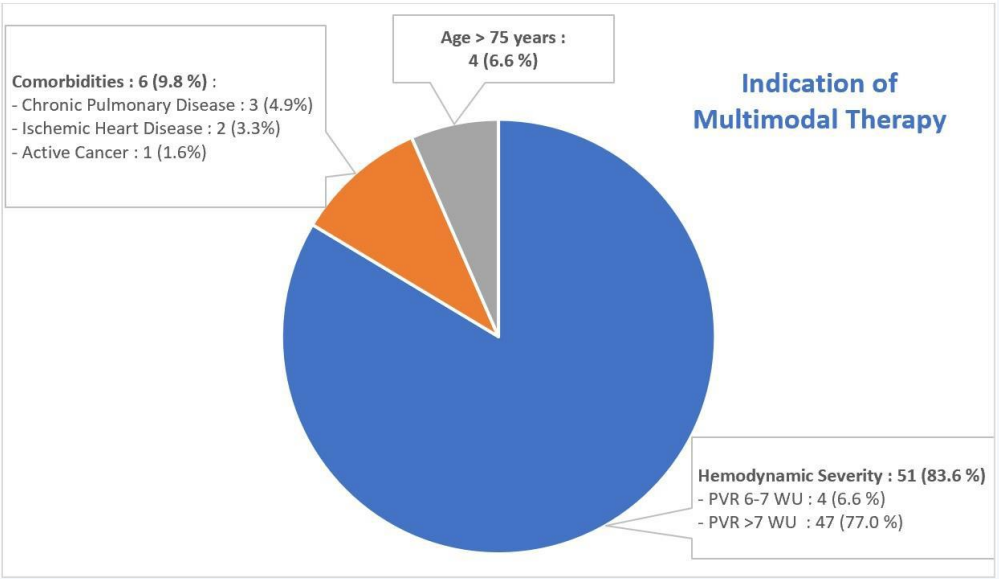
Proximal lung (ipsilateral)

Unilateral endarterectomy
Shorter CPB & circulatory arrest
Safer hemodynamic conditions

Goal: normalize PVR before surgery → comparable outcomes to low-risk patients

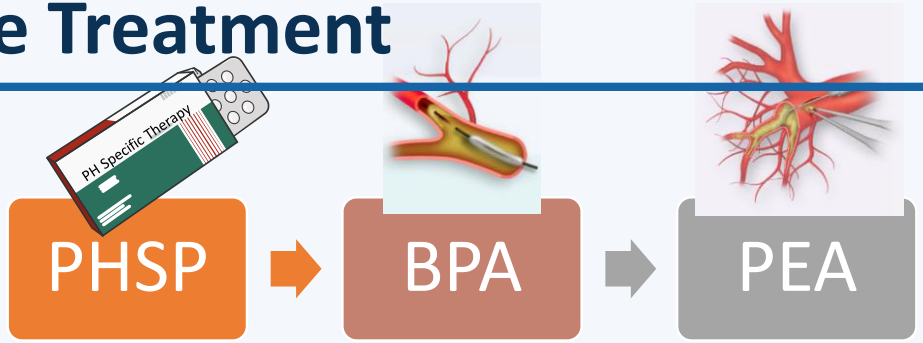
BPA before PEA: a Multimodal Approach





Andarelli JN, JHLT 2025

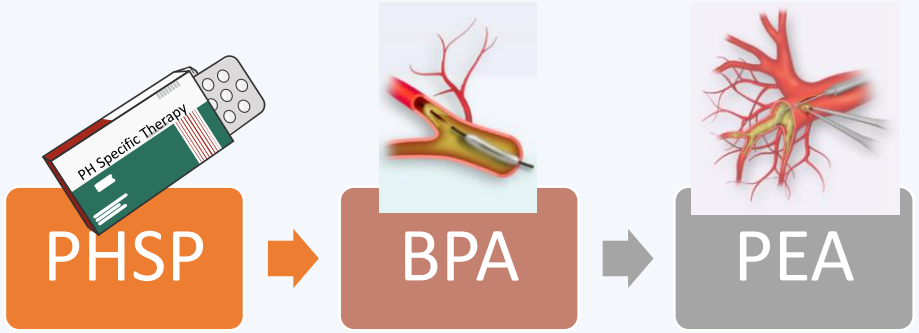
Pre-Operative Treatment

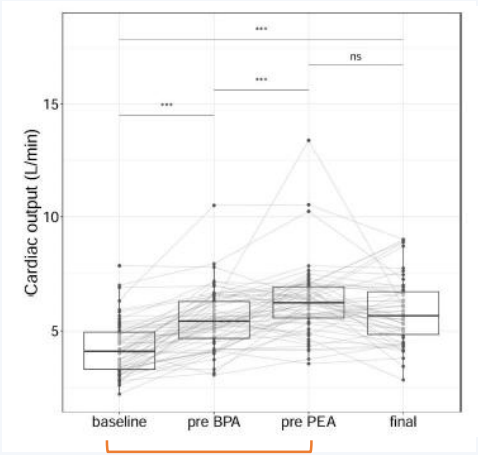


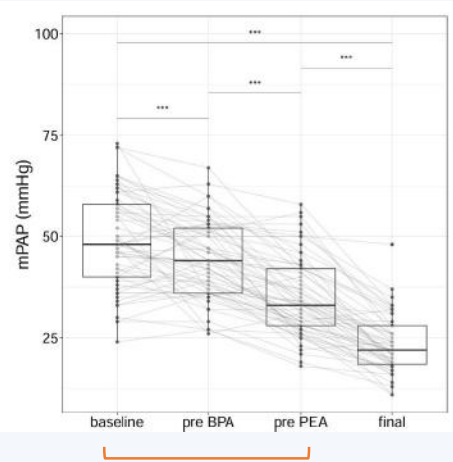
Variables	Baseline	Before BPA	After BPA	After PEA (Final)	*P* value
Hemodynamic variables, median [IQR]					
PAP, mmHg	48.0 [40.0–58.0]	44.0 [36.0–52.0]	33.0 [28.0–41.8]	22.0 [18.5–28.0]	<0.001[a]; <0.001[b]; <0.001[c]; <0.001[d]
PAWP, mmHg	9.0 [6.0–11.0]	10.0 [6.8–12.0]	8.5 [6.0–11.0]	8.0 [6.5–10.0]	>0.99[a]; >0.99[b]; >0.99[c]; >0.99[d]
Cardiac output L/min	4.1 [3.3–5.0]	5.4 [4.7–6.3]	6.3 [5.6–6.9]	5.7 [4.8–6.7]	<0.001[a]; <0.001[b]; 0.112[c]; <0.001[d]
Cardiac index L/min/m^2	2.2 [1.8–2.7]	2.9 [2.4–3.5]	3.4 [3.1–3.7]	3.1 [2.6–3.7]	<0.001[a]; <0.001;[b] 0.075[c]; <0.001[d]
PVR, WU	9.5 [7.0–12.0]	6.17 [5.0–8.2]	3.9 [3.4–5.0]	2.4 [1.9–3.0]	<0.001[a]; <0.001[b]; <0.001[c]; <0.001[d]

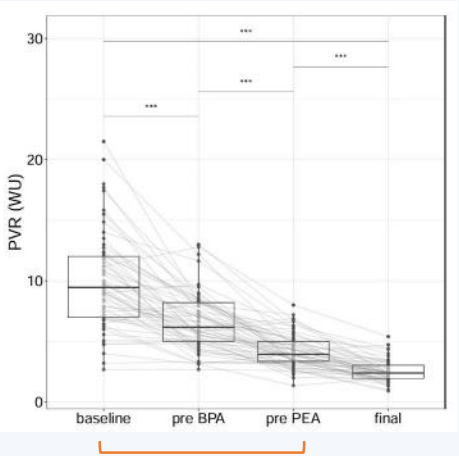
Andarelli JN, JHLT 2025

Pre-Operative Treatment









Andarelli JN, JHLT 2025

Patient Selection: Who Gets SMS?

CTEPH Diagnosed

↓

Multidisciplinary CTEPH Expert Board
(surgeons · BPA specialists · pulmonologists · radiologists)

↓

Upfront PEA	**PHSP → PEA**	**SMS: PHSP→BPA→PEA**
Standard risk Proximal bilateral disease	PVR >6 WU Age >75 · Comorbidities	High risk + asymmetric disease

Patient Cohort: 248 PEAs (2022–2023)

248

Total PEA Procedures
2022–2023

120 (48%)

Upfront PEA

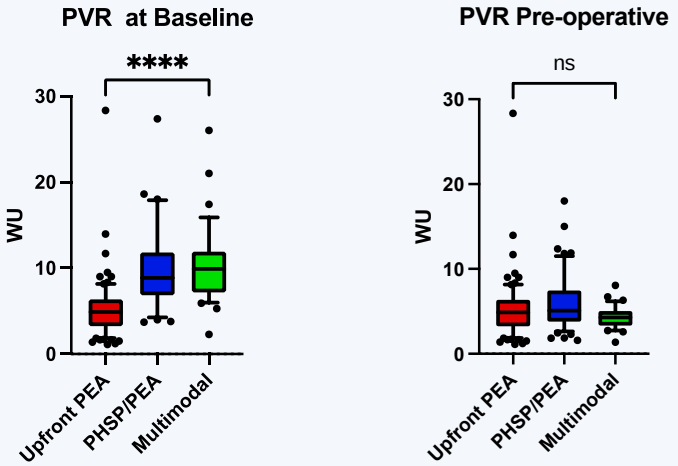
82 (33%)

PHSP → PEA

46 (19%)

SMS
(PHSP+BPA+PEA)

Upfront PEA vs. Combined Multimodal Therapy



High-risk profile in PHSP & SMS groups at baseline:

- Higher MPAP (45–47 vs 38 mmHg; p<0.005)
- Higher PVR (9.9–10 vs 5.3 WU; p<0.001)
- Shorter 6MWD (360–403 vs 483 m; p<0.05)
- Older age in SMS group (64 vs 56 years; p=0.001)

	Upfront PEA n=120	PHSP n=82	CMT n=46	p (PEA vs PHSP)	p (PEA vs CMT)	p (PHSP vs CMT)
Age	56±16	58±15	64±12	0.3	0.001	0.02
Female	61 (51)	35 (43)	24 (52)			
BMI	28±6	28±6	27±5	1	0.9	0.8
NYHA (%)						
I-II	62	30	18	0.07	ns	ns
III-IV	60	52	28			
CTEPH risk factor						
Splenectomy	1 (1)	0	1 (2)	ns	ns	ns
Ventricular deviation	1 (1)	0	0	ns	ns	ns
PaceMaker		1 (1)	1 (2)	ns	ns	ns
Portacath	1 (1)	1 (1)	0	ns	ns	ns
APLS	4 (3)	4 (5)	2 (4)	ns	ns	ns
Baseline Hemodynamics				ns	ns	ns
MPAP	38±13	45±11	47±12	0.002	<0.001	0.48
CO	5.5±1.5	5±1	4±1	ns	ns	ns
PVR	5.3±4	9.9±5	10±4	<0.001	<0.001	0.46
6MWT	483±18	403±30	360±42	0.03	0.01	0.36
Preoperative Hemodynamics						
MPAP	38±13	38±12	36±11	1	0.6	0.5
CO	5.5±1.5	5±1	6±1	0.2	0.002	<0.001
PVR	5.3±4	6±3	4±1	0.2	0.2	0.02

Pre-operative Hemodynamic Improvement

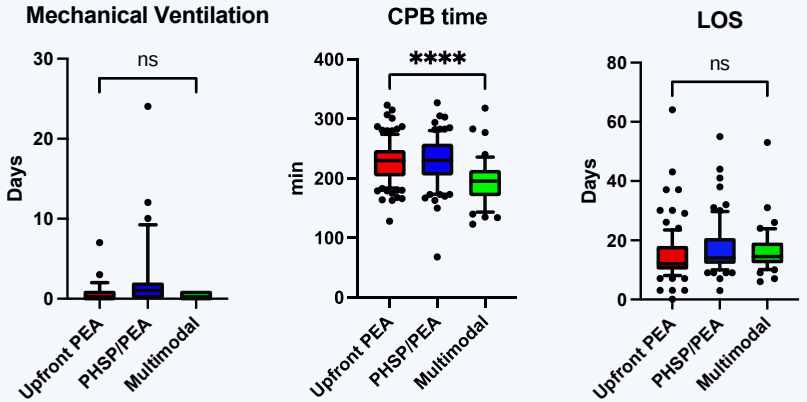
After PHSP (n=82)		
MPAP	45 → 38 mmHg	**p<0.001**
PVR	9.9 → 6.1 WU	**p<0.001**
CO	4 → 5 L/min	**p<0.001**
NYHA	Class III → II	**p<0.001**

After PHSP + BPA (n=46)		
MPAP	47 → 34 mmHg	**p<0.001**
PVR	10 → 4.3 WU	**p<0.001**
CO	4 → 6 L/min	**p<0.001**
NYHA	Class III → II	**p=0.001**
6MWD	355 → 455 m	**p<0.001**

Postoperative Outcomes: Multimodal vs. Upfront PEA

	Upfront PEA n=120	PHSP n=82	CMT n=46	p (PEA vs PHSP)	p (PEA vs CMT)
CPB time, min	227±34	230±40	196±39	0.4	<0.001
Aortic cross-clamping	55±14	59±15	39±12	0.2	<0.001
Circulatory arret	24±12	22±7	18±6	0.5	<0.001
Clavien Dindo, n(%)					
I	21(18)	18(22)	15(33)	0.3	0.4
II	21(18)	15(18)	14(30)	0.8	1
IIIa-IIIb	7(6)	6(7)	2(4)	0.8	1
IVa-IVb	6(5)	4(5)	1(2)	1	0.7
LOS, days	15±9	17±9	16±9	0.08	0.07
Mechanical ventilation, days	0.6±1	2.5±5	0.4±0.5	0.01	1
90d mortality, n(%)	1 (1)	3 (4)	1(2)	0.4	1
Reperfusion edema	17 (14)	12 (15)	12 (26)	1	0.1
AKI (KDIGO 1-2)	19 (16)	16 (20)	14 (30)	0.6	0.05
Renal replacement therapy	1 (1)	2 (2)	1 (2)	0.6	0.5
Hemoptysis	4 (3)	1 (1)	0 (0)	0.7	0.6
ECMO	6 (5)	4 (5)	1 (2)	1	0.67
Supraventricular tachycardia	4 (3)	3 (4)	4 (9)	1	0.2
Stroke	0 (0)	0 (0)	1 (2)	1	0.3
In-hospital surgical bleeding	1 (1)	1 (1)	2 (4)	1	0.2

- **Upfront PEA vs. Multimodal**



Postoperative Complications: Comparable Between Groups

Complication	Upfront PEA (n=120)	PHSP→PEA (n=82)	SMS (n=46)	p PEA vs PHSP	p PEA vs SMS
Clavien-Dindo I	18%	22%	33%	0.30	0.40
Clavien-Dindo II	18%	18%	30%	0.80	1.00
Clavien-Dindo IIIa–b	6%	7%	4%	0.80	1.00
Clavien-Dindo IVa–b	5%	5%	2%	1.00	0.70
Reperfusion edema	14%	15%	26%	1.00	0.10
AKI (KDIGO 1–2)	16%	20%	30%	0.60	0.05
ECMO required	5%	5%	2%	1.00	0.67
Supraventricular tachycardia	3%	4%	9%	1.00	0.20
90-day mortality	1%	4%	2%	0.40	1.00

No significant differences in any complication category across treatment groups

Key Postoperative Outcomes

90-day Mortality	
Upfront PEA	1%
PHSP→PEA	4%
SMS	2%

p = ns

Length of Stay	
Upfront PEA	15 days
PHSP→PEA	17 days
SMS	16 days

p = ns

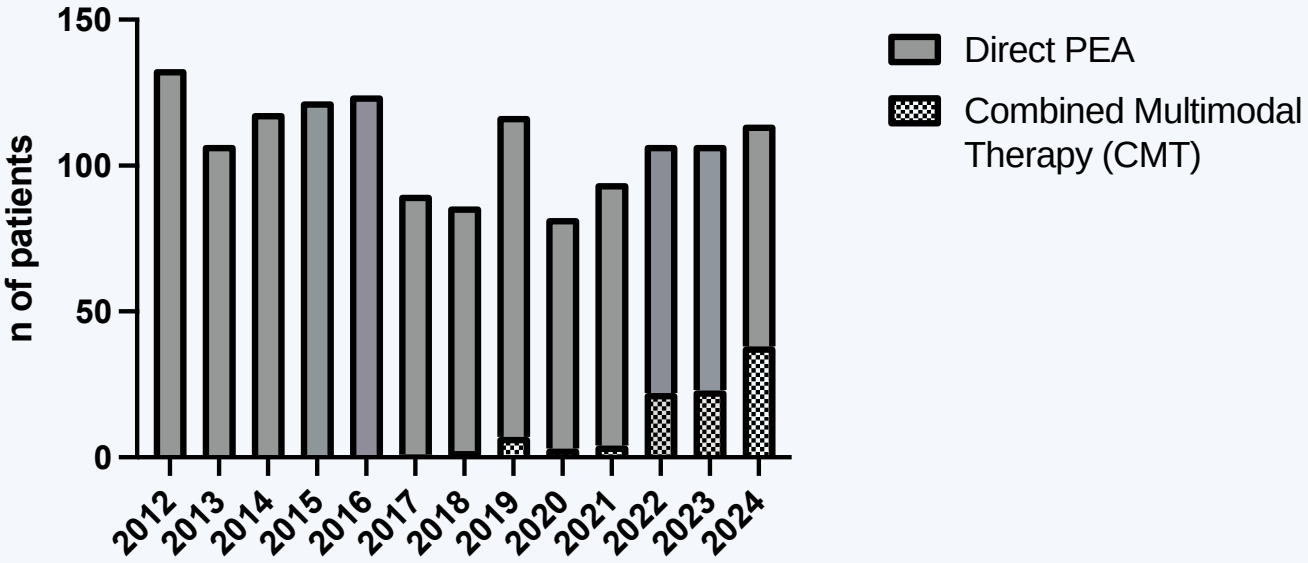
Mech. Ventilation	
Upfront PEA	0.6 days
PHSP→PEA	2.5 days
SMS	0.4 days

PHSP p=0.01
(ns multivariate)

Key finding: High-risk patients treated with preoperative multimodal therapy achieved postoperative outcomes equivalent to low-risk upfront PEA patients

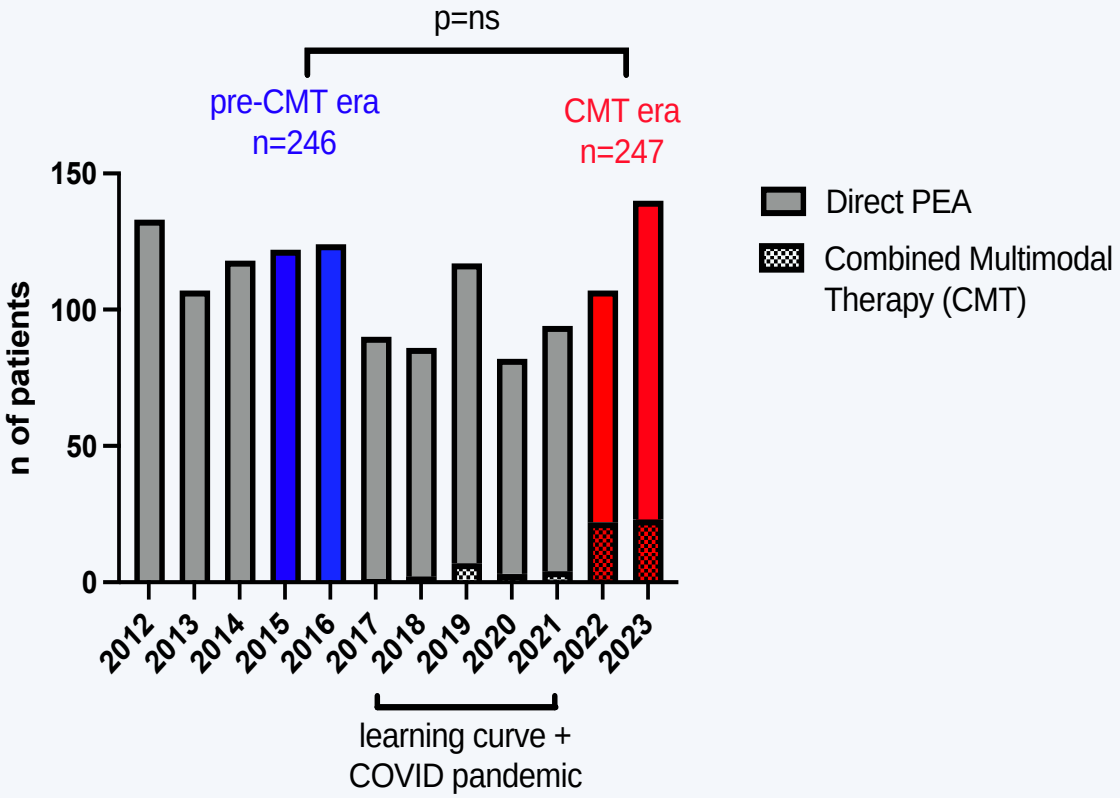
Mortality: 1% vs 4% vs 2% | LOS: 15 vs 17 vs 16 days — all p=ns

Impact on Surgical Activity



Annual number of patients with chronic thromboembolic pulmonary hypertension (CTEPH) undergoing pulmonary endarterectomy (PEA) before and after the implementation of combined multimodal therapy (CMT).

Impact on post-operative outcomes vs historical cohort



Impact on post-operative outcomes vs historical cohort

	Before-CMT	CMT	p-value
Hemodynamic			
PVR (Wood units)	8	4.8	< 0.0001
6MWD (m)	385	455	< 0.0001
Baseline (avant PHSP/BPA)			
PVR (Wood units)	8	9	0.07
6MWD (m)	385	412	0.09
Postoperative outcomes			
90d Mortality(%)	4.8%	1.2%	0.03
ECMO (%)	9%	1.2%	< 0.001
Mechanical ventilation (days)	2	0	< 0.001
LOS(days)	19	14	< 0.001

ECMO

Pre-CMT **9 %**

CMT era **1.2 %**

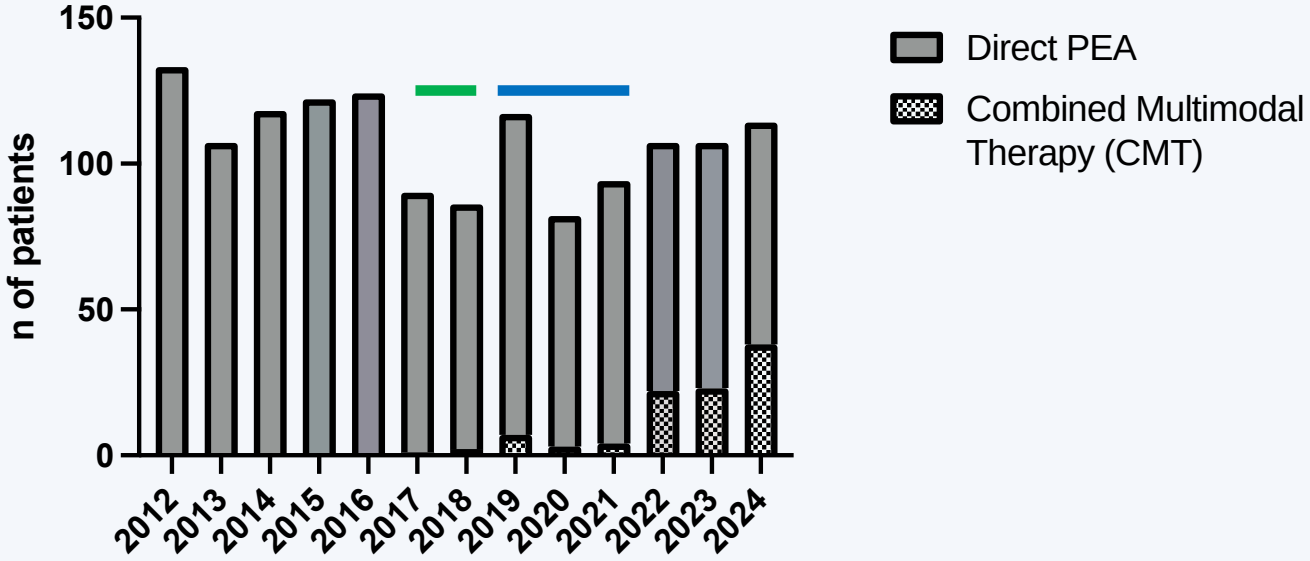
p <0.001

90-day Mortality

Pre-CMT **4.8%**

CMT era **1.2%**

Impact on Residual PH



- **Compared 2017–2018 to 2019–2022**
  - Baseline severity was similar between groups
  - Residual PH was significantly reduced: 25.4% vs 10.1% (−72%, p<0.001)

Why Does SMS Work? Mechanistic Rationale

① Hemodynamic Optimization

PHSP reduces PVR and mPAP before BPA → lower procedural risk during BPA sessions and safer surgical hemodynamic conditions at time of PEA

② Anatomical Targeting

BPA treats distal lesions on one side (which would require prolonged circulatory arrest during PEA) → PEA then performed only on the proximal lung

③ Shorter Ischemia

Unilateral PEA: CPB 196 vs 227 min · Cross-clamping 39 vs 55 min · Circulatory arrest 18 vs 24 min — all $p<0.001$

④ Comprehensive Vascular Treatment

Sequential targeting: proximal thrombus (PEA) + distal microvascular disease (BPA) + residual vasculopathy (PHSP) → complete response

Limitations

Single-center

All BPA and PEA performed at Marie Lannelongue — one of the world's highest-volume CTEPH centers. Generalizability requires multi-center validation.

Non-randomized design

Patient allocation was determined by the expert multidisciplinary board — inherent selection bias. High-risk patients were preferentially directed to multimodal therapy.

Sample size

Larger prospective multi-center cohorts are needed to confirm these findings with greater statistical power.

Follow-up scope

Long-term hemodynamic and functional outcomes beyond 6 months are not yet published.



Conclusions

1. Sequential multimodal strategy (PHSP → BPA → PEA) effectively normalizes pre-operative PVR in high-risk CTEPH patients, regardless of baseline severity

2. Despite significantly higher baseline PVR, SMS patients achieve equivalent 90-day mortality, length of stay, and complication rates to upfront PEA patients

3. Unilateral PEA after BPA significantly shortens CPB, cross-clamping, and circulatory arrest times (all $p<0.001$) — reducing ischemic burden

4. SMS expands surgical eligibility — enabling curative PEA in patients who would otherwise face prohibitive operative risk due to severe hemodynamics or distal disease

Take-Home Messages

1. High PVR alone should not preclude surgical candidacy — multimodal optimization can bridge the gap to safe PEA

2. SMS (PHSP → BPA → PEA) is safe, feasible, and achieves comparable postoperative outcomes to standard upfront PEA

3. Treating distal disease first by BPA simplifies subsequent PEA and significantly reduces ischemic burden

4. Expert multidisciplinary CTEPH teams are essential: patient selection is the key to success of this strategy

Thank You

Questions & Discussion

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