University of Pavia - School of Medicine
Foundation I.R.C.C.S. Policlinico "San Matteo"
Cardiac Surgery - Intrathoracic Transplantation - Pulmonary Hypertension
Pavia, Italy

Prof. Andrea M. D'Armini, M.D.

BEST PRACTICE FOR DIAGNOSIS AND TREATMENT OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

FINANCIAL DISCLOSURE

Last three years

Actelion Pharmaceuticals Ltd
Bayer HealthCare
Merk Sharp Dohme

REFERENCE

Terapia chirurgica dell'ipertensione polmonare cronica tromboembolica mediante endoarteriectomia polmonare

Andrea Maria D'Armini, Giorgio Zanotti, Matteo Pozzi, Salvatore Nicolardi, Corrado Tramontin, Vito G. Ruggieri, Marco Morsolini, Fabrizio Tancredi, Cristian Monterosso, Mario Viganò, a nome del Pavia Pulmonary Endarterectomy Study Group (vedi Appendice)

Cattedra e Divisione di Cardiochirurgia, Università degli Studi di Pavia, IRCCS Policlinico San Matteo, Pavia

(G Ital Cardiol 2006; 7 (7): 454-463)

DIAGNOSIS

Tabella 2. Esami diagnostici di primo livello.

Test diagnostico	Razionale	Quadro tipico
ECG	Evidenziare dilatazione/sovraccarico ventricolare	Precoce: solitamente normale Tardivo: segni di dilatazione/ipertrofia VD e dilatazione AD
Rx torace	Visualizzare l'ombra cardiaca e gli ambiti polmonari (parenchimale/vascolare)	Precoce: solitamente normale Tardivo: area avascolare, dilatazione dell'arteria polmonare, trama vascolare irregolare (aumentato flusso bronchiale) e asimmetrica, esiti cicatriziali pleurici
Ecocardiogramma	Stimare le pressioni arteriose polmonari, valutare anatomia e funzione delle principali strutture cardiache, ricercare la presenza di shunt intracardiaci	Dilatazione/disfunzione delle camere cardiache destre, insufficienza tricuspidale destra, aumento delle pressioni polmonari, movimento paradosso del SIV, disfunzione VS, possibile comunicazione interatriale (FOP)

AD = atrio destro; ECG = elettrocardiogramma; FOP = forame ovale pervio; Rx = radiografia; SIV = setto interventricolare; VD = ventricolo destro; VS = ventricolo sinistro.

(G Ital Cardiol 2006; 7 (7): 454-463)

DIAGNOSIS

Tabella 3. Esami diagnostici di secondo livello.

Test diagnostico	Razionale	Quadro tipico
Scintigrafia V/P	Diagnosi differenziale IPCTE vs IPI	Uno o più segmenti polmonari con "mismatch" ventilo-perfusorio
Cateterismo cardiaco destro	Misurare le pressioni in AP e IC, calcolare le RVP	Pressioni polmonari prossime a valori sistemici o sovrasistemiche, IC < 2.0 1/min/m^2 e RVP notevolmente elevate (spesso > 1000 dynes*s*cm^{-5})
PFR/EGA	Escludere/valutare cause parenchimali di IP, valutare la funzione respiratoria	Non anomalie significative/lieve quadro restrittivo (dovuto a precedenti infarti polmonari), ipossiemia, alcalosi respiratoria compensatoria, ridotta DL_{co}

AP = arteria polmonare; DL_{co} = capacità polmonare di diffusione per il monossido di carbonio; EGA = emogasanalisi; IC = indice cardiaco; IP = ipertensione polmonare; IPCTE = ipertensione polmonare cronica tromboembolica; IPI = ipertensione polmonare idiopatica; PFR = prove di funzionalità respiratoria; RVP = resistenze vascolari polmonari; V/P = ventilo-perfusoria.

(G Ital Cardiol 2006; 7 (7): 454-463)

DIAGNOSIS

Tabella 4. Esami diagnostici di terzo livello.

Test diagnostico	Razionale	Quadro tipico
Angiografia polmonare	Valutare l'anatomia arteriosa polmonare, l'estensione/localizzazione degli emboli cronici (per porre diagnosi, valutare l'elegibilità all'intervento e prevedere l'outcome operatorio)	Irregolarità intimali, difetti "a tasca", bande o "reti" intravascolari, riduzione repentina del calibro vascolare o amputazione dello stesso
TC torace	Fase vascolare: identica a quella angiografica	Quadro vascolare: identico a quello angiografico
	Fase parenchimale/mediastinica: valutare il parenchima polmonare, escludere cause estrinseche di IP	Quadro parenchimale: perfusione a mosaico ed esiti cicatriziali subpleurici Quadro mediastinico: dilatazione delle arterie bronchiali

IP = ipertensione polmonare; TC = tomografia computerizzata.

(G Ital Cardiol 2006; 7 (7): 454-463)

European Heart Journal
doi:10.1093/eurheartj/ehv317

ESC/ERS GUIDELINES

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

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK4 mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital /acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

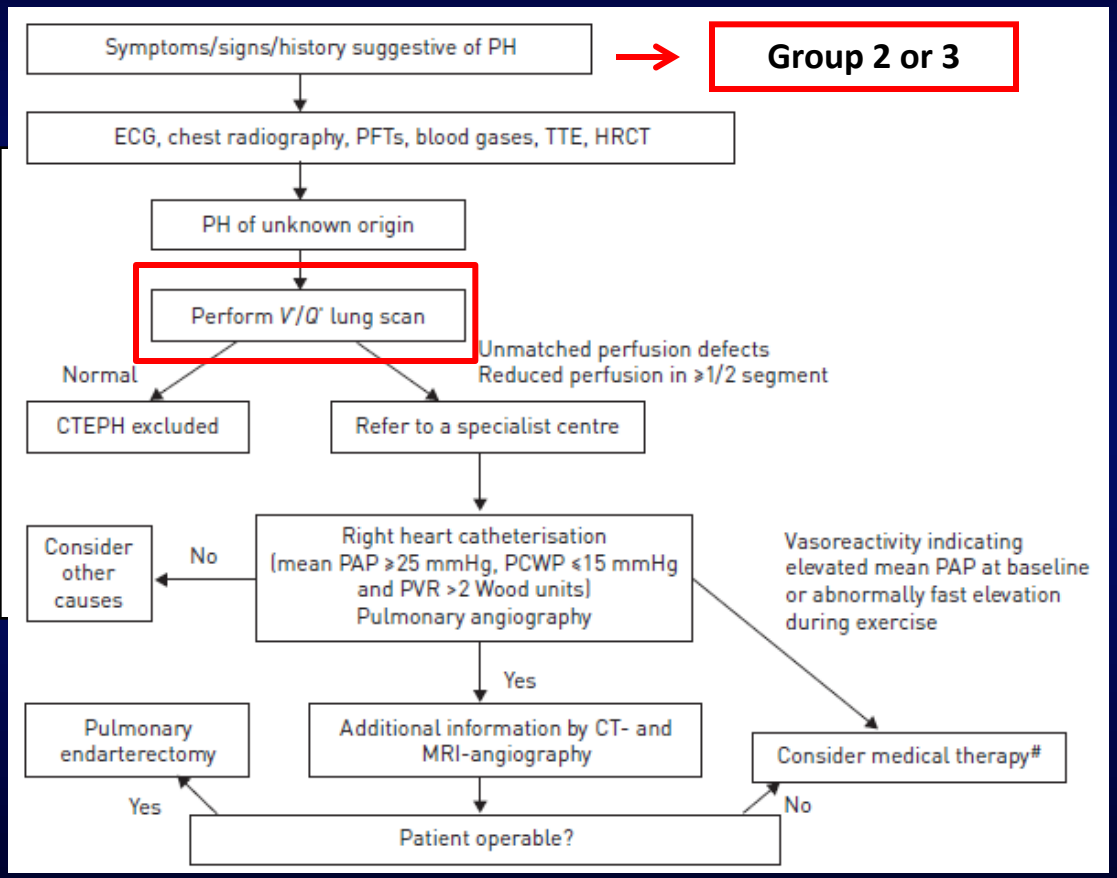
- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

4%

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

DIAGNOSIS


Symptoms/signs/history suggestive of PH
Group 2 or 3
ECG, chest radiography, PFTs, blood gases, TTE, HRCT
PH of unknown origin
Perform V/Q' lung scan
Normal
Unmatched perfusion defects
Reduced perfusion in ⩾1/2 segment
CTEPH excluded
Refer to a specialist centre
Consider other causes
No
Right heart catheterisation (mean PAP ⩾25 mmHg, PCWP ⩽15 mmHg and PVR >2 Wood units) Pulmonary angiography
Vasoreactivity indicating elevated mean PAP at baseline or abnormally fast elevation during exercise
Yes
Pulmonary endarterectomy
Additional information by CT- and MRI-angiography
Consider medical therapy#
Yes
No
Patient operable?

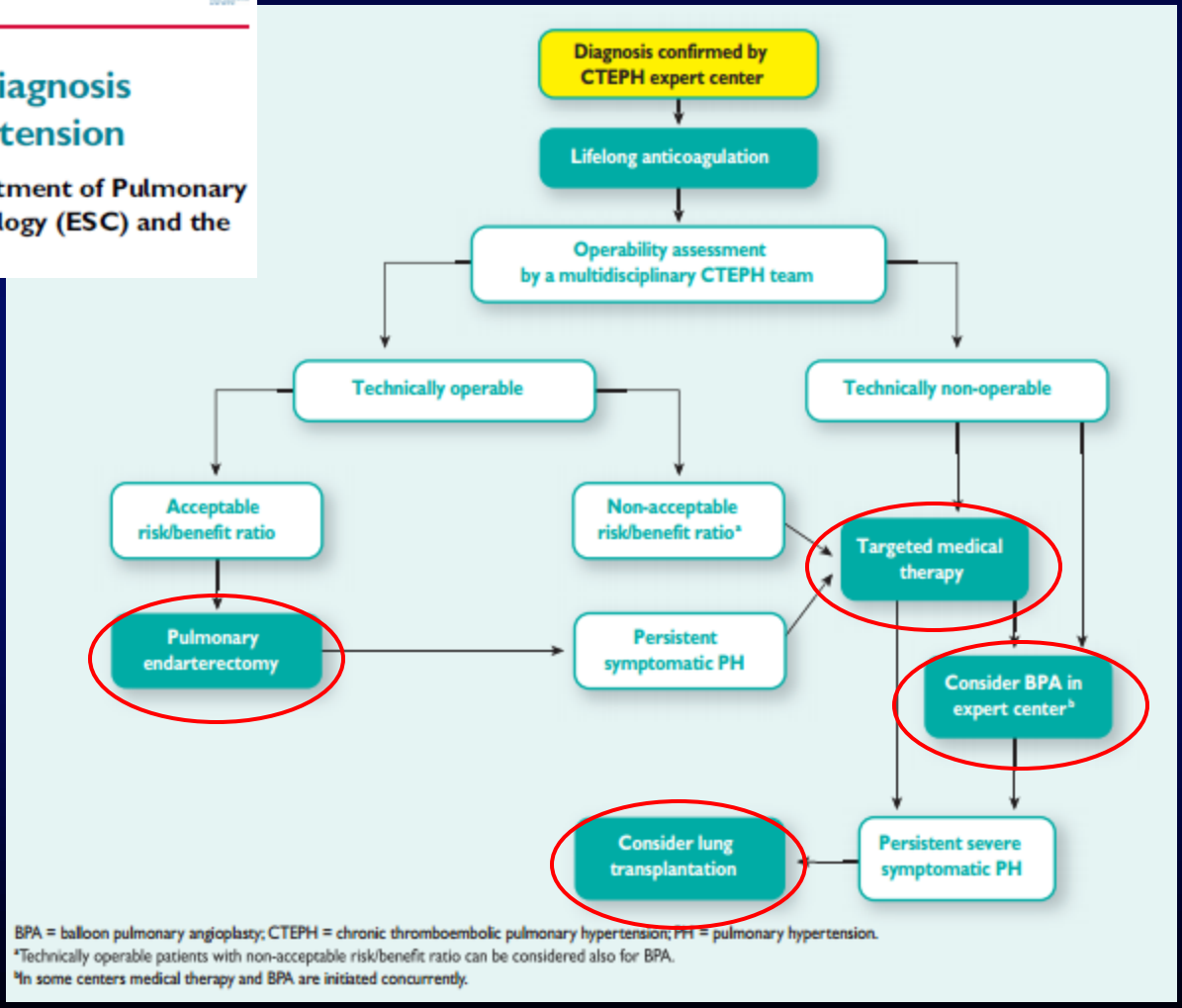
GUIDELINES FOR CTEPH

European Heart Journal
doi:10.1093/eurheartj/ehv317

ESC/ERS GUIDELINES

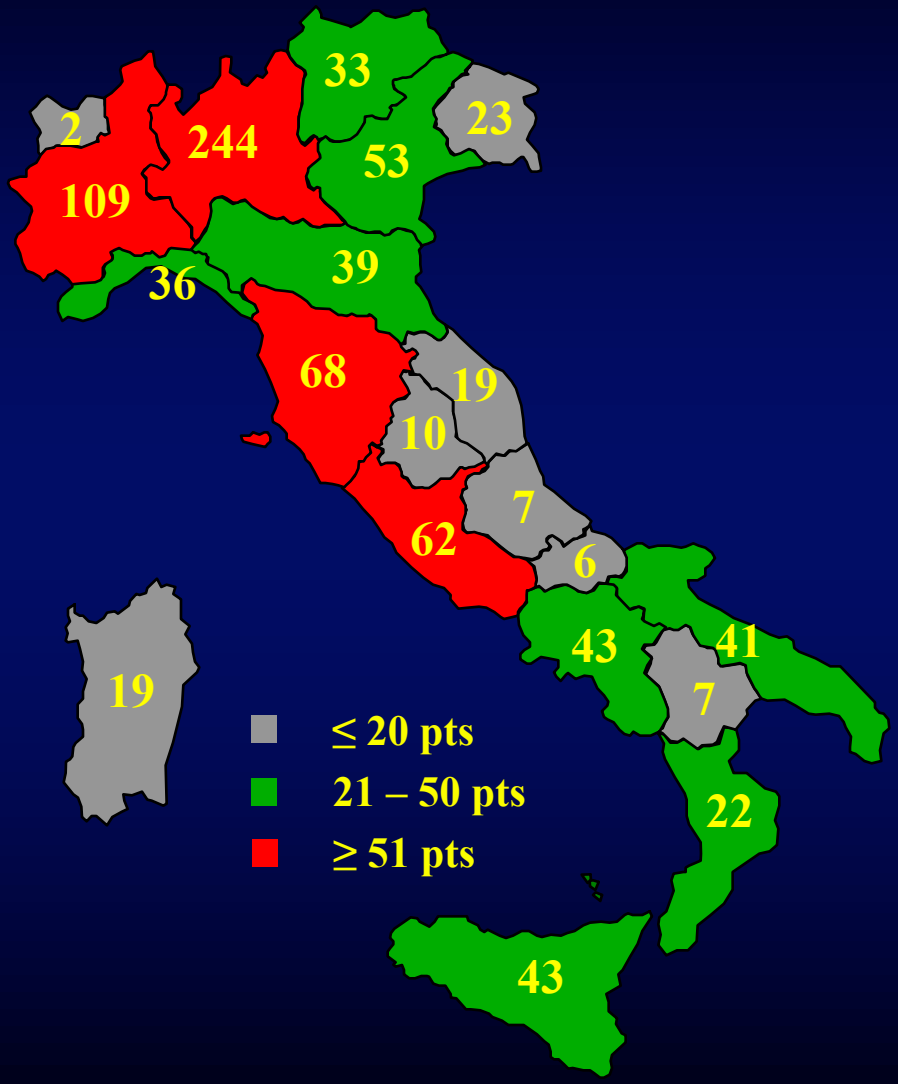
2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)



BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension.
[a]Technically operable patients with non-acceptable risk/benefit ratio can be considered also for BPA.
[b]In some centers medical therapy and BPA are initiated concurrently.

PATIENTS' REFERRAL



FROM 4/1994 TO 10/2018
897 PEAs

Pts coming from outside Italy: 11	
- Albania	3
- Greece	1
- Israel	1
- Kosovo	1
- Romania	2
- Russia	1
- Uganda	1
- U.S.A.	1

PATIENTS' REFERRAL

FROM 2009 TO 2013 → 322 PEAs
PTS / 10^6 / Year POPULATION

- ≤ 1 pt / 10^6 / Year
- 1 – 3 pts / 10^6 / Year
- ≥ 3 pts / 10^6 / Year

Update date population at 01/01/2014 (ISTAT)

SURGICAL TREATMENT OF CTEPH

PAVIA EXPERIENCE

First HLTx for CTEPH

First PEA

First DLTx for CTEPH

First PEA in patient listed for DLTx

First PEA in patient previously enrolled in RCT for inoperability

Reverse right ventricular remodeling after pulmonary endarterectomy

Andrea M. D'Armini, MD,[a] Giorgio Zanotti, MD,[a] Stefano Ghio, MD,[b] Giulia Magrini, MD,[b] Matteo Pozzi, MD,[a] Laura Scelsi, MD,[b] Giulia Meloni, MD,[c] Catherine Klersy, MD,[d] and Mario Viganò, MD[a]

J Thorac Cardiovasc Surg 2007;133:162-8

08-MAR-1991

11-APR-1994

25-DEC-1995

28-JUL-2003

30-NOV-2009

SURGICAL TREATMENT OF CTEPH

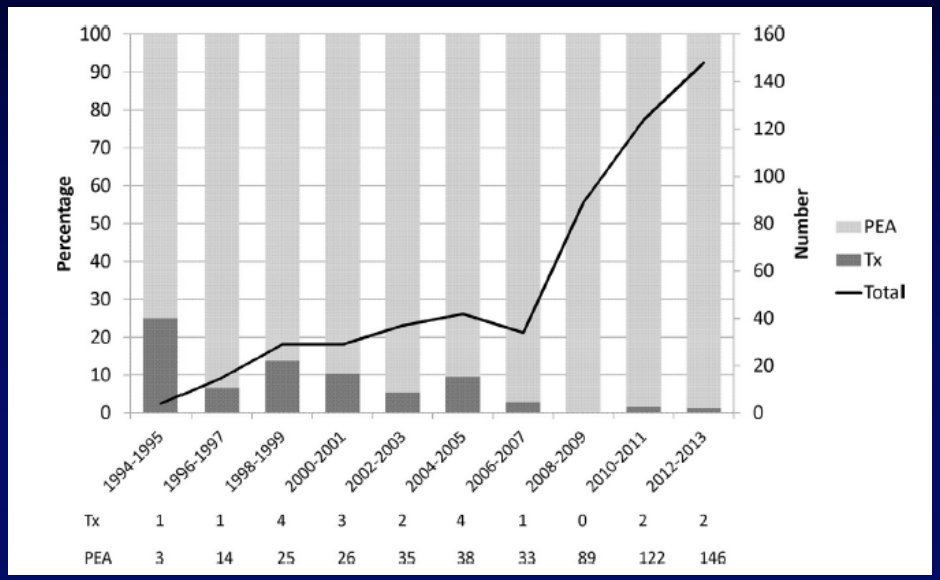
Chronic thromboembolic pulmonary hypertension: From transplantation to distal pulmonary endarterectomy

Andrea M. D'Armini, MD,[a]
Marco Morsolini, MD, PhD,[b]
Gabriella Mattiucci, MD,[b]
Valentina Grazioli, MD,[a]
Maurizio Pin, MD,[a] Antonio Sciortino, MD,[a]
Eloisa Arbustini, MD,[c] Claudio Goggi, MD,[a] and
Mario Viganò, MD[a]

The Journal of Heart and Lung Transplantation

J Heart Lung Transplant. 2016 Jun;35(6):827-31

SURGICAL TREATMENT OF CTEPH



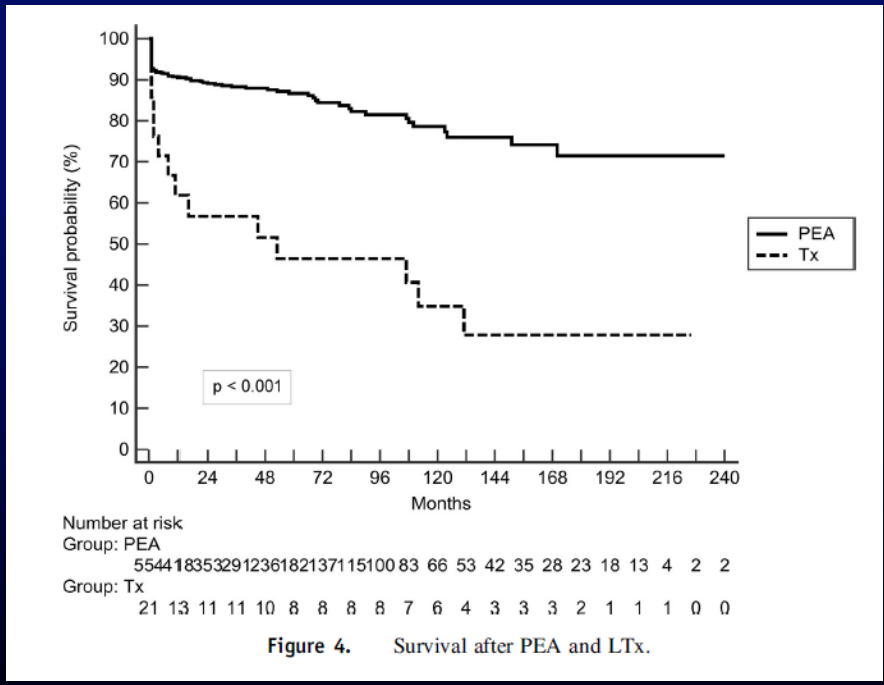


Figure 4. Survival after PEA and LTx.

CHARACTERISTICS

Optimal candidate	Poor candidate
• Age < 70 years	• Age ≥ 70 years
• NYHA II-III	• NYHA IV
• PVR < 800	• PVR > 1200
• Proximal CTE lesions	• Distal CTE lesions
• Plenty CTE occlusions	• Scarce CTE occlusions
• Absence of comorbidities	• Presence of comorbilities

CHARACTERISTICS

- Age
- NYHA functional class
- PVR
- Distribution of CTE lesions
- Amount of CTE occlusions
- Comorbidities

AGE

European Journal of Cardio-Thoracic Surgery 41 (2012) e154–e160
doi:10.1093/ejcts/ezs188

ORIGINAL ARTICLE

Pulmonary endarterectomy: outcomes in patients aged >70†

Marius Berman[a], Gillian Hardman[b], Linda Sharples[c], Joanna Pepke-Zaba[b], Karen Sheares[b], Steven Tsui[a], John Dunning[a] and David P. Jenkins[a,*]

AGE

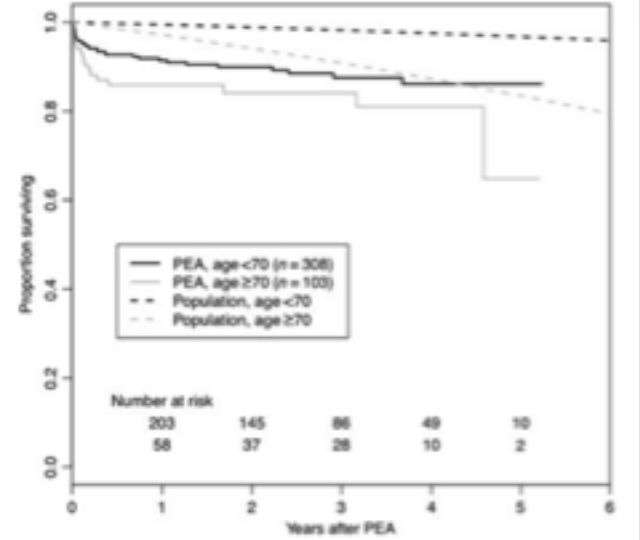


Figure 1: Observed and age-sex-matched population survival for PEA patients.

Eur J Cardiothorac Surg. 2012 Jun;41(6):e154-60

AGE

CONCLUSION

In the present study, septuagenarians showed a very good medium-term survival following PEA. PEA surgery has an acceptable safety profile, and the risk in the patients aged ≥70 is only slightly greater than that of the younger patients, but there is a greater resource use for older patients due to longer ICU and hospital stays. Advanced age should be taken into consideration when assessing suitability for PEA, but is not a contraindication to surgery.

Eur J Cardiothorac Surg. 2012 Jun;41(6):e154-60

AGE

Original article

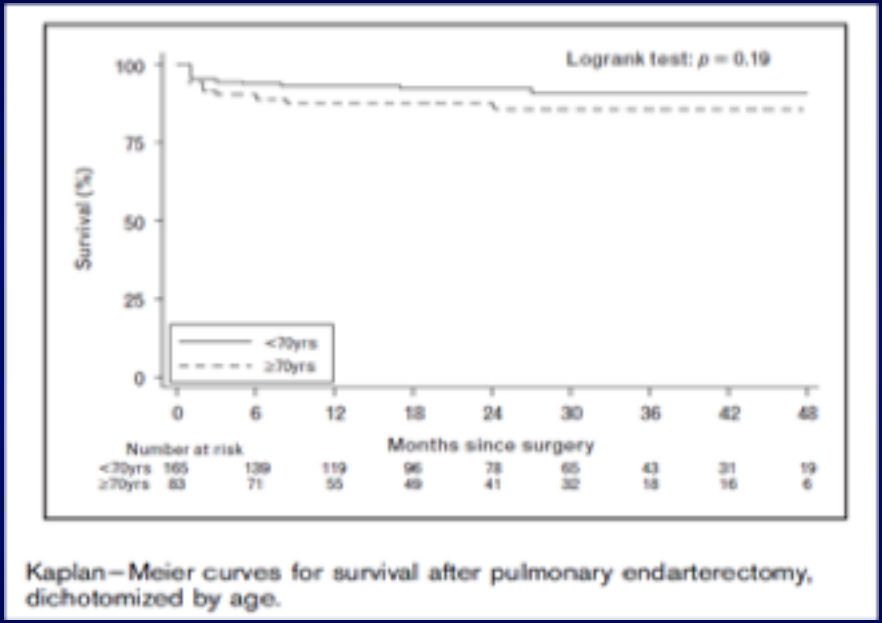
FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

Pulmonary endarterectomy in the elderly: safety, efficacy and risk factors

Nicola Vistarini[a], Marco Morsolini[a], Catherine Klersy[b], Gabriella Mattiucci[a], Valentina Grazioli[a], Maurizio Pin[a], Stefano Ghio[c] and Andrea Maria D'Armini[a]

J Cardiovasc Med 2016, 17:144–151

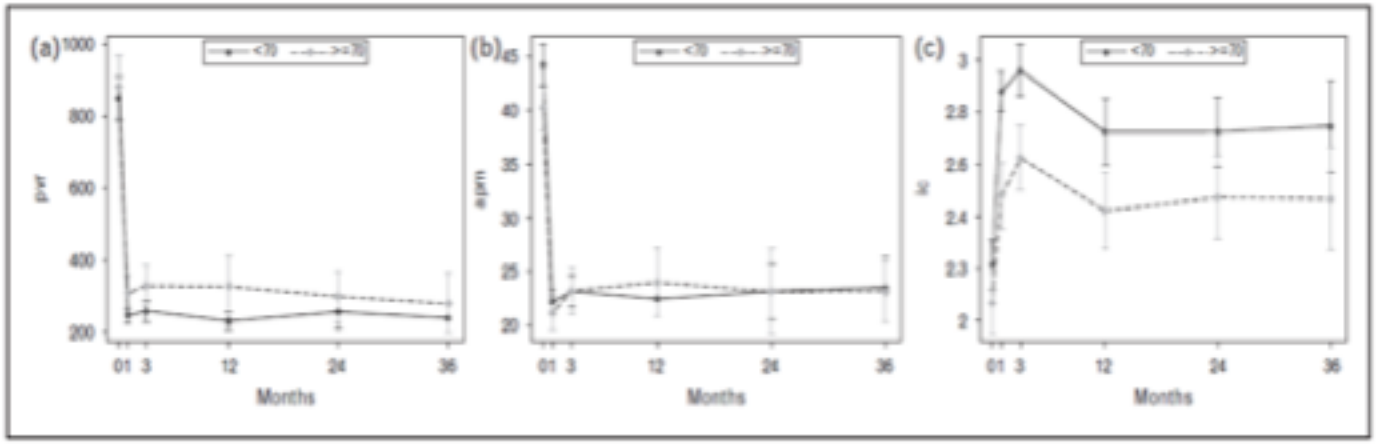
AGE



Kaplan–Meier curves for survival after pulmonary endarterectomy, dichotomized by age.

J Cardiovasc Med 2016, 17:144–151

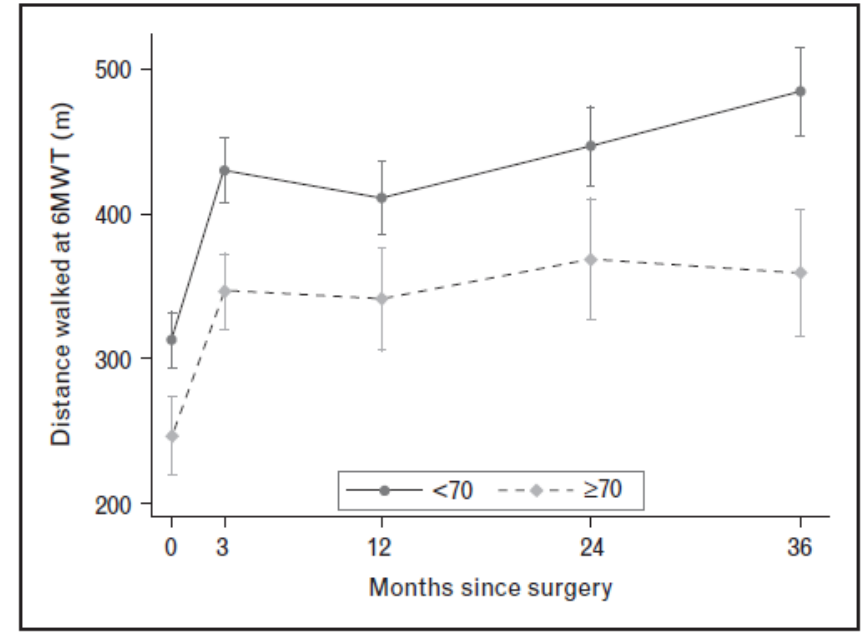
AGE



Hemodynamic evaluations over time in the two study populations. (a) Pulmonary vascular resistances (pvr); (b) pulmonary arterial pressure (apm); (c) cardiac output (ic).

J Cardiovasc Med 2016, 17:144–151

AGE



J Cardiovasc Med 2016, 17:144–151

AGE

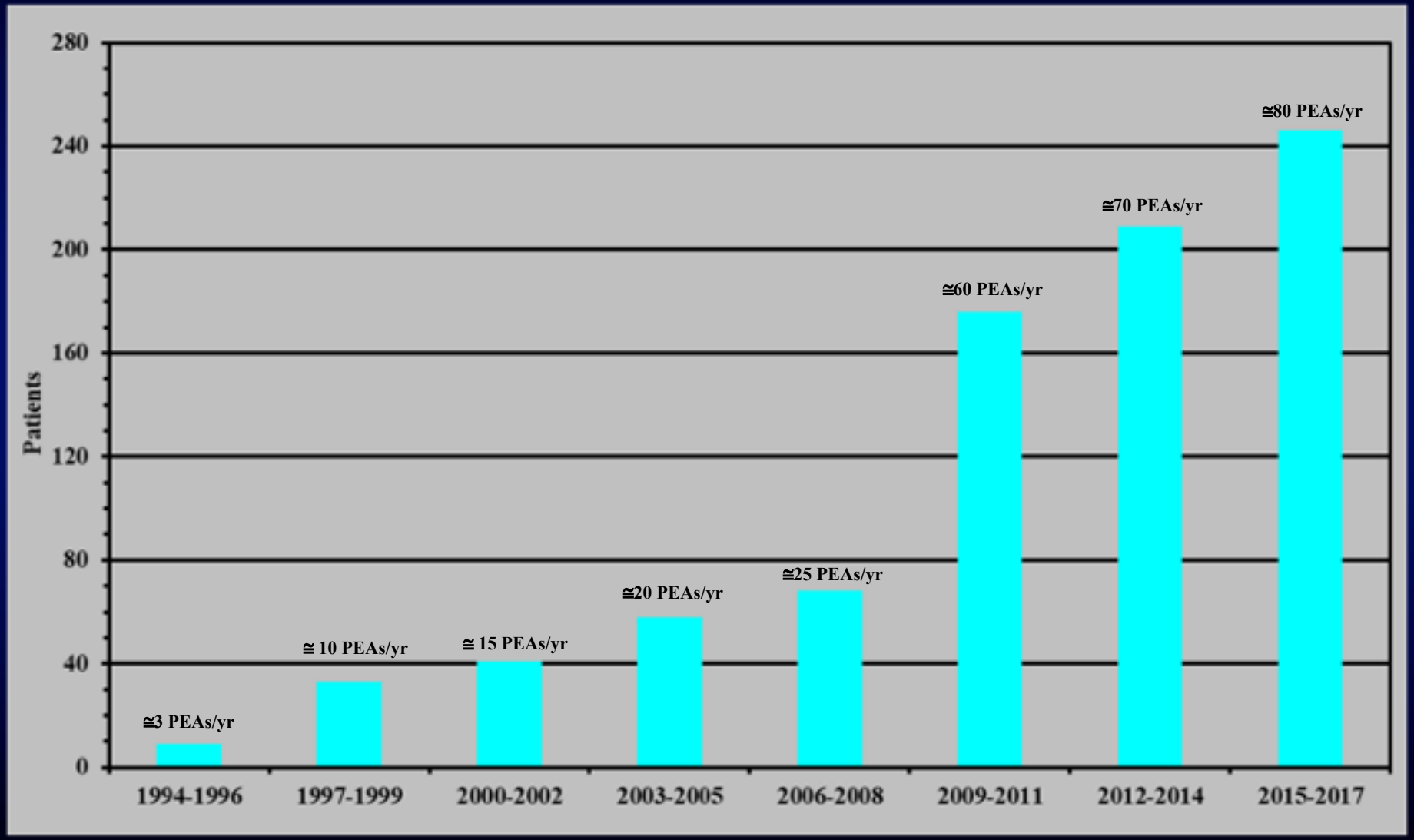
In conclusion, the present study demonstrates that PEA is a well tolerated and effective treatment for CTEPH in the elderly. The clinical and hemodynamic improvement

but also by a real improvement of the functional status. In conclusion, we believe that PEA should not be denied to CTEPH patients merely on the basis of advanced age; these patients should be properly identified and surgical treatment recommended at any center with consolidated surgical experience.

25 YEARS OF OUR PROGRAM

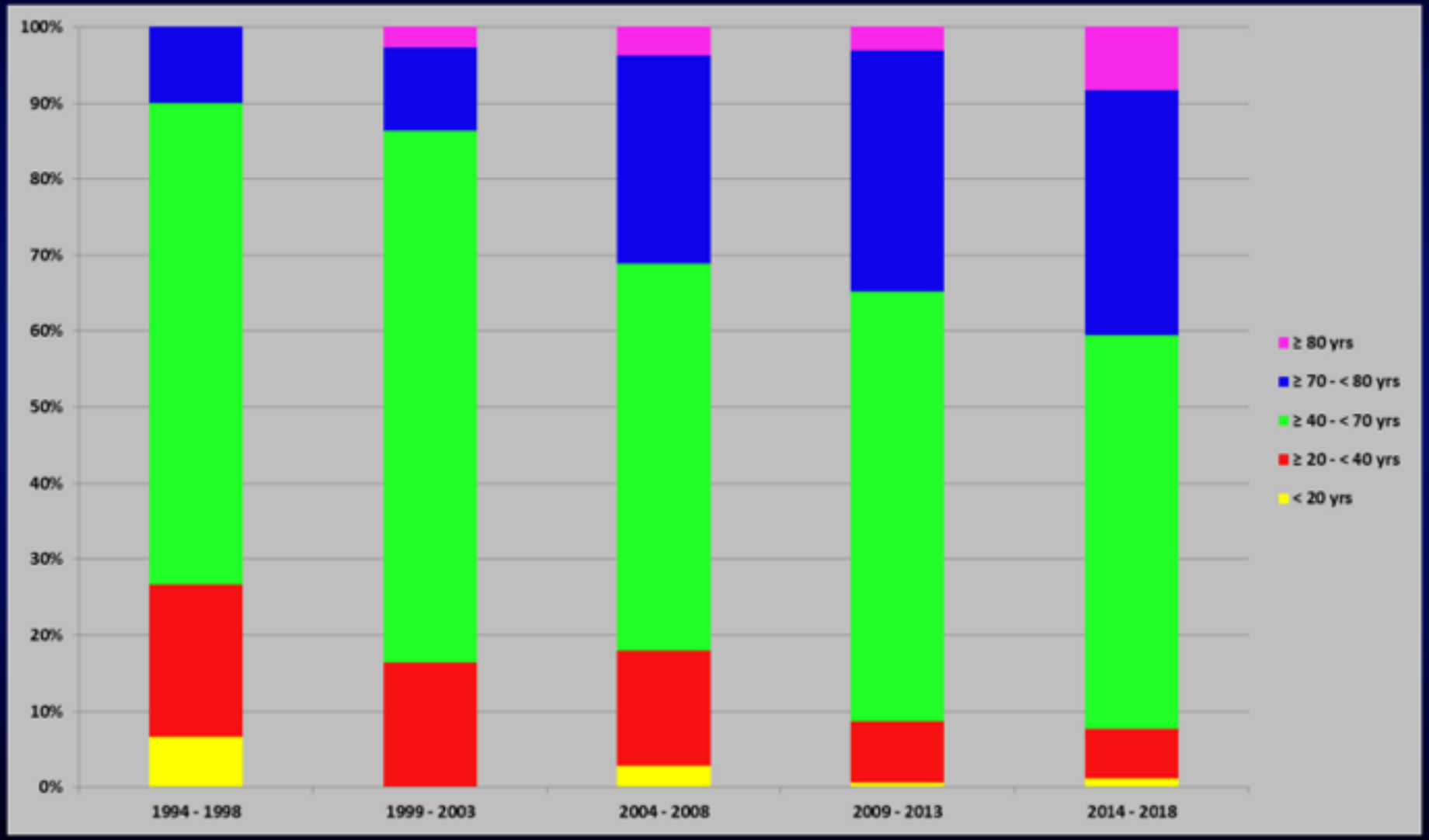
- National referral program
- Begin: April 1994
- September 2018: 897 PEAs performed

NUMBER OF PEAs BY THREE YEARS



AGE DISTRIBUTION BY FIVE YEARS

OF 897 PEAs



PAVIA CTEPH PROGRAM

January, 1st – December, 31st 2017 → 516

NewEvaluations (232 pts) CTEPH-PEA FUP (279 pts) PAS-PEA FUP (5 pts)

CONFIRMED (125 pts - 54%)

- PROXIMAL LESIONS (110 pts)
  - 81 PEAs (3 pts evaluated in 2016)
  - 4 waiting for PEA
  - 15 refused evaluation for PEA
  - 3 refused PEA
  - 8 with severe co-morbidities
  - 2 died before evaluation or before PEA

OPERABILITY RATE *thecnically* ***88%***
+ comorbidity ***82%***
+ refused ***67%***

- BPA program (12 pts)
  - 3 BPAs (7 pts evaluated in 2016)
  - 11 waiting for BPA
  - 1 too early for BPA
- DISTAL LESIONS (3 pts)
  - 2 controindication for DLTx
  - 1 too early for DLTx

OTHER DIAGNOSIS (107 pts - 46%)

- RECENT APE (22 pts)
  - 22 medical therapy
- PREVIOUS APE WITHOUT SIGNS (14 pts)
  - 14 medical therapy
- APE OVER CTE LESIONS (9 pts)
  - 9 3-month medical teraphy→new evaluation
- MINIMAL CTE LESIONS WITHOUT/LOW PH (12 pts)
  - 12 medical therapy
- PULMONARY ARTERY SARCOMA (10 pts)
  - 5 PEAs - 5 inoperable
- PULMONARY ARTERY ANEURYSM (3 pts)
  - 2 pulmonary artery resection
  - 1 interventional therapy
- MISCELLANEOUS (37 pts)
  - 7 Eisenmenger
  - 1 PH by hydatid cystic
  - 1 Mediastinal fibrosis
  - 1 PH by RA mixoma
  - 2 PH in Sclerodermia
  - 12 PAH
  - 7 Group 5 PH
  - 6 Other

CHARACTERISTICS

- Age
- NYHA functional class
- PVR
- Distribution of CTE lesions
- Amount of CTE occlusions
- Comorbidities

NYHA FUNCTIONAL CLASS

Usually patients referred for PEA are in NYHA functional class II, III or IV

The NYHA functional class distribution of PEA referred patients is however very different from center to center

Also some countries do not even have a CTEPH-PEA center → the diagnosis can therefore be very delayed and sending a patient to a PEA center could be very difficult

Consequently late referral is still a big issue in these patients

NYHA FUNCTIONAL CLASS

- *CTEPH* patients *must be* in *NYHA functional class III or IV* before being *evaluated for PEA!*
- *Only in 2003* we have performed our *first PEA* in *NYHA functional class II* patient…with a program that was active *since 1994!*

NYHA FUNCTIONAL CLASS

ACQUIRED CARDIOVASCULAR DISEASE

(J Thorac Cardiovasc Surg 2011;141:702-10)

Surgical management and outcome of patients with chronic thromboembolic pulmonary hyperte… international prospective registry

Eckhard Mayer, MD,[a] David Jenkins, FRCS,[b] Jaroslav …
Jaap Kloek, MD,[e] Bart Meyns, MD,[f] Lars Bo Ilkjaer, MI…
Irene Lang, MD,[h] Joanna Pepke-Zaba, MD,[b] Gerald Sir…

Study Design

This prospective registry was designed to include newly diagnosed (≤6 months) consecutive patients with CTEPH in participating centers in Europe and Canada, from February 2007 to January 2009. The registry proto-

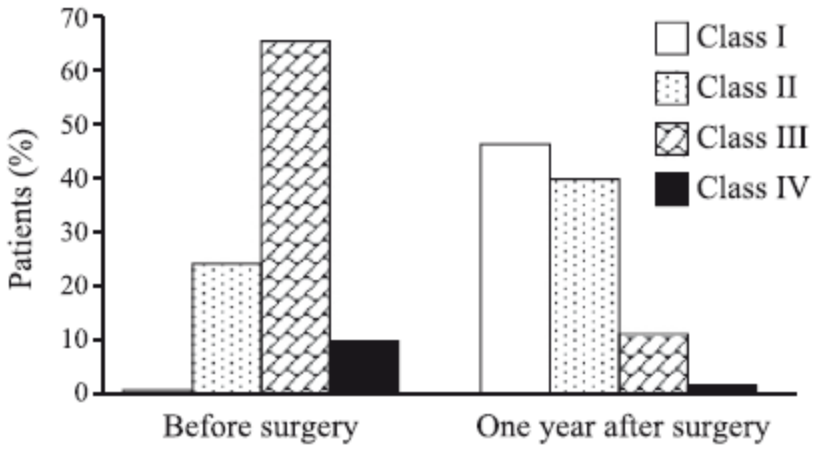


FIGURE 1. NYHA functional class before surgery and within 1 year after surgery (n = 221).

NYHA FUNCTIONAL CLASS

	INTERNATIONAL REGISTRY 2007-2008	PAVIA 2007-2008
II	25%	5%
III	65%	50%
IV	10%	45%

NYHA FUNCTIONAL CLASS

	INTERNATIONAL REGISTRY 2007-2008	PAVIA 2007-2008	PAVIA 2017-2018
II	25%	5%	20%
III	65%	50%	55%
IV	10%	45%	25%

NYHA FUNCTIONAL CLASS

Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension

Results From an International Prospective Registry

Marion Delcroix, MD; Irene Lang, MD; Joanna Pepke-Zaba, MD; Pavel Jansa, MD; Andrea M. D'Armini, MD; Repke Snijder, MD; Paul Bresser, MD; Adam Torbicki, MD; Soren Mellemkjaer, MD; Jerzy Lewczuk, MD; Iveta Simkova, MD; Joan A. Barbera, MD; Marc de Perrot, MD; Marius M. Hoeper, MD; Sean Gaine, MD; Rudolf Speich, MD; Miguel A. Gomez-Sanchez, MD; Gabor Kovacs, MD; Xavier Jais, MD; David Ambroz, MD; Carmen Treacy, BSc; Marco Morsolini, MD; David Jenkins, MD; Jaroslav Lindner MD; Philippe Dartevelle, MD; Eckhard Mayer, MD; Gerald Simonneau, MD

Circulation. 2016;133:859-871

NYHA FUNCTIONAL CLASS

NYHA class IV is one of the most important predictor of death increasing mortality by 4 to 5 times

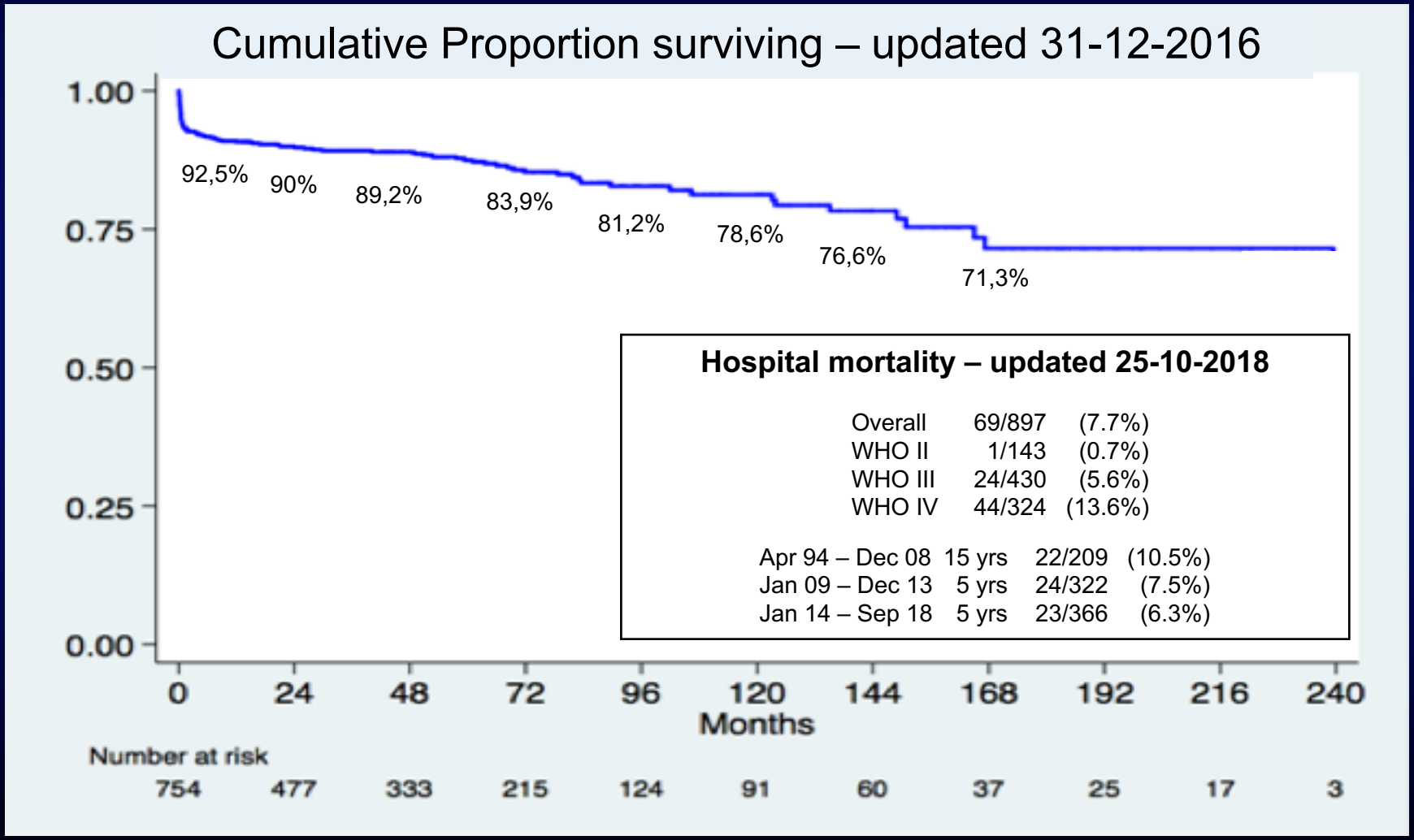
Table 4. Independent Correlates of Mortality for Operated and Not-Operated Patients

	Operated (n=346)			Not-Operated (n=219)		
Covariate	HR	95% CI	*P* Value	HR	95% CI	*P* Value
NYHA class III vs I–II				2.43	1.00–5.89	0.0489
NYHA class IV vs I–II	4.16	1.49–11.62	0.0065	4.76	1.76–12.88	0.0021

Circulation. 2016;133:859-871

CUMULATIVE PROPORTION SURVIVING

OF 897 PEAs



Hospital mortality – updated 25-10-2018

Overall		69/897	(7.7%)
WHO II		1/143	(0.7%)
WHO III		24/430	(5.6%)
WHO IV		44/324	(13.6%)
Apr 94 – Dec 08	15 yrs	22/209	(10.5%)
Jan 09 – Dec 13	5 yrs	24/322	(7.5%)
Jan 14 – Sep 18	5 yrs	23/366	(6.3%)

CHARACTERISTICS

- Age
- NYHA functional class
- PVR
- Distribution of CTE lesions
- Amount of CTE occlusions
- Comorbidities

PVR

ACQUIRED CARDIOVASCULAR DISEASE

Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: Results from an international prospective registry

Eckhard Mayer, MD,[a] David Jenkins, FRCS,[b] Jaroslav Lindner, MD,[c] Andrea D'Armini, MD,[d] Jaap Kloek, MD,[e] Bart Meyns, MD,[f] Lars Bo Ilkjaer, MD,[g] Walter Klepetko, MD,[h] Marion Delcroix, MD,[f] Irene Lang, MD,[h] Joanna Pepke-Zaba, MD,[b] Gerald Simonneau, MD,[i] and Philippe Dartevelle, MD[j]

J Thorac Cardiovasc Surg. 2011 Mar;141(3):702-10

PVR

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%)‡
NYHA functional class, n = 386			
I and II	n = 75	0‡	[illegible] NS
III	n = 262	12 (4.6%)*	[illegible]
IV	n = 49	6 (12.2%)‡	[illegible]
History of confirmed pulmonary embolism, n = 386			
Yes	n = 308	12 (3.9%) NS	19 (6.2%) [illegible]
No	n = 78	6 (7.7%)‡	[illegible]
Presence of an inferior vena cava filter, n = 298			
Yes	n = 42	—	[illegible]
No	n = 256	—	[illegible]
Circulatory arrest duration, n = 378			
≤ 20 min	n = 52	2 (3.8%) NS	[illegible]
21–40 min	n = 185	5 (2.7%) NS	[illegible]
1–60 min	n = 103	8 (7.8%) NS	[illegible]
> 60 min	n = 38	3 (7.9%)‡	[illegible]
Presence of coronary disease or myocardial infarction, n = 276			
Yes	n = 40	4 (10.0%)*	[illegible]
No	n = 236	5 (2.1%)‡	[illegible]
Presence of thrombophilic disorder, n = 254			
Yes	n = 141	7 (5.0%) NS	[illegible]
No	n = 113	2 (1.8%)‡	[illegible]

PVR, Pulmonary vascular resistance; NS, not significant; NYHA, New York Heart Association. Values are presented as numbers of patients (percentage). *P < .05 compared with 1. †P < .005 compared with 1. NS compared with 1 (Fisher's exact test)

PVR (dyn.s.cm^{-5}), n = 340		
<400	n = 48	0 (0%)*
400–800	n = 141	4 (2.8%)*
800–1200	n = 104	6 (5.8%) NS
> 1200	n = 47	5 (10.6%)†
NYHA functional class, n = 386		
I and II	n = 75	0‡
III	n = 262	12 (4.6%)*
IV	n = 49	6 (12.2%)†

J Thorac Cardiovasc Surg. 2011 Mar;141(3):702-10

PVR

Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension

David Jenkins1, Michael Madani2, Elie Fadel3, Andrea Maria D'Armini4 and Eckhard Mayer5

Eur Respir Rev 2017 Mar 15;26(143)

PVR

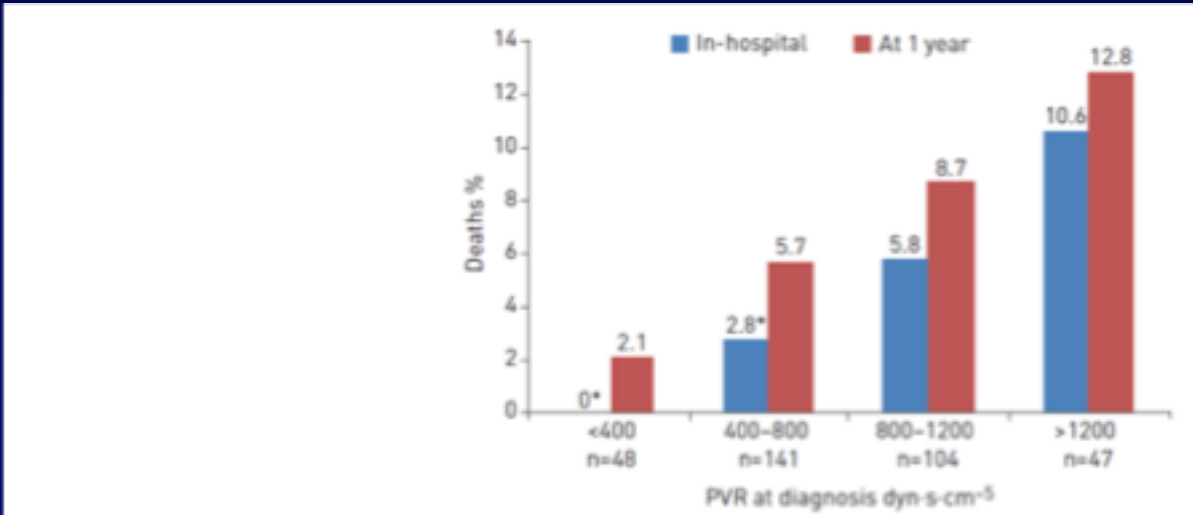


FIGURE 1 Effects of pulmonary vascular resistance (PVR) at diagnosis on in-hospital and 1-year mortality in patients with chronic thromboembolic pulmonary hypertension (CTEPH) undergoing pulmonary endarterectomy. Data from the international CTEPH registry [23]. *: $p<0.05$ compared with group with PVR >1200 dyn·s·cm^{-5}.

Eur Respir Rev 2017 Mar 15;26(143)

PVR

The changing landscape of chronic thromboembolic pulmonary hypertension management

Michael Madani1, Takeshi Ogo2 and Gérald Simonneau3,4,5

Eur Respir Rev. 2017 Dec 20;26(146)

PVR

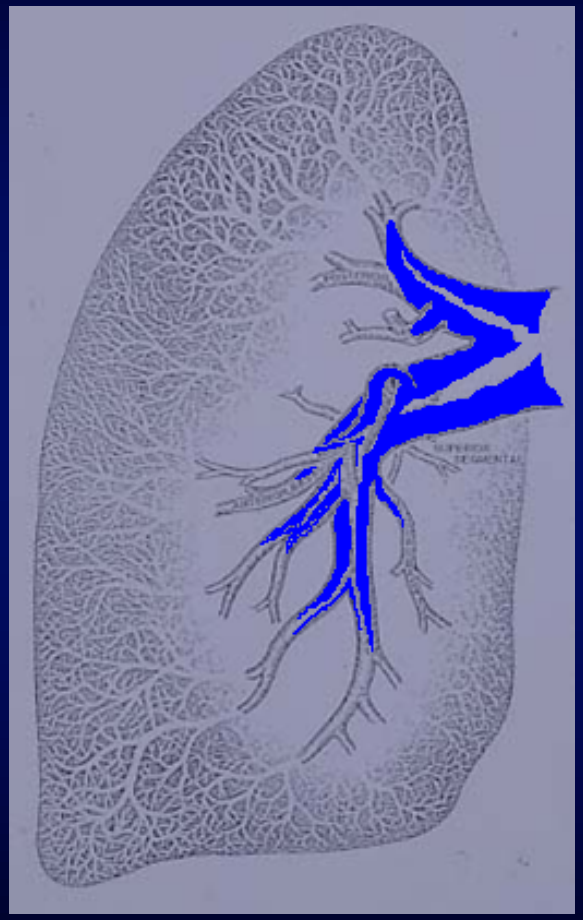
Measurement of a patient's haemodynamic status by right heart catheterisation is also an important part of risk assessment [1, 2]. Although high pre-operative PVR (>1000–1200 dyn·s·cm^{-5}) is correlated with an increased risk of post-operative mortality [13, 14, 35, 36], patients with a high PVR are in a position to gain the most benefit from surgery, as they often show the greatest relative improvement in PVR after the procedure [13, 14]. Therefore, high PVR should not necessarily be considered a contraindication for pulmonary endarterectomy [14, 37]. High pre-operative PVR in conjunction with comparatively low levels of surgically accessible thrombotic material is indicative of significant microvascular disease [36, 38].

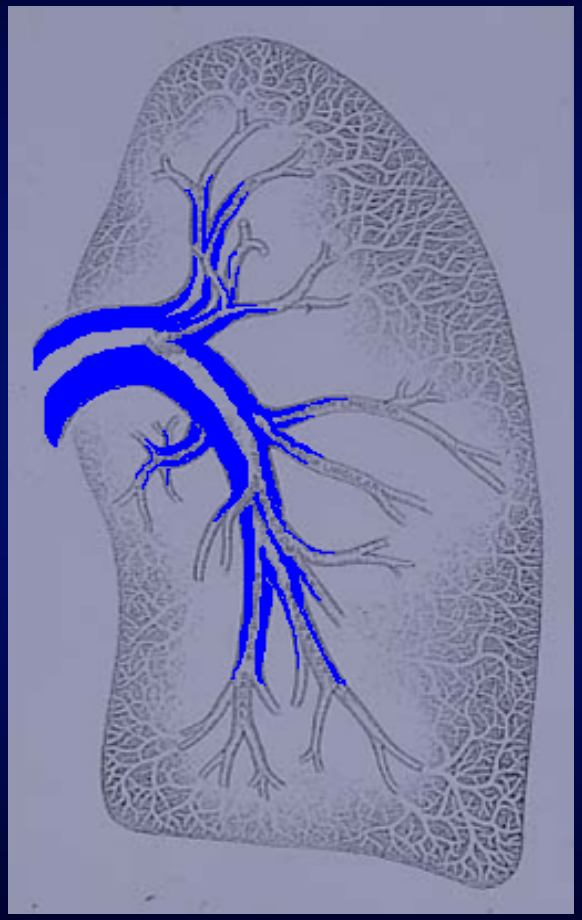
Eur Respir Rev. 2017 Dec 20;26(146)

CHARACTERISTICS

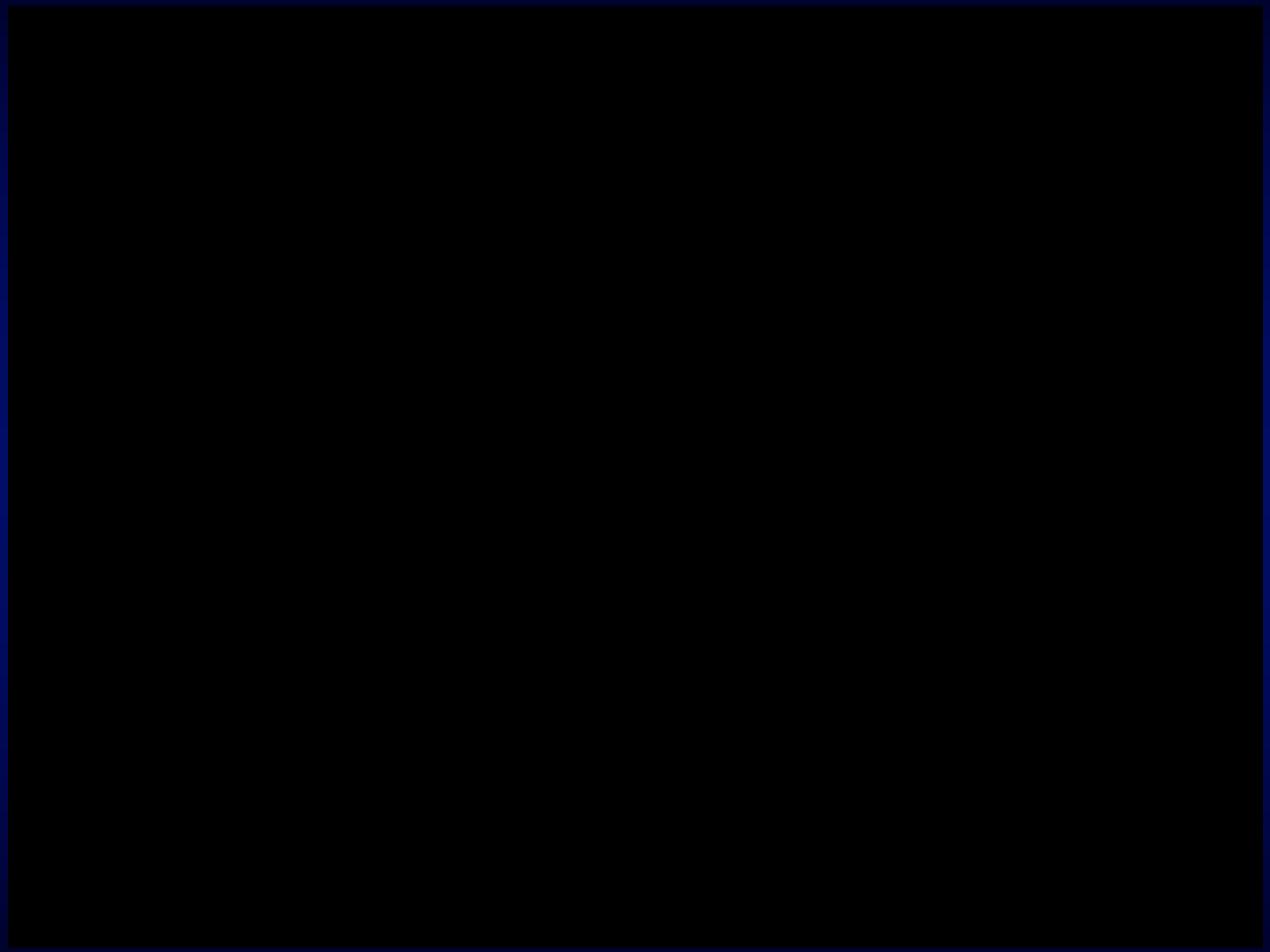
- Age
- NYHA functional class
- PVR
- Distribution of CTE lesions
- Amount of CTE occlusions
- Comorbidities

PROXIMAL LESIONS

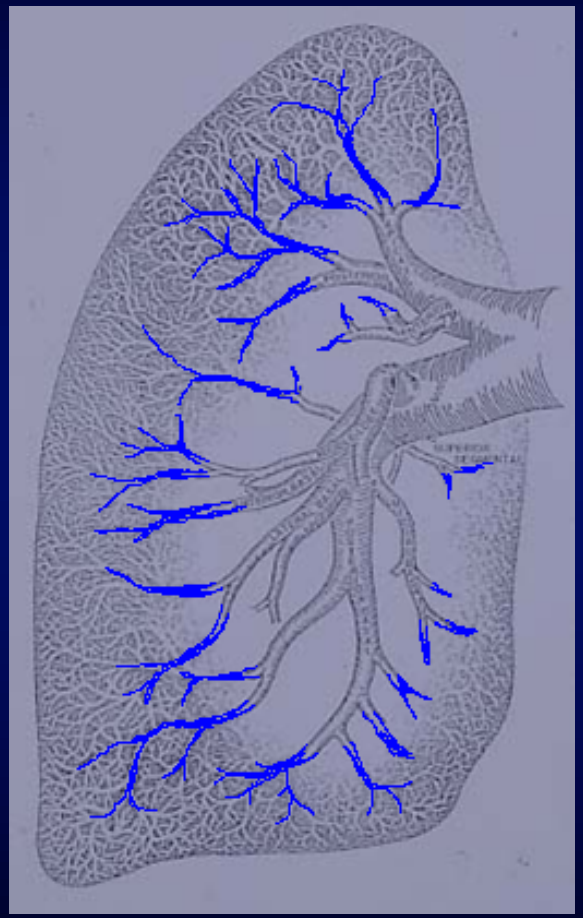


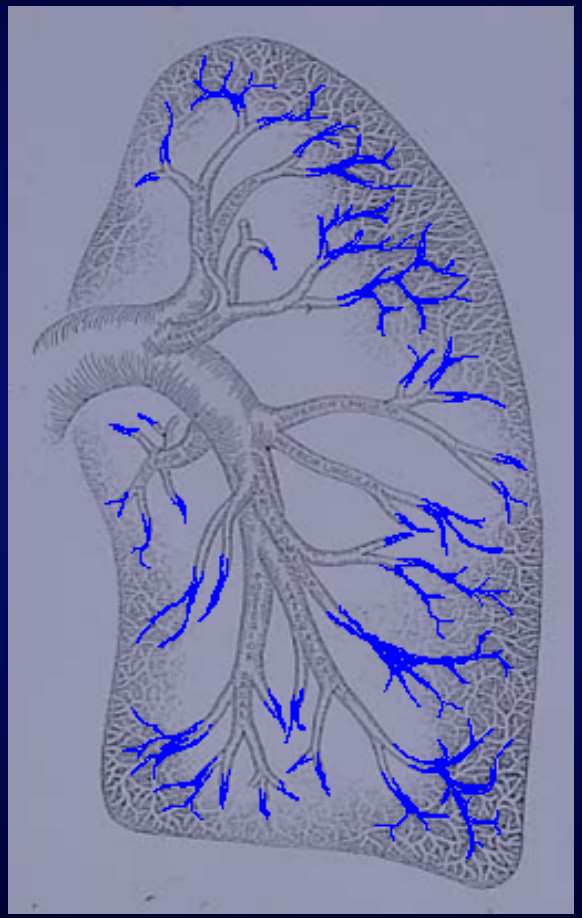


SURGICAL TECHNIQUE



DISTAL LESIONS





EVOLVING SURGICAL TECHIQUE

Evolving surgical techniques for pulmonary endarterectomy according to the changing features of chronic thromboembolic pulmonary hypertension patients during 17-year single-center experience

Marco Morsolini, MD,[a,b] Salvatore Nicolardi, MD,[a,b] Elisa Milanesi, MD,[c] Eleonora Sarchi, MD,[d] Gabriella Mattiucci, MD,[a] Catherine Klersy, MD, MSc,[e] and Andrea Maria D'Armini, MD[a]

(J Thorac Cardiovasc Surg 2012;144:100-7)

SURGICAL PROTOCOL

	Original San Diego protocol	Actual Pavia protocol
Aortic clamp	Yes	No
Cardioplegia	Yes	No
Hypothermia	Deep (18°C)	Moderate (24°C)
Circulatory arrest	A single (20 minutes) period of circulatory arrest for each side (with a maximum of a third)	Intermittent short periods of circulatory arrest (≈7-10 minutes) followed by short re-perfusion periods (≈5-7 minutes)
Total arrest time	Maximum 60 minutes	Maximum 180 minutes

Since 15-10-2009 (#245)

TAILORED AND LESS INVASIVE SURGERY

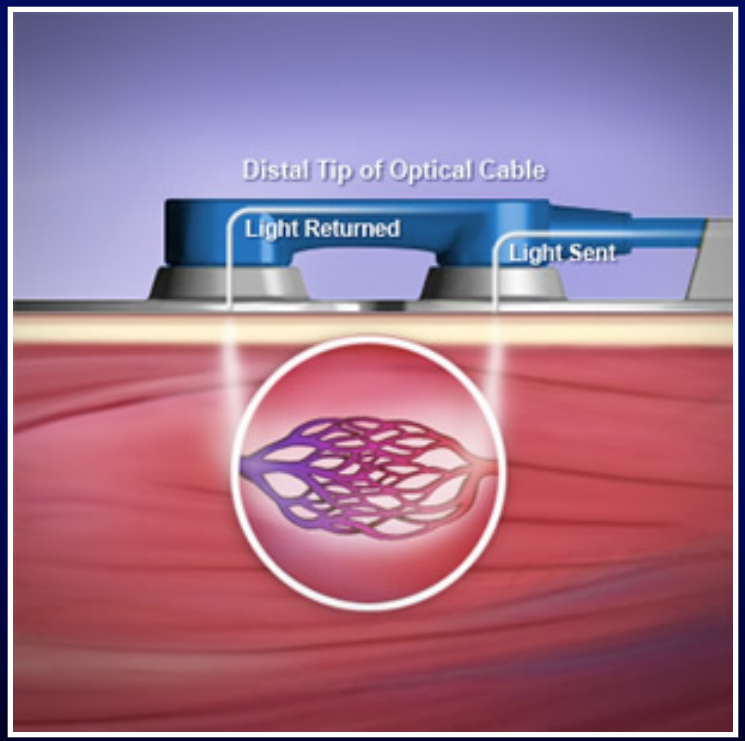
SURGICAL PROTOCOL

More than 650 PEAs with this technique

CEREBRAL PROTECTION

NIRS MONITORING

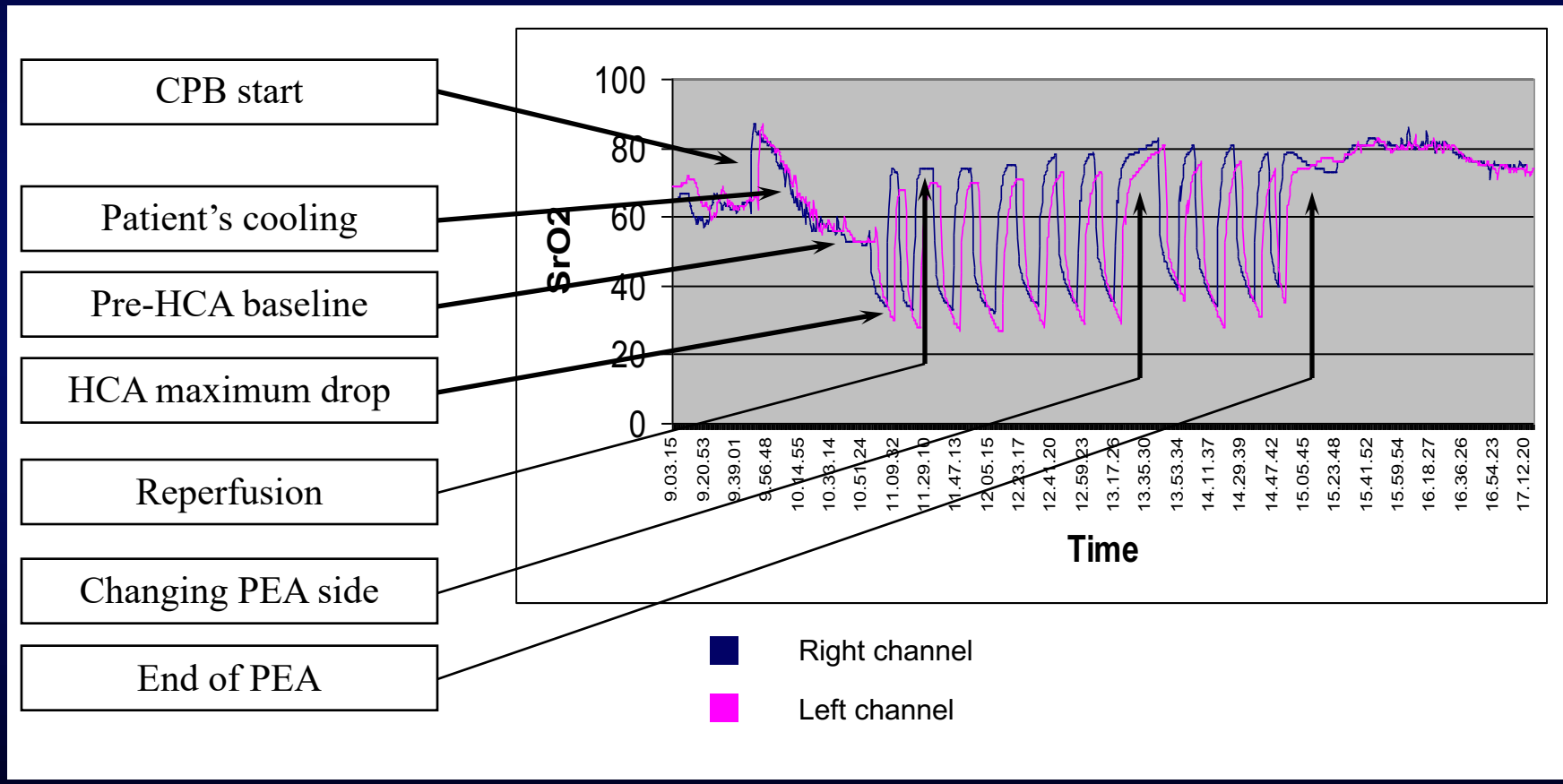
Near-InfraRed Spectroscopy



CEREBRAL PROTECTION

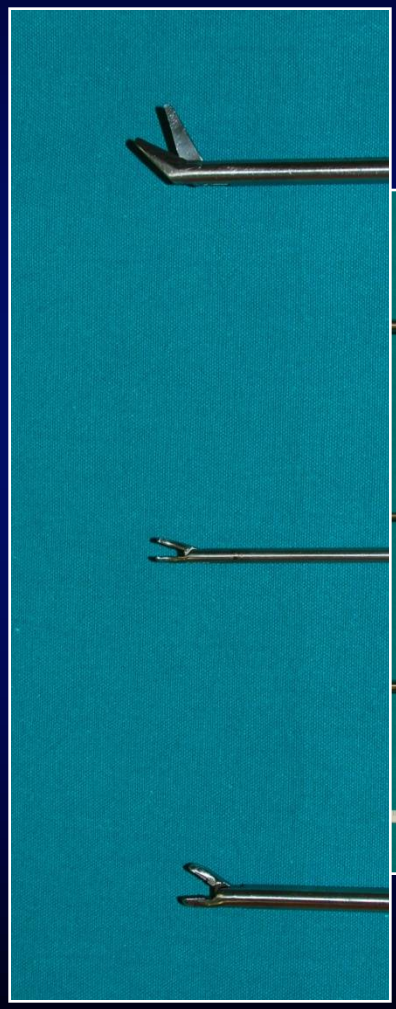
NIRS MONITORING

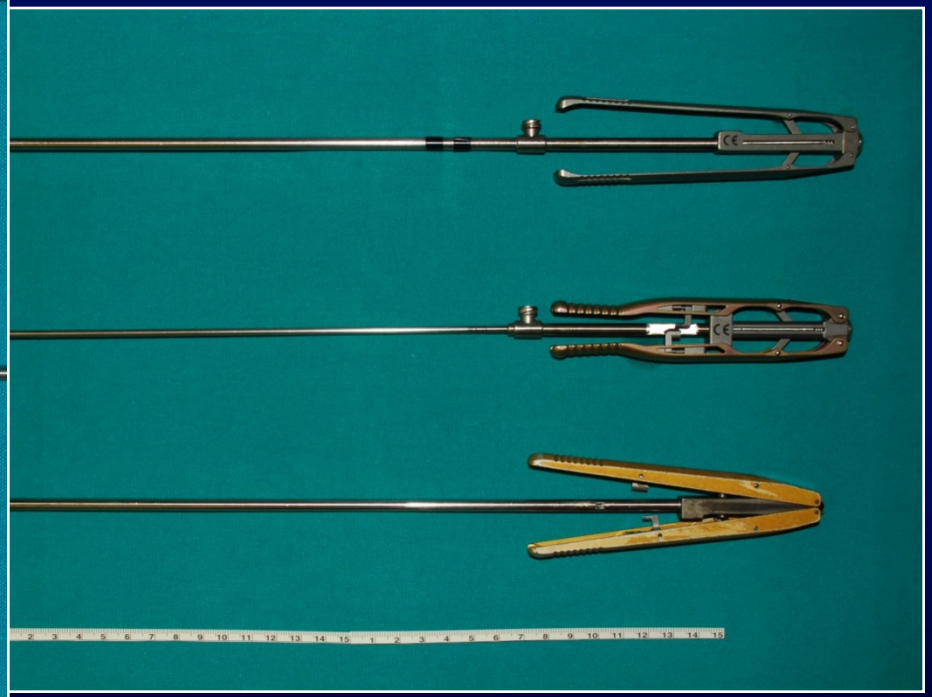
Near-InfraRed Spectroscopy



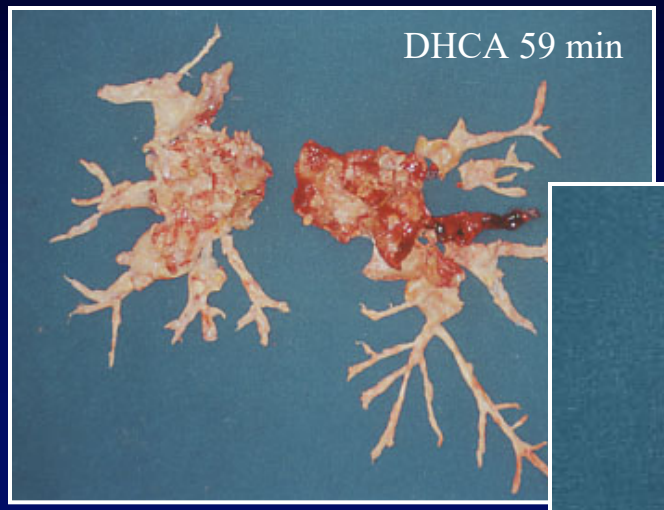
SURGICAL INSTRUMENTS

Derived from minimally-invasive cardiac surgery





JAMIESON TYPE1 vs. TYPE2 vs. TYPE3

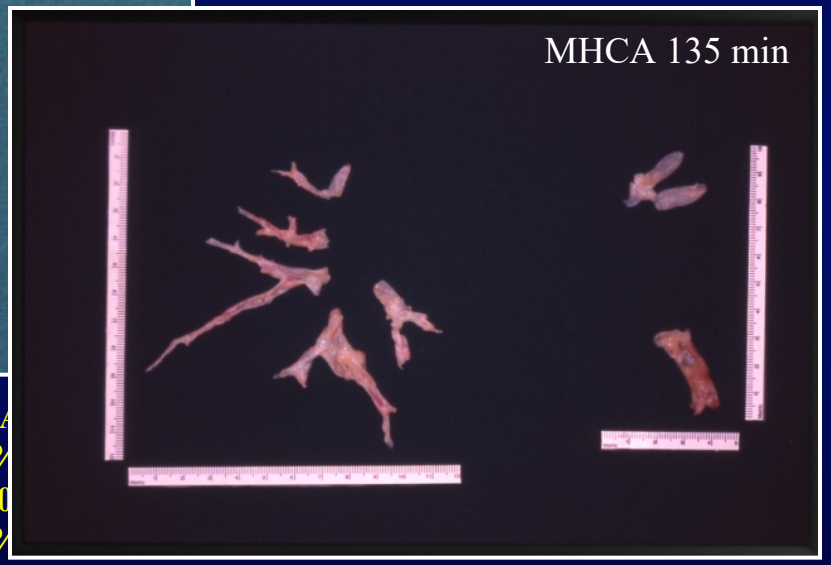


L.M.E.L. - 65 yrs M - Oct 2004 - PE

mPAP	39	→	19	(-51%)
CO	4.4	→	5.4	(+23%)
PVR	665	→	222	(-66%)

G.A.C. - 52 yrs F - Jul 2003 - PE

mPAP	48	→	27	(-44%
CO	2.1	→	4.2	(+100
PVR	1638	→	381	(-77%



B.A. - 43 yrs F - May 2009 - PEA #233

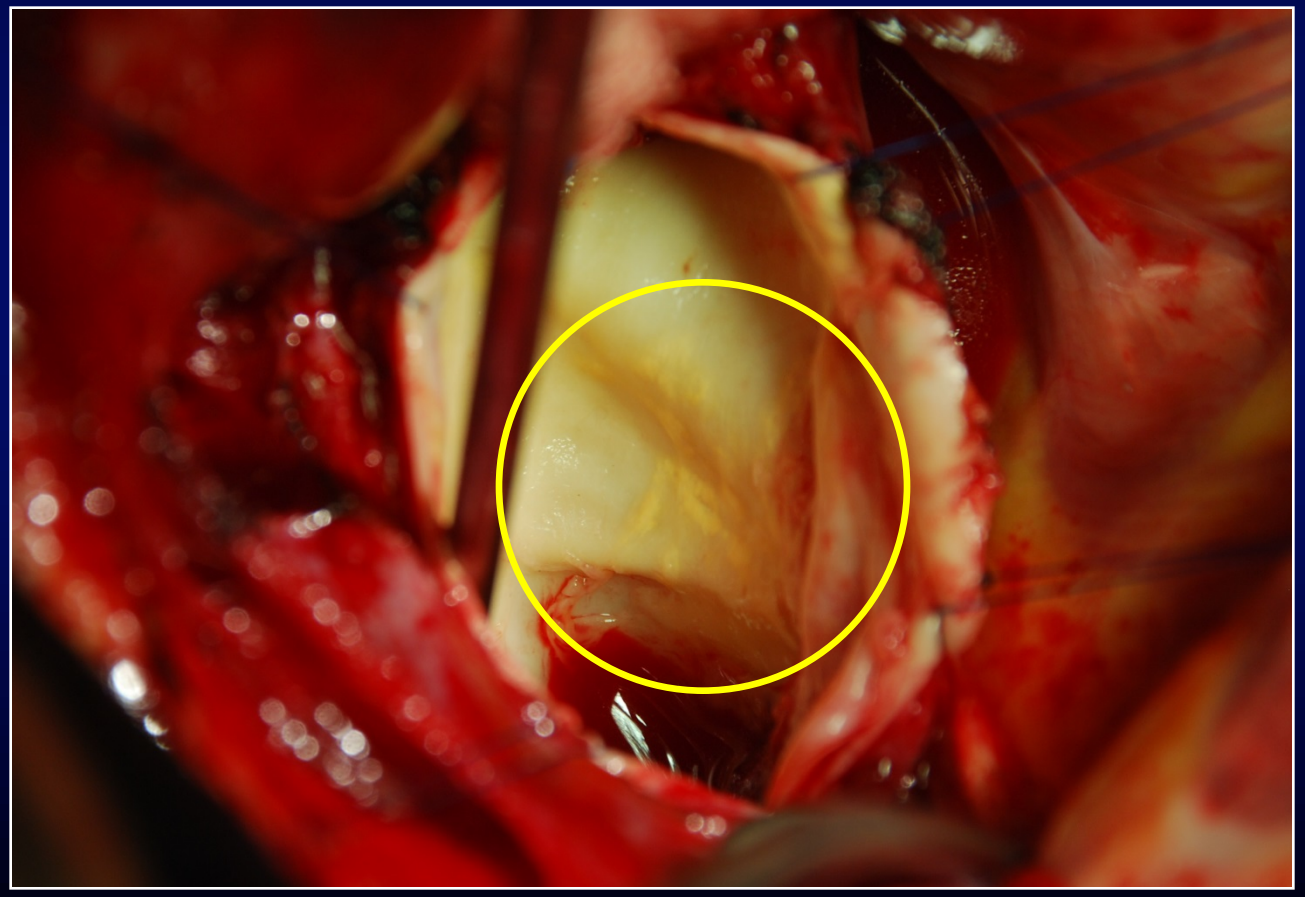
mPAP	49	→	19	(-61%)
CO	3.3	→	5.0	(+52%)
PVR	1067	→	224	(-79%)

DHCA: Deep Hypothermic Circulatory Arrest

MHCA: Moderate Hypothermic Circulatory Arrest

CORRECT ARTERIAL DISSECTION PLANE

Yellow-fibro-lipid plaques included into the removed cast



CORRECT ARTERIAL DISSECTION PLANE

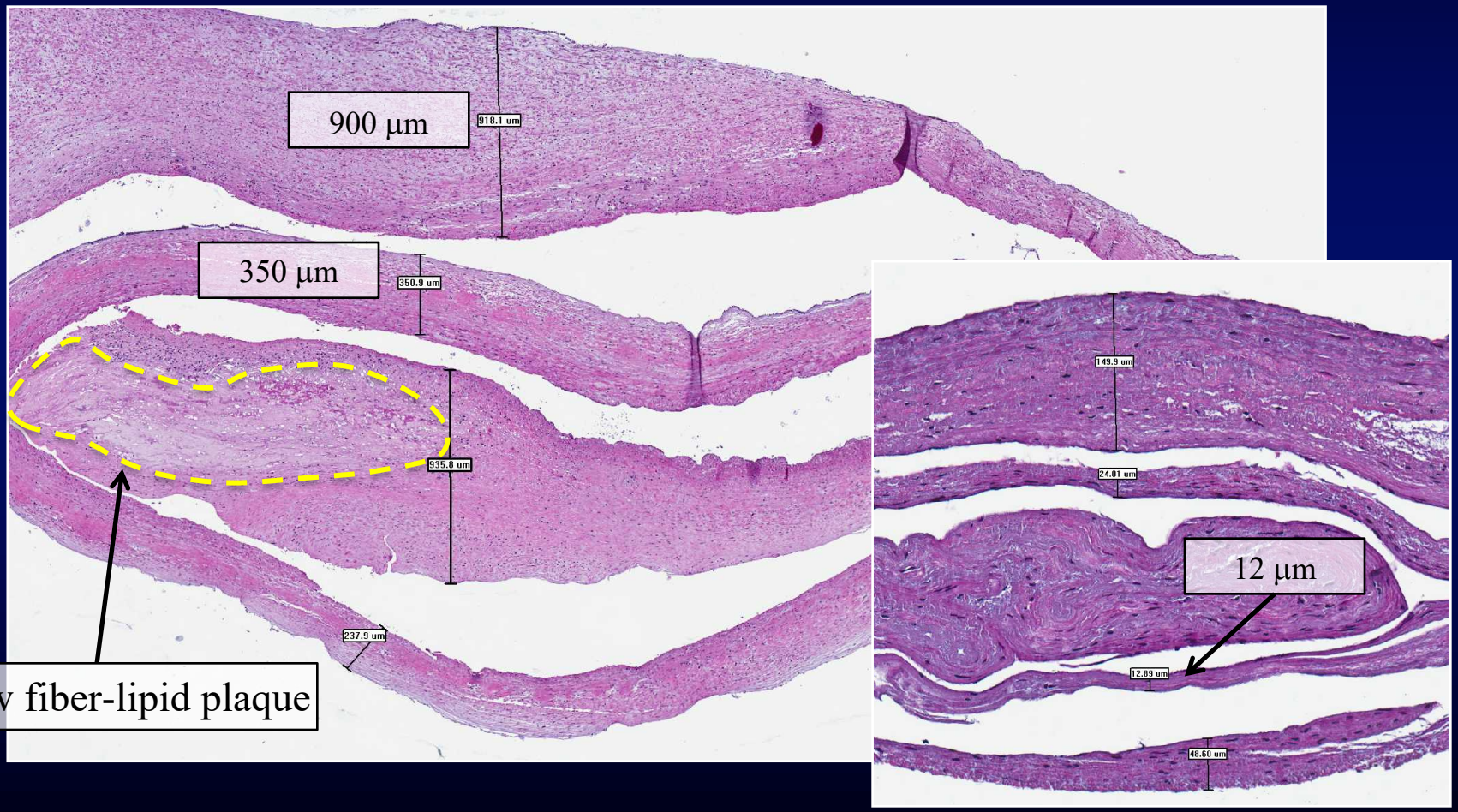
Reverse Ariadne's thread

CORRECT ARTERIAL DISSECTION PLANE

Proximal dissection for the clearance of distal obstructions

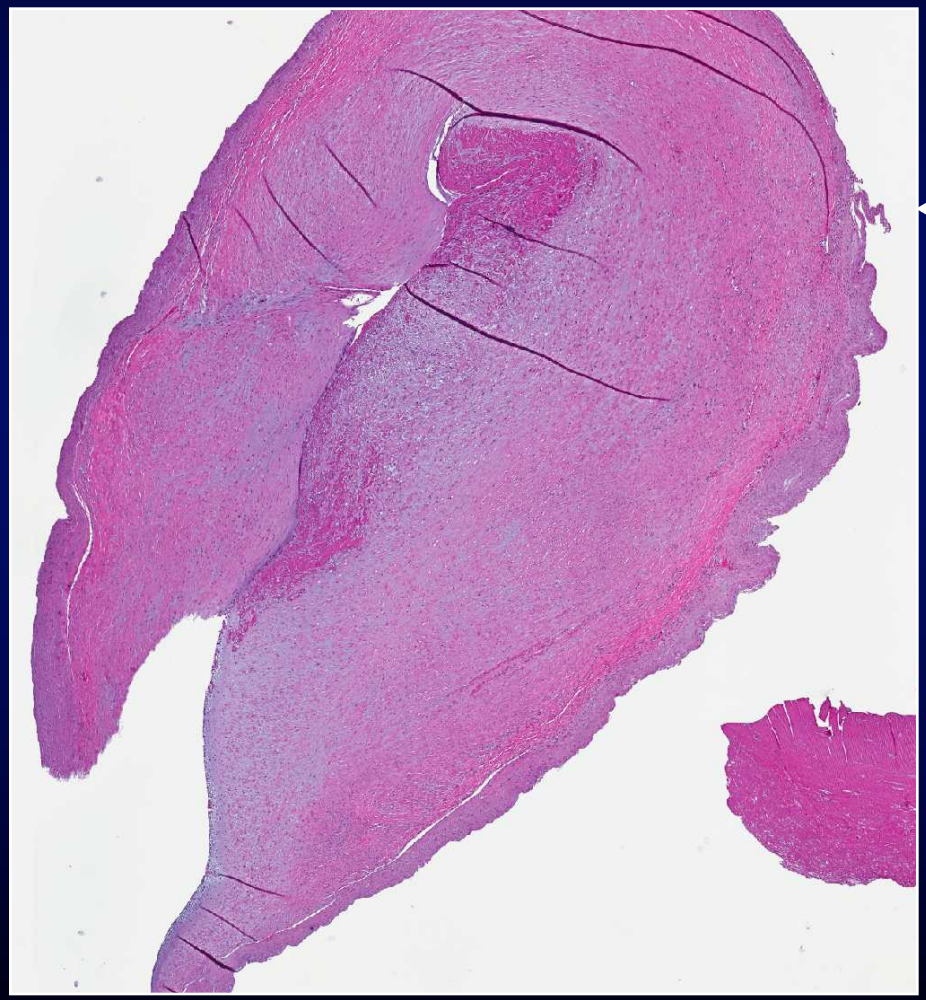
CORRECT ARTERIAL DISSECTION PLANE

Proximal dissection for the clearance of distal obstructions



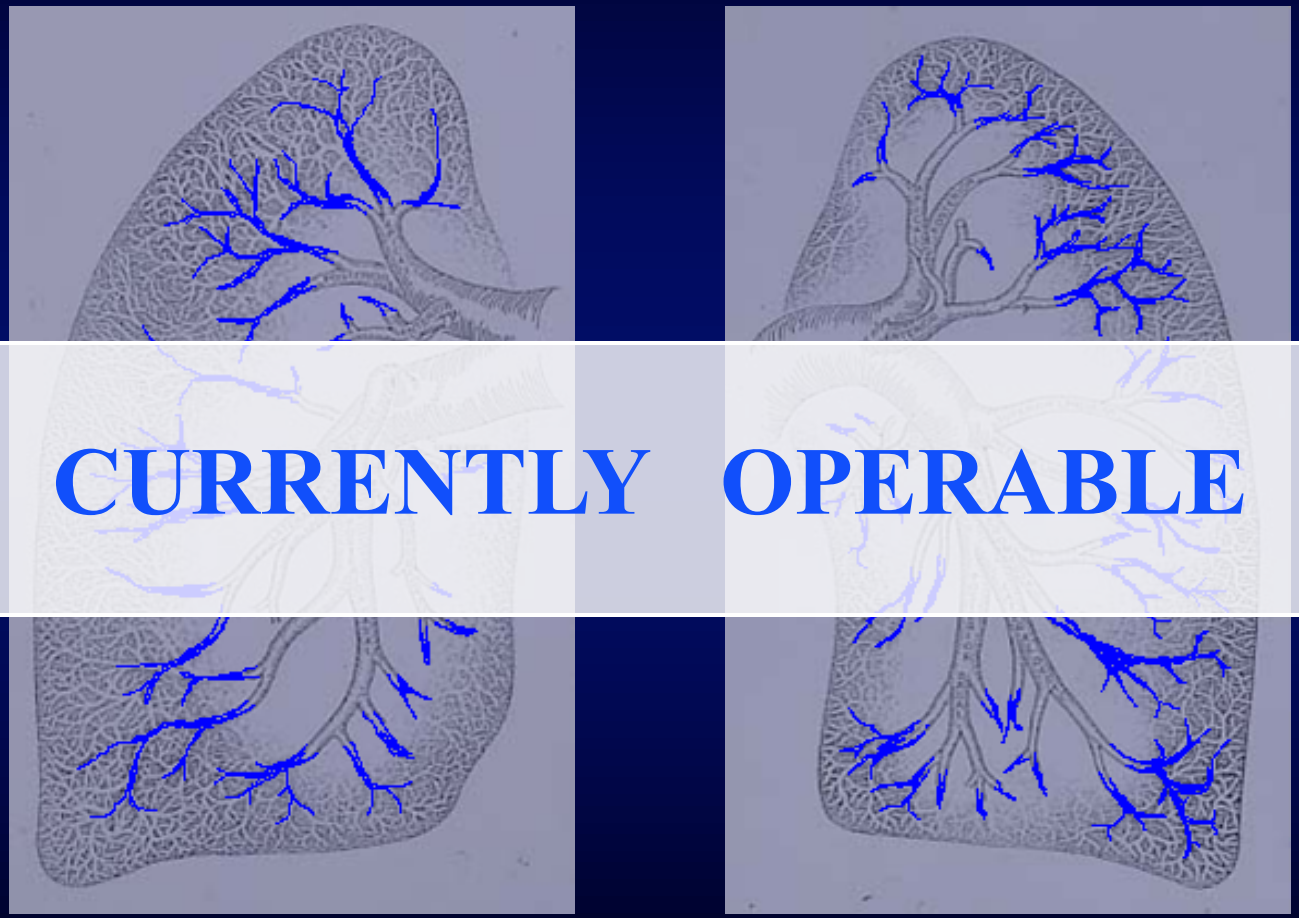
CORRECT ARTERIAL DISSECTION PLANE

Proximal dissection for the clearance of distal obstructions



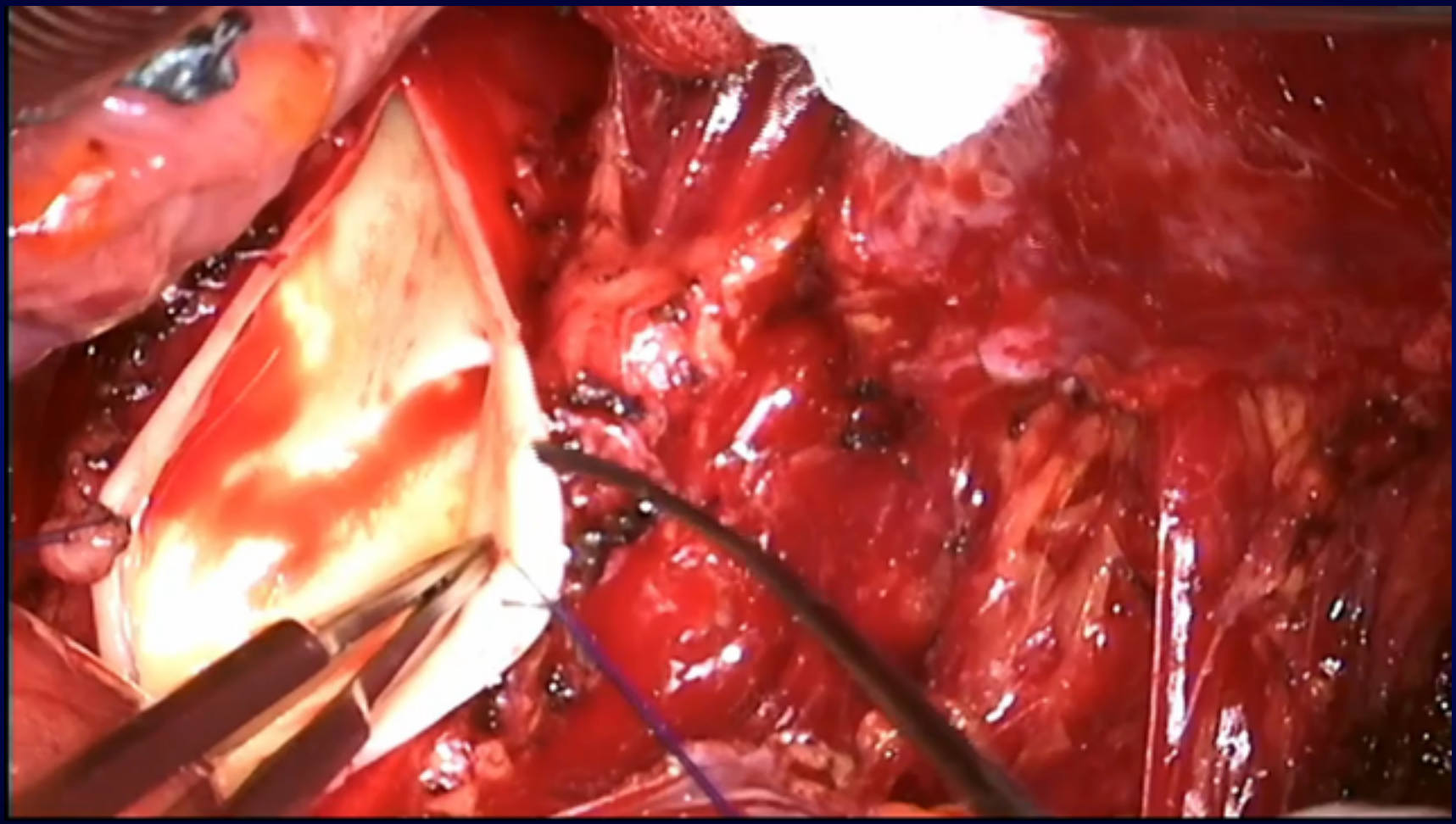
Sample

DISTAL LESIONS

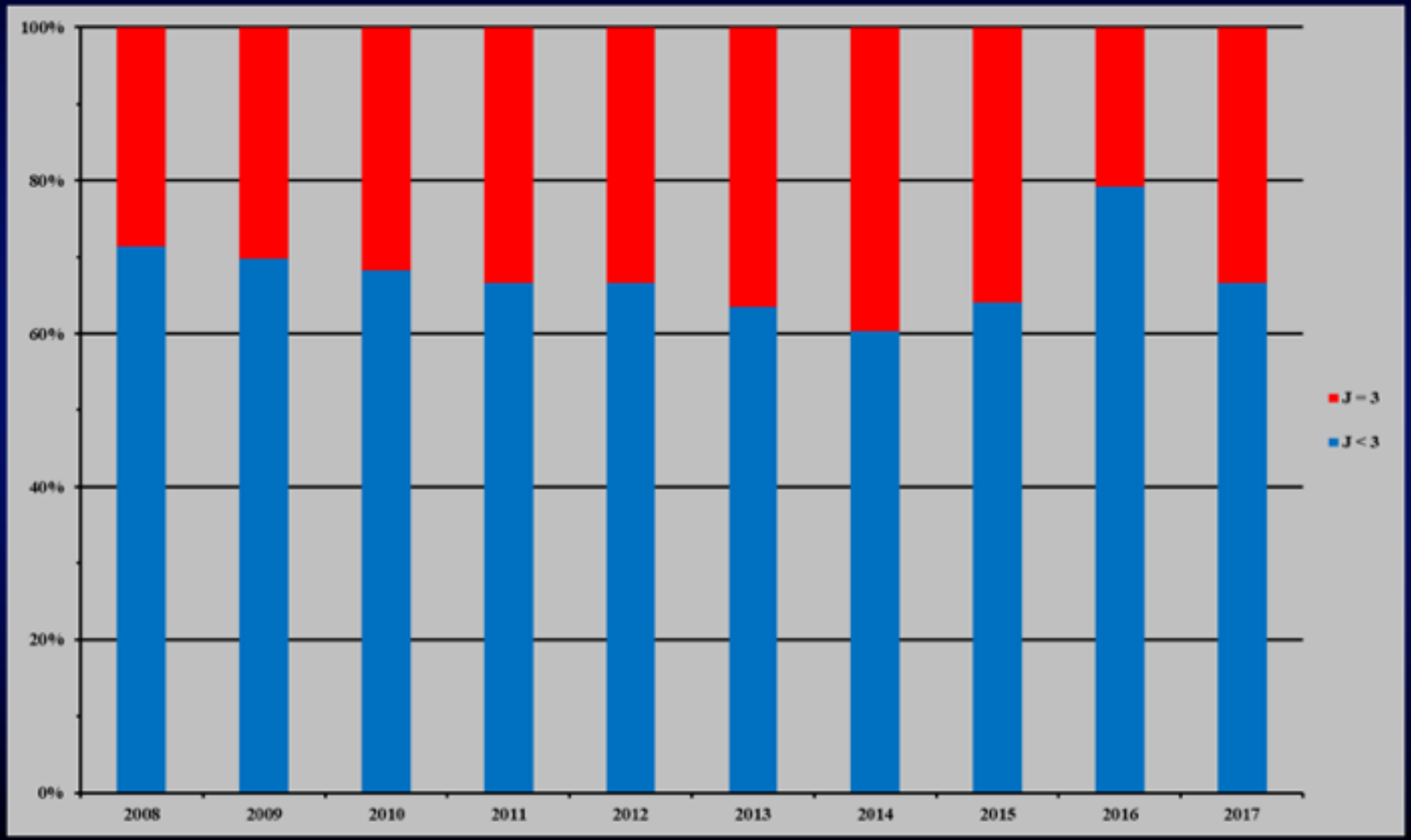


CURRENTLY OPERABLE

EVOLVING SURGICAL TECHNIQUE



JAMIESON TYPE3



DISTAL LESIONS

Pulmonary endarterectomy for distal chronic thromboembolic pulmonary hypertension

Andrea M. D'Armini, MD,[a,b] Marco Morsolini, MD, PhD,[a] Gabriella Mattiucci, MD,[a,b] Valentina Grazioli, MD,[a,b] Maurizio Pin, MD,[b] Adele Valentini, MD,[c] Giuseppe Silvaggio, MD,[b] Catherine Klersy, MD, MSc,[d] and Roberto Dore, MD[c]

(J Thorac Cardiovasc Surg 2014;148:1005-12)

DISTAL LESIONS

TABLE 2. Intraoperative comparison and early postoperative outcome

	Proximal	Distal	*P* value
Bilateral PEA (n)	192 (86.9)	95 (86.4)	1.000
Associated procedures (n)	38 (17.2)	19 (17.3)	1.000
Total CPB time (min)	338 ± 81 (327-348)	361 ± 64 (349-373)	**.005**
Hypothermia (°C)	24.0 ± 0.9 (23.9-24.1)	23.7 ± 1.0 (23.5-23.8)	**.003**
Total HCA time (min)	84 ± 32 (80-89)	102 ± 28 (97-107)	**<.001**
P_{AO_2}/F_{IO_2} 6 h	284 ± 91 (271-296)	280 ± 112 (259-301)	.758
MV duration (d)	2 (1-3)	2 (1-4)	.565
ICU stay (d)	4 (3-7)	4 (3-8)	.962
Postoperative hospital stay (d)	13 (10-16)	13 (11-17)	.541

	Risk	Risk difference (95% CI)	*P* value
Univariate analysis			
Hospital mortality		1.8 (−4.2 to 7.9)	.647
Proximal	6.3%		
Distal	8.1%		
Lung reperfusion edema		−0.5 (−4.4 to 3.4)	1.000
Proximal	3.2%		
Distal	2.7%		
Tracheostomy		−1.9 (−7.8 to 3.9)	.662
Proximal	8.3%		
Distal	6.4%		
Neurologic event		−4.7 (−10.6 to 1.1)	.209
Proximal	10.2%		
transient 13/22			
permanent 9/22			
Distal	5.5%		
transient 5/6			
permanent 1/6			

Bold values indicate significance ($P < .05$). *CI*, Confidence interval; *CPB*, cardiopulmonary bypass; *HCA*, hypothermic circulatory arrest; *ICU*, intensive care unit; *MV*, mechanical ventilation; P_{AO_2}/F_{IO_2} *6 h*, partial pressure of oxygen in arterial blood/fraction of inspired oxygen ratio 6 hours after admission to ICU; *PEA*, pulmonary endarterectomy.

DISTAL LESIONS

TABLE 3. Hemodynamic time course after pulmonary endarterectomy

	Proximal	Distal
Mean pulmonary arterial pressure (mm Hg)		
Preoperative	44 ± 10	46 ± 11
At discharge	22 ± 7	24 ± 6
3-mo follow-up	24 ± 9	25 ± 7
12-mo follow-up	23 ± 7	24 ± 8
P value*	<.001	<.001
PVR (dyne·s·cm^{-5})		
Preoperative	876 ± 392	926 ± 337
At discharge	251 ± 146	295 ± 161
3-mo follow-up	270 ± 175	300 ± 139
12-mo follow-up	243 ± 115	300 ± 224
P value*	<.001	<.001
Cardiac output (L/min)		
Preoperative	3.9 ± 1.3	3.7 ± 1.2
At discharge	5.0 ± 1.2	4.7 ± 1.2
3-mo follow-up	5.2 ± 1.1	5.0 ± 1.2
12-mo follow-up	5.0 ± 1.1	4.7 ± 1.0
P value*	<.001	<.001

PVR, Pulmonary vascular resistance. *Each time point versus preoperative. Test of interaction: $P = .975$ (mean pulmonary arterial pressure); $P = .777$ (PVR); $P = .825$ (cardiac output).

DISTAL LESIONS

TABLE 4. Partial pressure of oxygen in arterial blood, modified Bruce exercise test, and 6-minute walking distance time course after pulmonary endarterectomy

	Proximal	Distal
Arterial partial pressure of oxygen (mm Hg)		
Preoperative	65 ± 12	66 ± 11
3-mo follow-up	82 ± 13	80 ± 11
12-mo follow-up	80 ± 11	80 ± 11
P value*	<.001	<.001
Modified Bruce exercise test (m)		
Preoperative	51 (0-143)	52 (0-102)
3-mo follow-up	495 (182-658)	435 (143-586)
12-mo follow-up	520 (261-709)	474 (225-620)
P value*	<.001	<.001
6-min walking distance (m)		
Preoperative	277 ± 118	289 ± 112
3-mo follow-up	391 ± 118	398 ± 107
12-mo follow-up	389 ± 118	396 ± 112
P value*	<.001	<.001

*Each time point versus preoperative. Test of interaction: $P = .317$ (partial pressure of oxygen in arterial blood); $P = .205$ (modified Bruce exercise test); $P = .962$ (6-min walking distance).

NEUROPSYCHOLOGICAL OUTCOMES

ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

INNOVATION

Neuropsychological outcomes after pulmonary endarterectomy using moderate hypothermia and periodic circulatory arrest

Benedetta Vanini, PsyD, PhD,[a,b] Valentina Grazioli, MD,[a] Antonio Sciortino, MD,[a] Maurizio Pin, MD,[a] Vera N. Merli, MD,[a] Anna Celentano, MD,[a] Ilaria Parisi,[a] Catherine Klersy, MD,[c] Lucia Petrucci, MD,[d] Maurizio Salati, MD,[a] Pierluigi Politi, MD, PhD,[b] and Andrea M. D'Armini, MD[a]

J Heart Lung Transplant. 2018 Feb in press

NEUROPSYCHOLOGICAL OUTCOMES

Table 1 Baseline Characteristics of Study Patients ($n = 70$)

Variable	
Male sex	31 (44%)
Age (years)	48 ± 10
Education (years)	10 ± 4
Presence of a partner	60 (86%)
Total circulatory arrest (minutes)	89 ± 27
Bilateral surgery	61 (87%)
Duration of anesthesia (minutes)	525 ± 78
Cerebral oxygen saturation (%)	29 ± 10

J Heart Lung Transplant. 2018 Feb in press

Table 2 Changes in Neuropsychological Parameters From Baseline to 3 Months After Surgery

Variable	Baseline score	3-month score	Normal value*	Generalized linear model p-value
Global cognition				
MMSE	28.48 ± 2.73	28.88 ± 2.03	≥24	0.195
Long-term verbal memory				
RAVLT-I	40.86 ± 8.93	37.01 ± 8.67	>28.53	<0.001†
RAVLT-D	9.42 ± 3.09	8.07 ± 3.13	>4.70	<0.001†
Short-term verbal memory				
FDS	5.86 ± 1.24	6.12 ± 1.23	>3.75	0.280
Selective attention				
AM	48.07 ± 8.04	48.77 ± 6.69	>31	0.754
Divided attention, processing speed, planning, and flexibility				
TMT A	38.14 ± 39.44	36.95 ± 37.39	<93	0.656
TMT B	90.16 ± 78.44	87.66 ± 89.48	<282	0.132
TMT B-A	54.31 ± 65.46	54.22 ± 72.12	<186	0.078
Motor speed				
GP-DH (seconds)	109.79 ± 61.47	105.40 ± 55.79	<170	0.007†
GP-NDH (seconds)	114.22 ± 56.95	113.63 ± 64.14	<180	<0.001†
Verbal fluency				
PVF	33.51 ± 11.62	36.76 ± 16.02	>17	0.239
SVF	39.08 ± 9.34	43.76 ± 11.14	>25	0.078
Executive function				
FAB	16.26 ± 1.97	16.65 ± 1.66	>13.5	0.224
Anxiety				
HADS-A	7.70 ± 4.34	5.95 ± 3.64	≤7	<0.001†
Depression				
HADS-D	6.11 ± 3.48	4.48 ± 3.37	≤7	0.002†
Quality of life				
SF-36 PCS	35.80 ± 8.63	45.08 ± 9.75	>50	<0.001†
SF-36 MCS	47.58 ± 10.70	54.75 ± 8.93	>50	<0.001†

Data expressed as number (%) or as mean ± standard deviation. AM, Attentional Matrices; FAB, Frontal Assessment Battery; FDS, Forward Digit Span; GP-DH, Grooved Pegboard—dominant hand; GP-NDH, Grooved Pegboard—non-dominant hand; HADS-A, Hospital Anxiety and Depression Scale—Anxiety; HADS-D, Hospital Anxiety and Depression Scale—Depression; MMSE, Mini-Mental State Examination; PF, Phonological Verbal Fluency; RAVLT-D, Rey Auditory Verbal Learning Test—delayed recall; RAVLT-I, Rey's Auditory Verbal Learning Test—immediate Recall; TMT A, TMT B, TMT B-A, Trail Making Test A, B, B-A; SVF, Semantic Verbal Fluency; SF-36 MCS, 36-Item Short Form—Mental Component Summary; SF-36 PCS, 36-Item Short Form—Physical Component Summary.

*Normal value for the Italian population (refer to Table S1 in the Supplementary Material online).

†Significant change at follow-up.

NEUROPSYCHOLOGICAL OUTCOMES

The main findings of our study show that *repeated short periods of MHCA* during PEA in patients with CTEPH *did not result in any neuropsychological complications*

Although *learning ability* and *delayed memory* showed a slight deterioration among study patients at 3 months after PEA, they continued to *remain well* and in the *normal range* for both age and years of study

More remarkably, we found a *statistically significant postsurgical improvement* in motor speed, which was accompanied by a *better quality of life* and *reduced symptoms* of *depression* and *anxiety*

CHARACTERISTICS

- Age
- NYHA functional class
- PVR
- Distribution of CTE lesions
- Amount of CTE occlusions
- Comorbidities

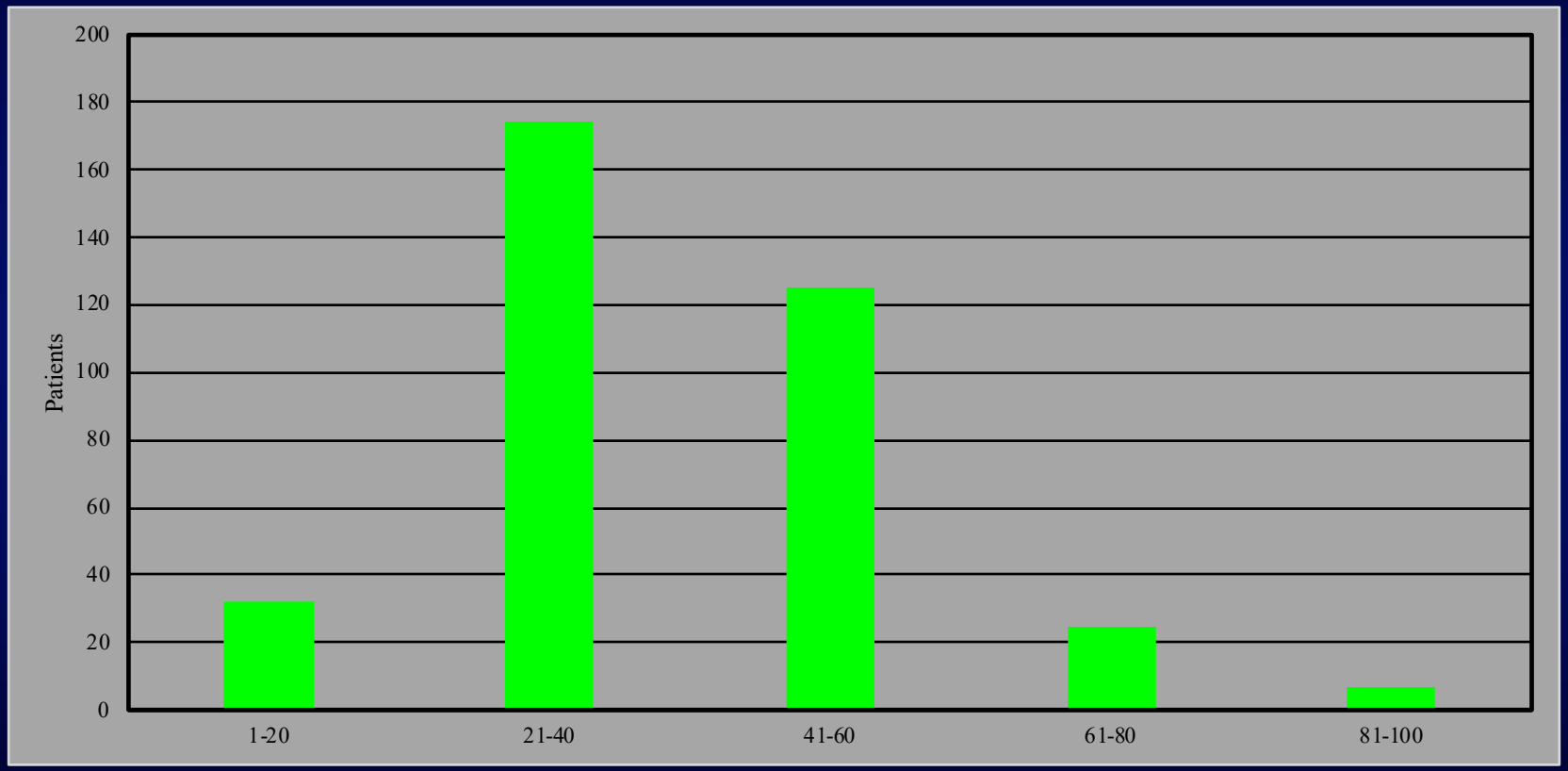
PLANTY vs. SCARSE CTE OCCLUSIONS

PULMONARY ENDARTERECTOMY: RELATIONSHIP BETWEEN TOTAL REOPENED BRANCHES AND OUTCOMES

UNIVERSITY OF PAVIA SCHOOL OF MEDICINE - SAN MATTEO HOSPITAL - PAVIA - ITALY

GROUPED BY REOPENED BRANCHES

344 PEA



REOPENED BRANCHES AND TCA

	N°	Mean	SD	Min	P25	P50	P75	Max
Reopened Branches	344	38.7	± 15.7	7	28	37	48	100
TCA (min)	344	93.5	± 26.9	0	77	93	113	162

ASSOCIATION OF HEMODYNAMIC AND PAO2 DATA AT 3 MONTHS AND THE NUMBER OF REOPENED BRANCHES

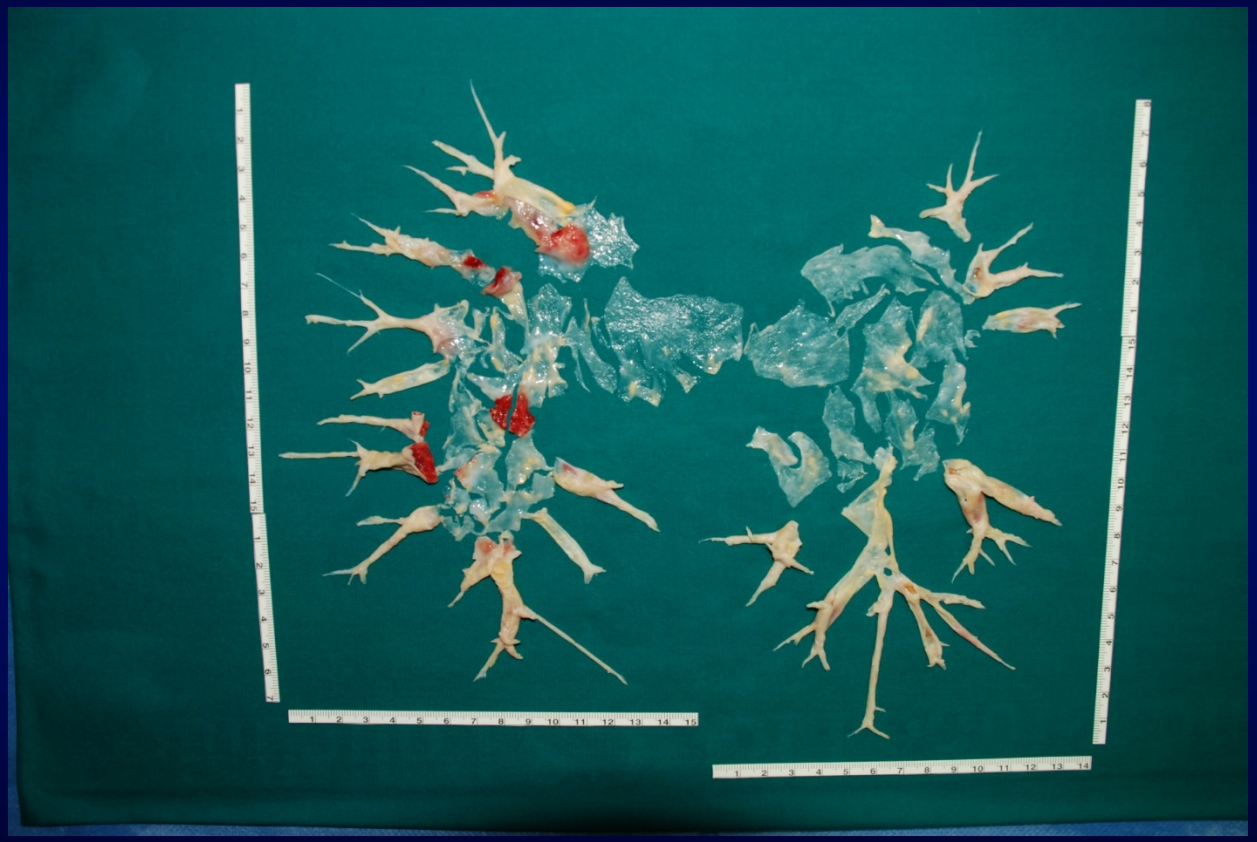
	Number of Reopened branches subgroups (tertiles)						Number of Reopened branches (continuous)		
Outcome measure at 3 months	(a) Branches reopened 7-26	(b) Branches reopened 27-41	(c) Branches reopened 42-100	Univariable Model P value*	Multivariable Model P value**		Sperman's rho	Univariable Model P value	Multivariable Model P value**
PVR (dyne/sec/cm^{-5})	315 ± 163	277 ± 148	232 ± 105	< 0.001 a vs b 0.35 a vs c 0.001 b vs c 0.06	0.045 a vs b 0.41 a vs c 0.040 b vs c 0.64		- 0.25	< 0.001	< 0.001
CO (l/min)	5.1 ± 1.1	5.0 ± 1.2	5.2 ± 1.1	0.31	0.33		0.07	0.37	0.83
CI (l/min/m^2)	2.8 ± 0.5	2.7 ± 0.5	2.8 ± 0.5	0.34	0.29		0.05	0.43	0.92
mPAP (mmHg)	26 ± 9	24 ± 8	22 ± 6	0.009 a vs b 0.25 a vs c 0.007 b vs c 0.46	0.027 a vs b 0.15 a vs c 0.022 b vs c 1.00		- 0.18	<0.001	<0.001
PAO2 (mmHg)	77.4 ± 13.1	79.7± 12.3	82.2 ± 11.3	0.06	0.35		0.17	0.003	0.05

ASSOCIATION OF FUNCTIONAL DATA AT 3 MONTHS AND THE NUMBER OF REOPENED BRANCHES

	Number of Reopened branches subgroups (tertiles)					Number of Reopened branches (continuous		
	(a) Branches reopened 7-26	(b) Branches reopened 27-41	(c) Branches reopened 42-100	Univariable Model P value*	Multivariable Model P value**	Mean ± SD	Univariable Model P value*	Multivariable Model P value**
WHO class I/II III/IV	5 (9%)	4 (4%)	0 (0%)	0.000	0.17	24 ± 7		
6 mWD (m) ≥400 <400	19 (38%)	42 (45%)	71 (64%)	0.003 a vs b 1.00 a vs c 0.009 b vs c 0.023	0.036 a vs b 1.00 a vs c 0.06 b vs c 0.20	43 ± 16 37 ± 15	0.004	0.013
Bruce (m) ≥400 <400	18 (43%)	39 (48%)	76 (72%)	<0.000 a vs b 1.00 a vs c 0.003 b vs c 0.003	0.021 a vs b 1.00 a vs c 0.047 b vs c 0.083	44 ± 16 36 ± 15	<0.001	0.003

SURGICAL SPECIMENTS – J1

SURGICAL SPECIMENTS – J2



SURGICAL SPECIMENTS – J3

RESULTS

Our study shows a *clear correlation* between the *number* of *reopened pulmonary artery branches* and *hemodynamic values* and *functional data (pO2, NYHA functional class, 6mwt and modified Bruce test) already at 3 months*

CONCLUSIONS

In our hands a *longer TCA time* allows the surgeon to explore *all the pulmonary vascular bed*, find *unexpected chronic thromboembolic material* and *clean more branches* even in more complex clinical conditions as well as in *distal vassels*

CHARACTERISTICS

- Age
- NYHA functional class
- PVR
- Distribution of CTE lesions
- Amount of CTE occlusions
- Comorbidities

COMORBIDITIES

- There are few studies that consider the comorbidities as a risk factor for the PEA

- The absolute contraindication is an important parenchymal lung disease

- PEA score could be usefull

COMORBIDITIES

Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension

Results From an International Prospective Registry

Marion Delcroix, MD; Irene Lang, MD; Joanna Pepke-Zaba, MD; Pavel Jansa, MD; Andrea M. D'Armini, MD; Repke Snijder, MD; Paul Bresser, MD; Adam Torbicki, MD; Soren Mellemkjaer, MD; Jerzy Lewczuk, MD; Iveta Simkova, MD; Joan A. Barbera, MD; Marc de Perrot, MD; Marius M. Hoeper, MD; Sean Gaine, MD; Rudolf Speich, MD; Miguel A. Gomez-Sanchez, MD; Gabor Kovacs, MD; Xavier Jais, MD; David Ambroz, MD; Carmen Treacy, BSc; Marco Morsolini, MD; David Jenkins, MD; Jaroslav Lindner MD; Philippe Dartevelle, MD; Eckhard Mayer, MD; Gerald Simonneau, MD

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COMORBIDITIES

Table 4. Independent Correlates of Mortality for Operated and Not-Operated Patients

	Operated (n=346)			Not-Operated (n=219)		
Covariate	HR	95% CI	*P* Value	HR	95% CI	*P* Value
NYHA class III vs I–II				2.43	1.00–5.89	0.0489
NYHA class IV vs I–II	4.16	1.49–11.62	0.0065	4.76	1.76–12.88	0.0021
RAP	1.34	0.95–1.90	0.0992	1.50	1.20–1.88	0.0004
PAP	0.67	0.47–0.94	0.0226			
History of acute VTE	0.48	0.24–0.97	0.0413			
History of cancer	3.02	1.36–6.69	0.0065	2.15	1.18–3.94	0.0129
Coronary disease/myocardial infarction	–			1.81	1.00–3.28	0.0492
CHF or LV dysfunction	–			1.98	1.02–3.83	0.0440
Dialysis-dependent renal failure	11.52	1.42–93.48	0.0221	–		
COPD	–			2.14	1.22–3.73	0.0075
PAH-targeted therapy started at diagnosis	2.62	1.30–5.28	0.0072	–	–	–
Postoperative PH	3.66	1.72–7.82	0.0008	–	–	–
All other complications	3.82	1.72–8.51	0.0010	–	–	–
Additional cardiac procedure	3.10	1.54–6.24	0.0015	–	–	–

Cox multivariable analysis of operated and not-operated patients, separately. CHF indicates congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LV, left ventricle; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PH, pulmonary hypertension; RAP, right atrial pressure; and VTE, venous thromboembolism

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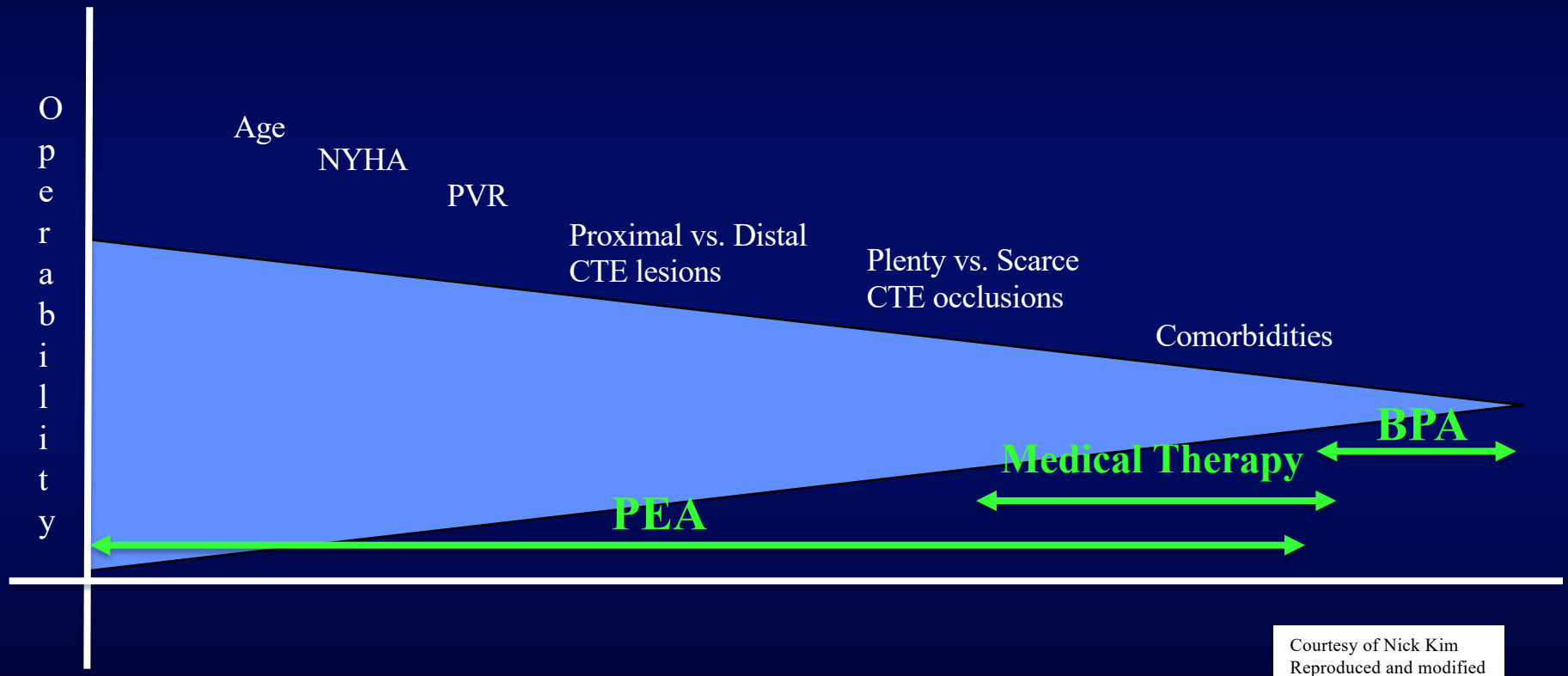
CONCLUSION

- A single characteristic usually is not enough to identify a poor or a good candidate for PEA

- Multidisciplinary CTEPH team (at least one experienced surgeos) is the basis for the correct selection of the patients

- For “less experienced centers” or in general for all centers a second opinion, in absence of PEA score, could be the optimal solution for complex patients

CONCLUSION



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CHEST STUDY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

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CHEST STUDY

ORIGINAL ARTICLE
PULMONARY VASCULAR DISEASES

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 R. Wilkins[9], Arno Fritsch[10], Neil Davie[10], Pablo Colorado[11] and Eckhard Mayer[12]

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BENEFiT STUDY

CLINICAL RESEARCH Clinical Trials

Bosentan for Treatment of Inoperable Chronic Thromboembolic Pulmonary Hypertension

BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a Randomized, Placebo-Controlled Trial

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