IV Congresso
Novas Fronteiras em Cardiologia

Intervenção na Hipertensão Pulmonar

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CHO/CHLN

7 a 9 de Fevereiro 2014
Hotel Vila Galé Ericeira

INTERVENÇÃO NA HIPERTENSÃO PULMONAR

Intervenção no Diagnóstico e Prognóstico

Intervenção como paliação/ ponte para transplante

Intervenção como tratamento de doentes com Hipertensão Pulmonar Tromboembólica Crónica

Novas estratégias de tratamento

-Desenervação das artérias pulmonares

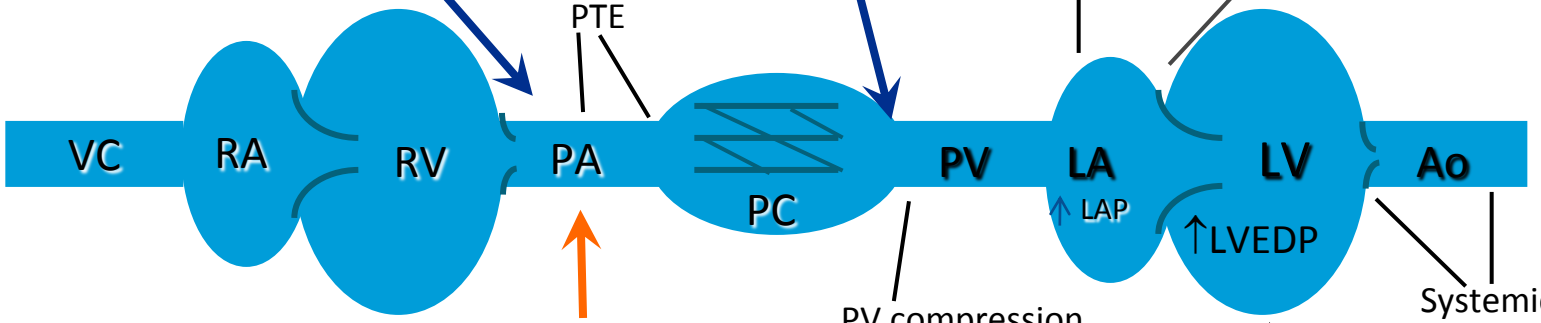
- Tratamento com células estaminais

INTERVENÇÃO NO DIAGNÓSTICO

Cateterismo Cardíaco no Diagnóstico de HTP

PRE-CAPILLARY PH
Mean PAP ≥ 25mmHg
PCWP ≤15 mmHg
CO nl or ↓

POST-CAPILLARY PH
Mean PAP ≥ 25mmHg
PCWP >15 mmHg
CO nl or ↓



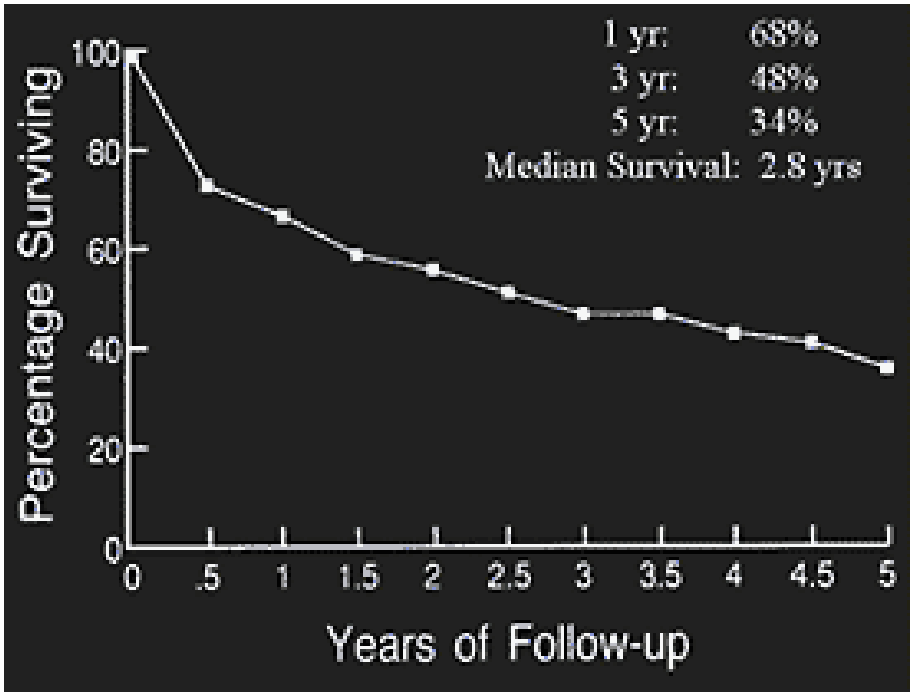
Haemodynamic definitions of pulmonary hypertension

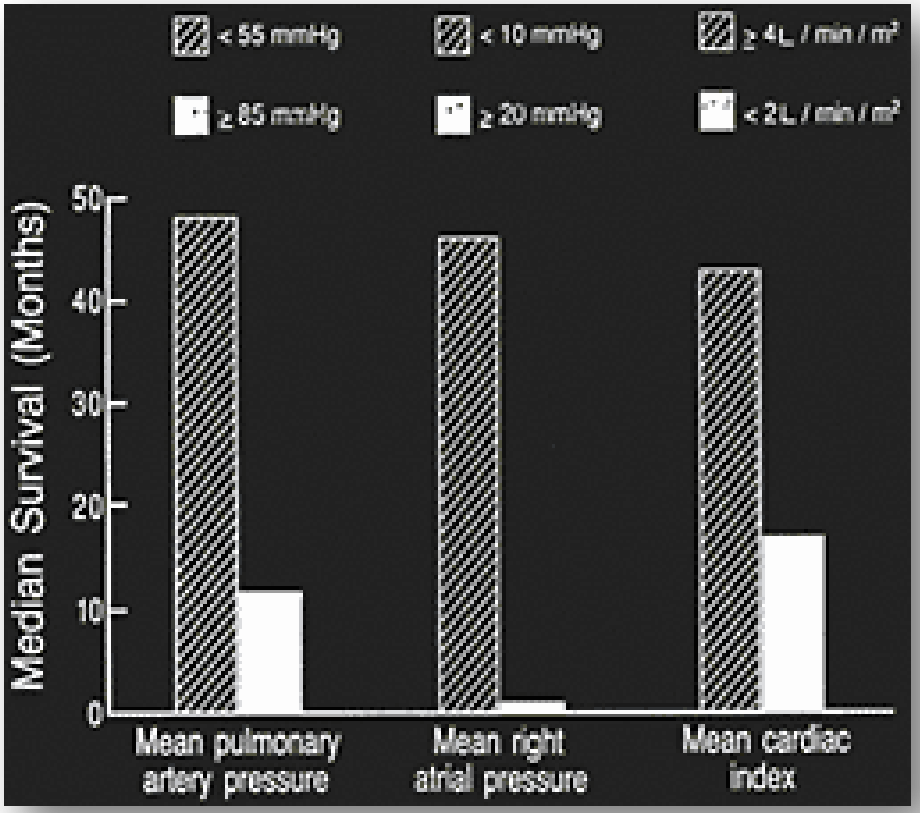
Definition	Characteristics	Clinical group(s)
Pulmonary hypertension (PH)	Mean PAP ≥ 25 mmHg	All

Myocardial Disease
Dilated CMP-ischemic/non-isc.
Hypertrophic CMP
Restrictive/infiltrative CMP
Pericardial ds.

INTERVENÇÃO NO DIAGNÓSTICO

Mortalidade e o impacto prognóstico da hemodinâmica





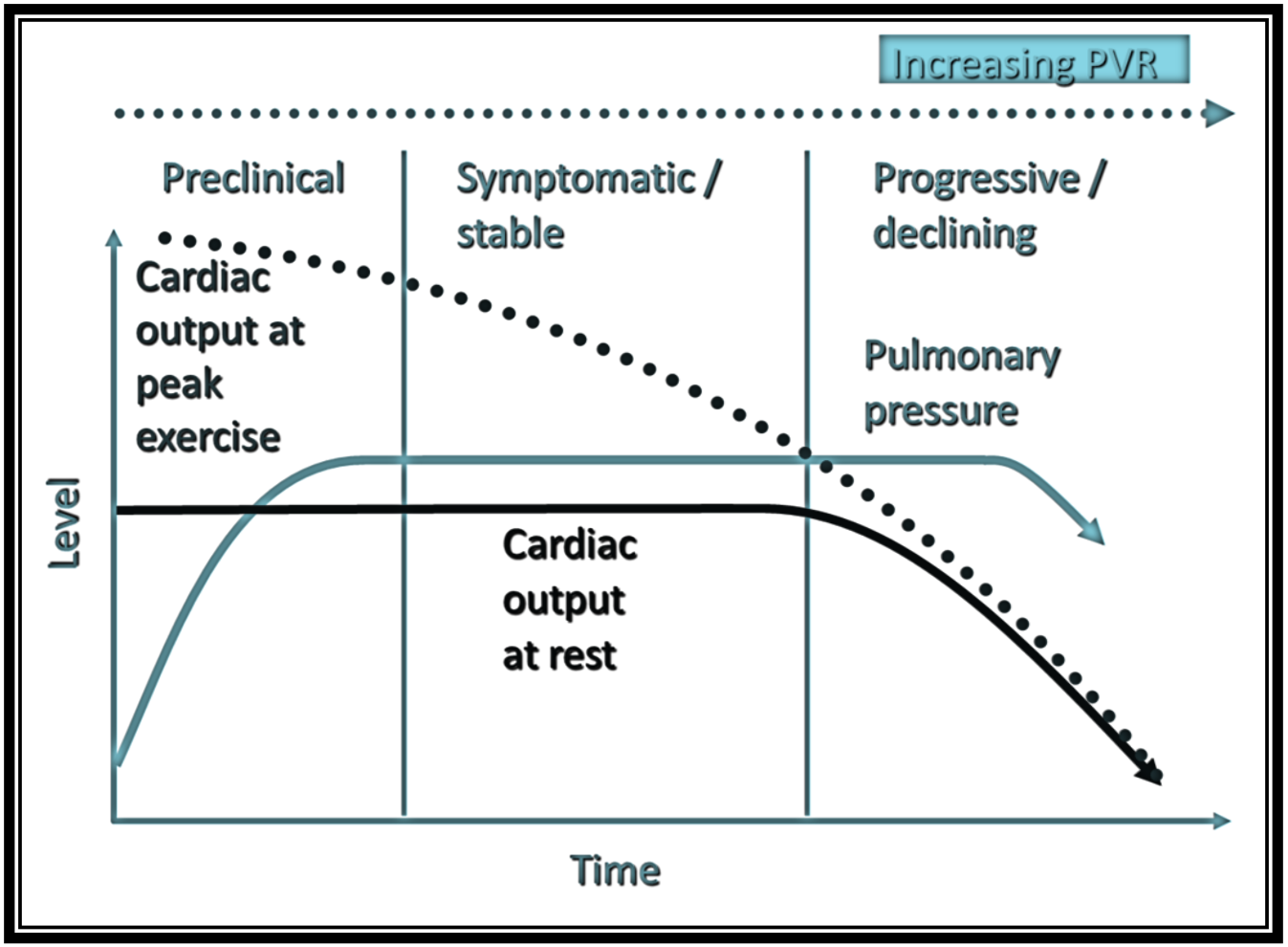
- Median survival among PAH pts in the US between 1981-85 was 2.8 years

D'Alonzo GE et al. Ann Intern Med 1991

INTERVENÇÃO NO DIAGNÓSTICO

A Pressão na Artéria Pulmonar traduz a gravidade da doença?

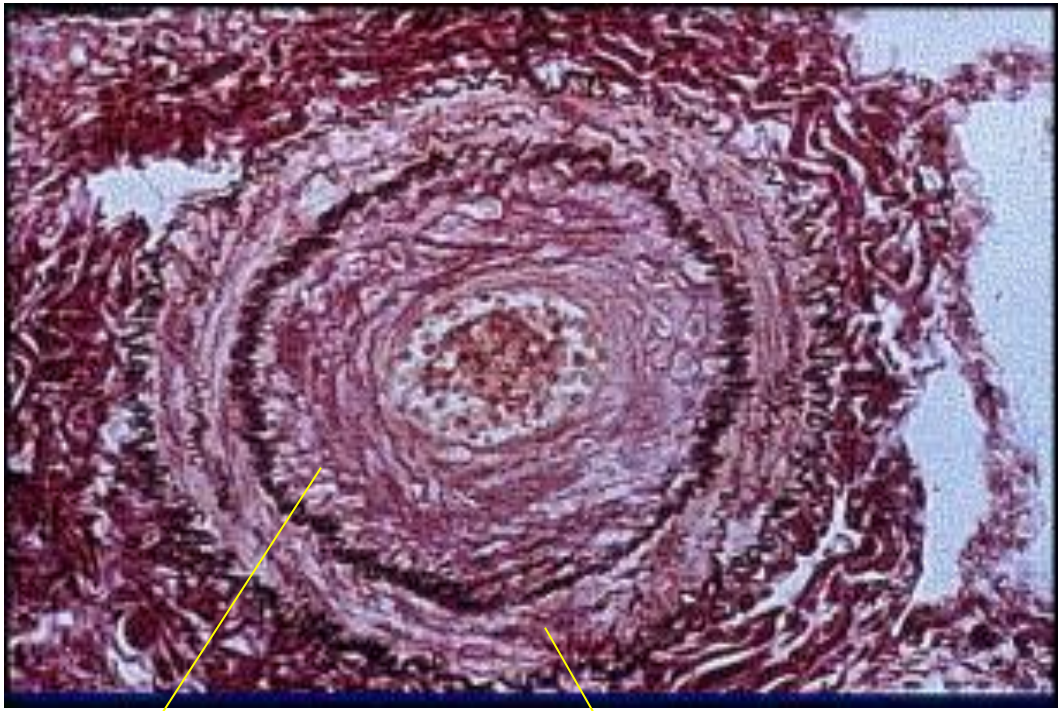
Pressão = Débito x Resistência Vascular



Histopathology

Main vascular changes of PAH

- Vasoconstriction
- SMC and endothelial-cell proliferation
- fibrosis
- thrombosis

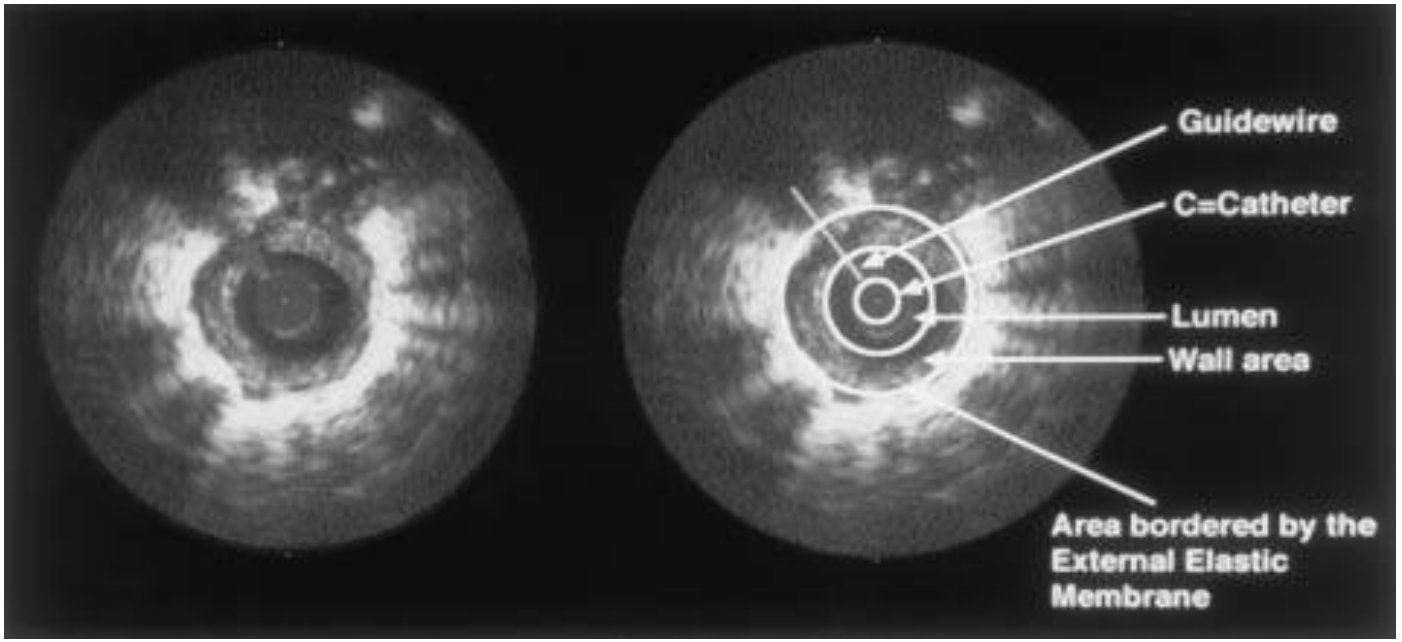


1. Severe concentric laminar intimal fibrosis
2. Medial hypertrophy
3. *in situ* thrombosis of the small residual lumen

IMAGIOLOGIA INTRAVASCULAR NA HTP- IVUS

Intravascular Ultrasound Assessment of Pulmonary Vascular Disease in Patients With Pulmonary Hypertension*

Erwan Bressollette, MD; Jocelyn Dupuis, MD, PhD; Raoul Bonan, MD; Serge Doucet, MD; Peter Cernacek, MD, PhD; and Jean-Claude Tardif, MD



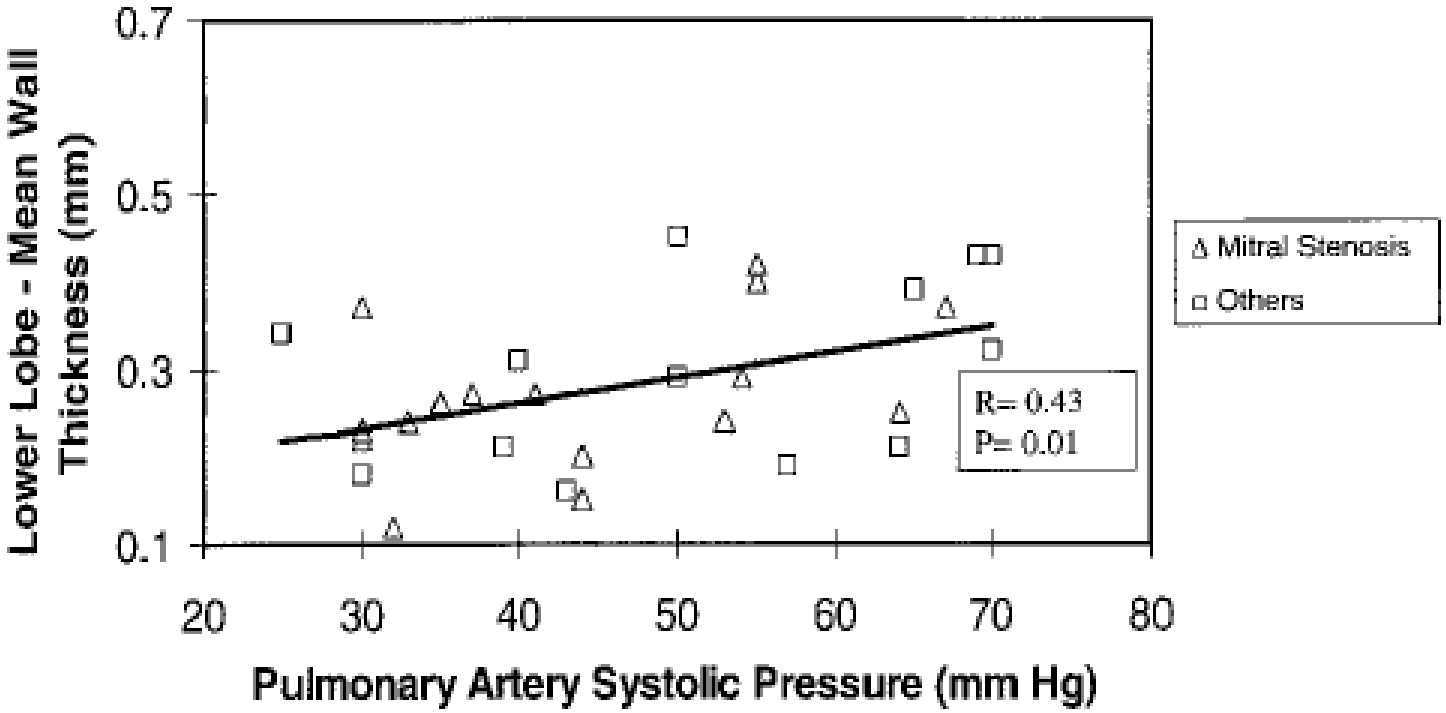
IVUS numa artéria pulmonar distal revelando marcada hipertrofia vascular

Bresolelette E et al. Chest 2001;120;809-815

IMAGIOLOGIA INTRAVASCULAR NA HTP- IVUS

Correlação entre a PSAP e a espessura da parede vascular pulmonar em IVUS

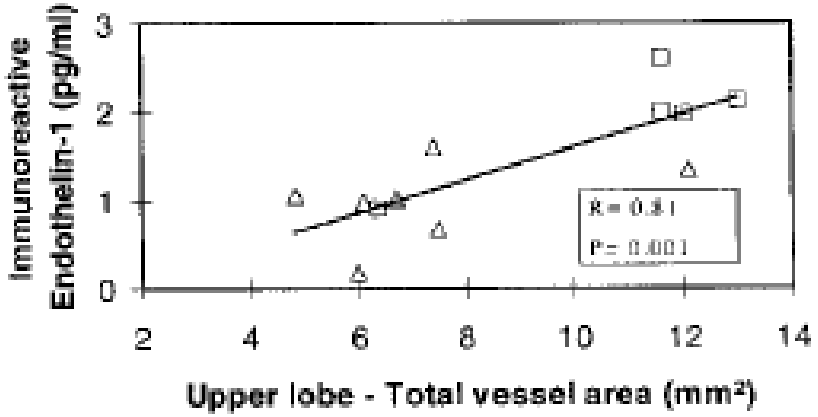
30 doentes com HAP em avaliação com IVUS

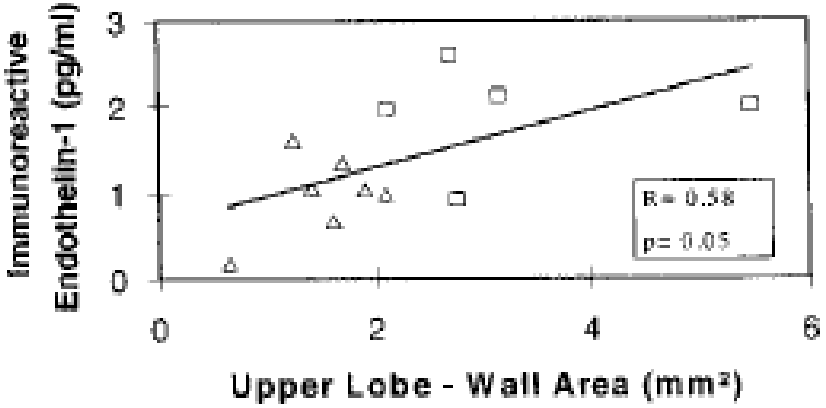


Bresolelette E et al. Chest 2001;120;809-815

IMAGIOLOGIA INTRAVASCULAR NA HTP- IVUS

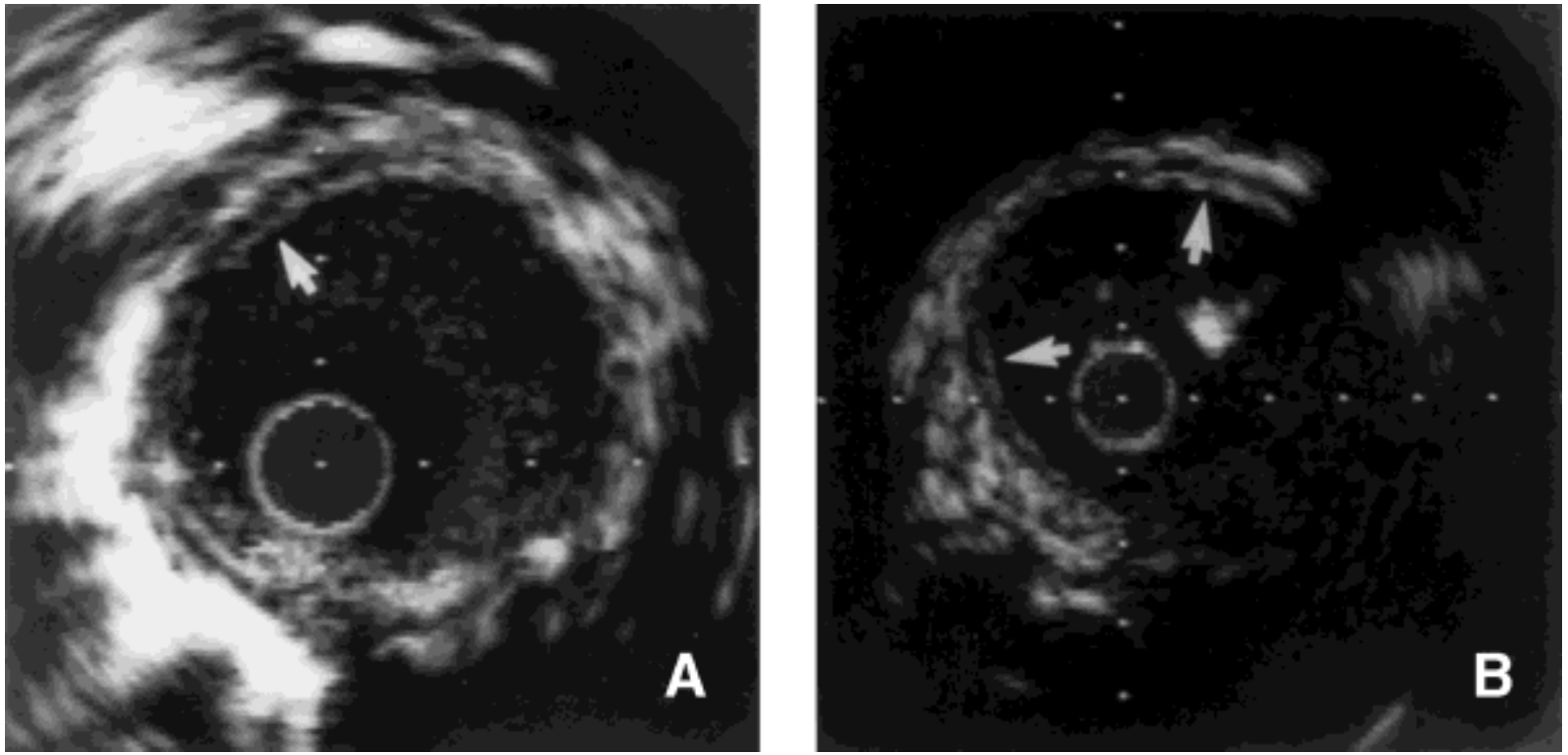
Correlação entre os níveis ET-1 e a área vascular pulmonar





Bresolelette E et al. Chest 2001;120;809-815

IMAGIOLOGIA INTRAVASCULAR NA HTP- IVUS

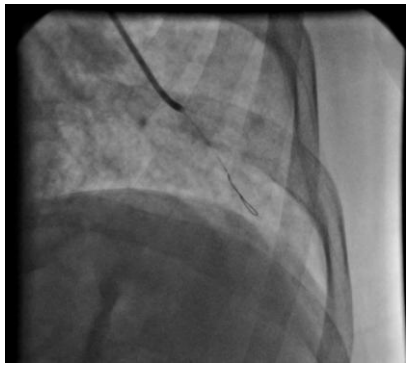


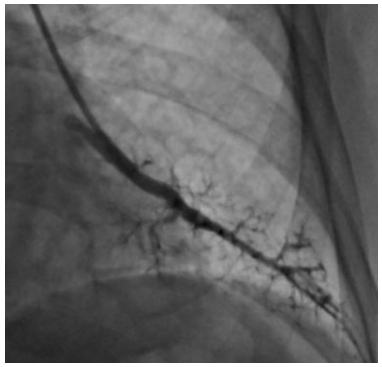
Identificam-se 3 camadas da parede arterial

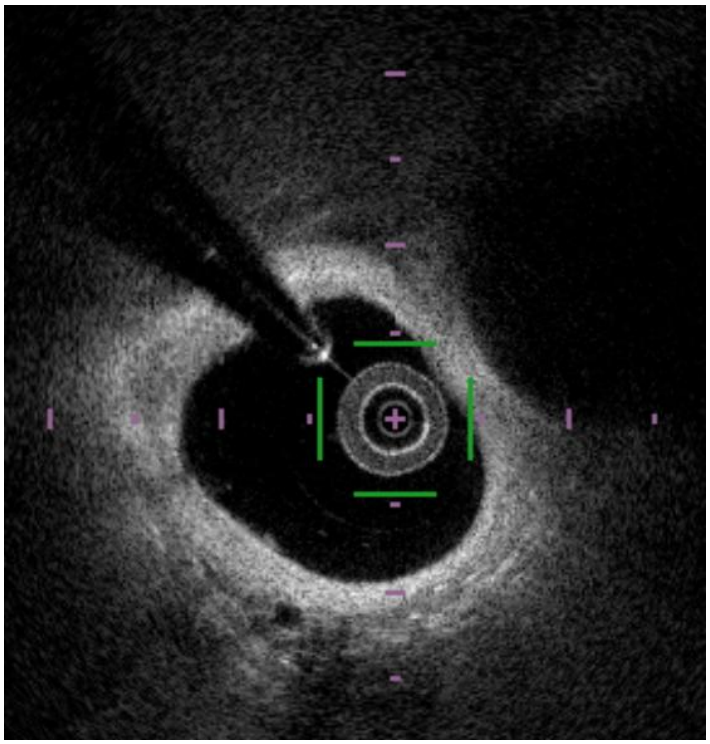
As setas indicam locais onde se visualizam 3 camadas na parede arterial pulmonar. Zona ecolucente = média.

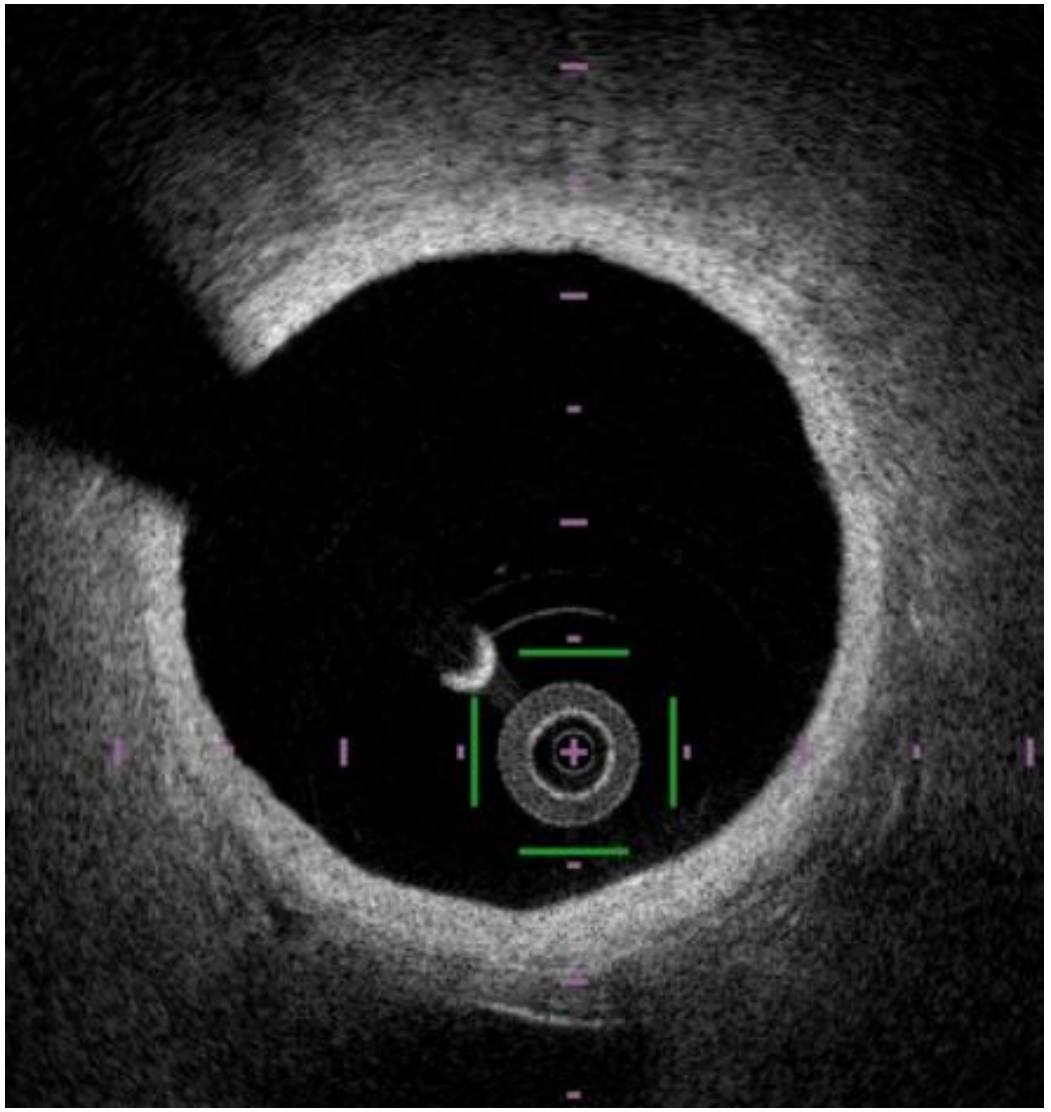
Day RW et al. Catheterization and Cardiovascular Diagnosis 1997. 44: 395-398

IMAGIOLOGIA INTRAVASCULAR NA HTP- OCT





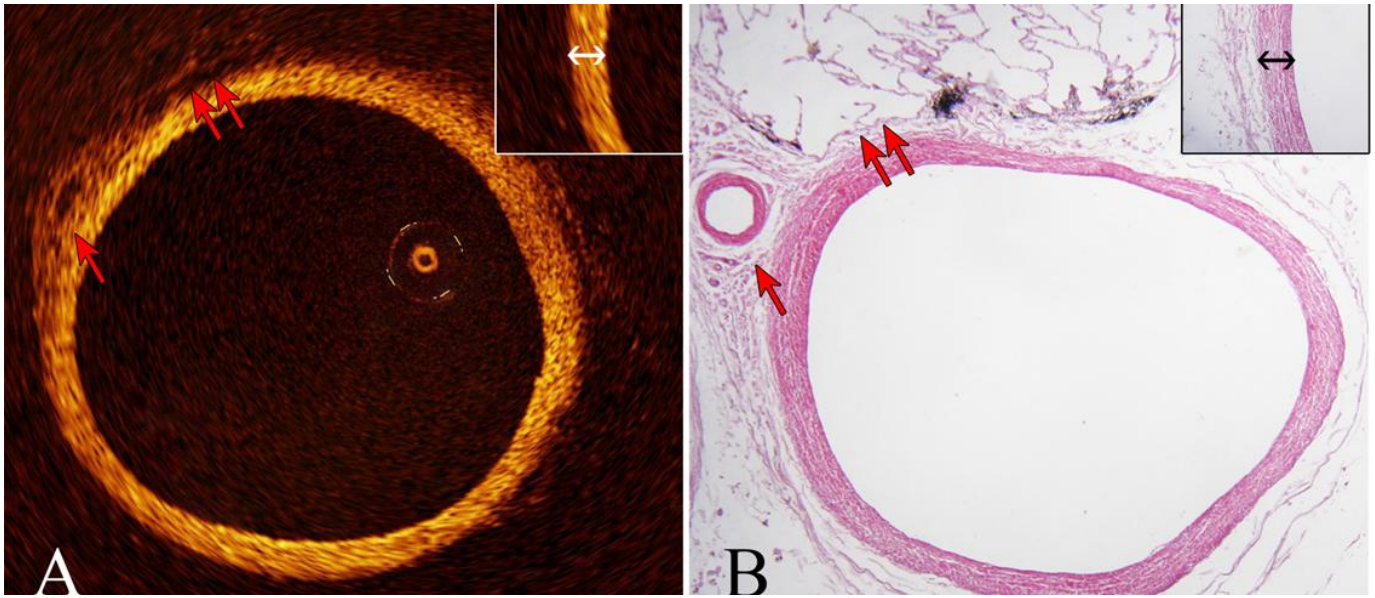


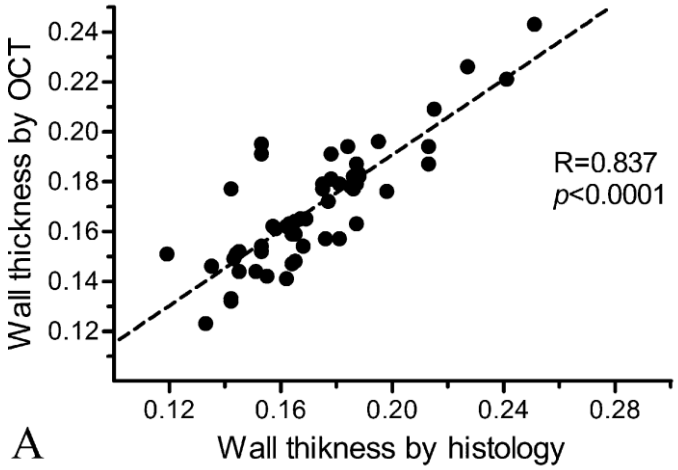


IMAGIOLOGIA INTRAVASCULAR NA HTP- OCT

Validação Histológica dos achados no OCT

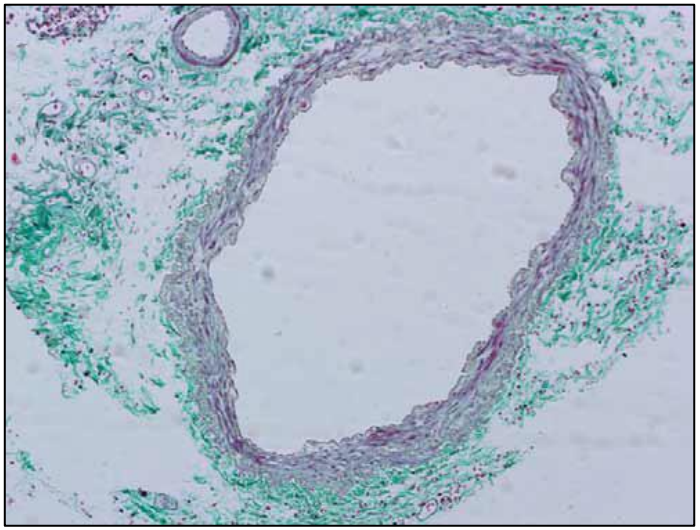
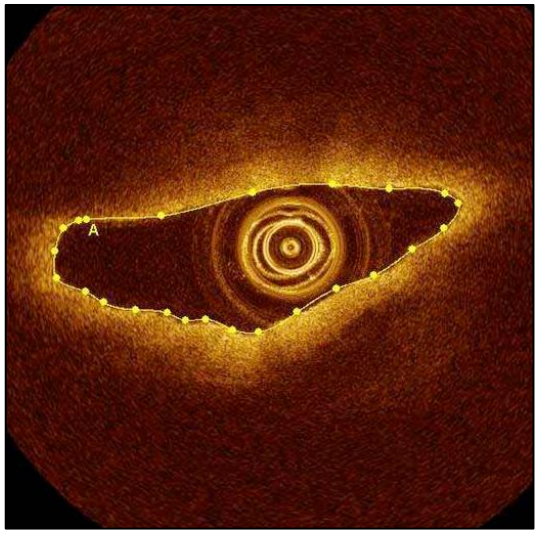
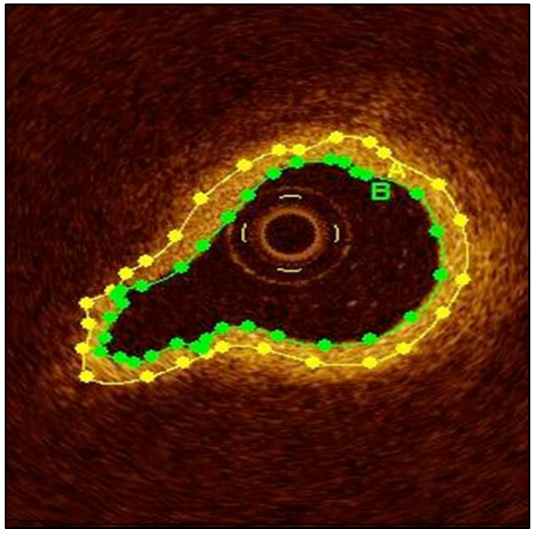
Análise de 27 artérias de cadáver





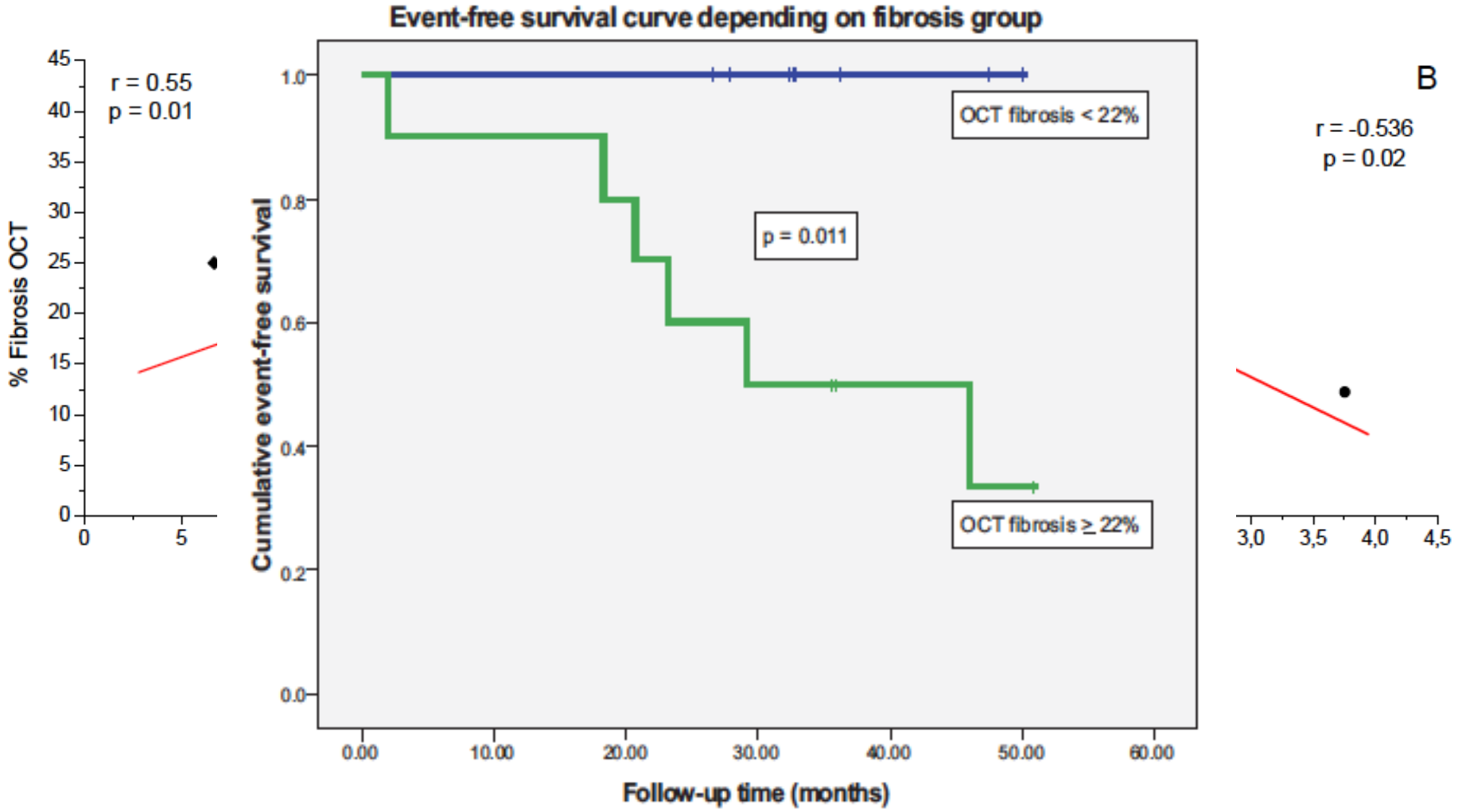
Heart, Lung and Circulation 2012;21:778–781

IMAGIOLOGIA INTRAVASCULAR NA HTP- OCT

	Histology	OCT
Normal Pulmonary Artery		
Pulmonary Artery of patient with PAH		

The Open respiratory Medicine Journal 2013; 7: 26-32

IMAGIOLOGIA INTRAVASCULAR NA HTP-OCT



The Open respiratory Medicine Journal 2013; 7: 26-32

IMAGIOLOGIA INTRAVASCULAR NA HTP

- As técnicas de imagiologia oferecem a possibilidade de identificar aspectos morfológicos das artérias pulmonares, antes só possíveis através de avaliação de peças histológicas post mortem ou pós transplante pulmonar
- Devem ser investigadas as suas possibilidades no:
  - Diagnóstico
  - Classificação da doença
  - Estratificação prognóstica
  - Resposta a terapêutica (remodelagem vascular)

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INTERVENÇÃO COMO PALIAÇÃO- SEPTOSTOMIA

- It has been observed that patients with primary pulmonary hypertension and an atrial communication have better survival than patients with pulmonary hypertension who lack an atrial shunt.

Rozkovec A et al. Br Heart J 1986
Glanville AR et al. Chest 1987

Factor	*Number*	*%*	*Mean survival (yr)*
Familial disease	2	5·9	6
Connective tissue disease	3	8·8	3·4
Pregnancy	5	14·7	14·2
Patent foramen ovale	4	11·8	11·5
No related factors	20	58·8	5·5
All patients	34	100	7·3

- Similarly, patients with Eisenmenger's syndrome have a better rate of survival than patients with pulmonary hypertension without intracardiac shunts.

Young D et al. Am J Cardiol 1971
Hopkins WE et al. J Heart Lung Transplant 1996

- Rich and Lam first reported transcatheter creation of an atrial septal defect (ASD) in a patient with pulmonary hypertension.

Rich S, Lam W. Am J Cardiol 1983

INTERVENÇÃO COMO PALIAÇÃO- SEPTOSTOMIA

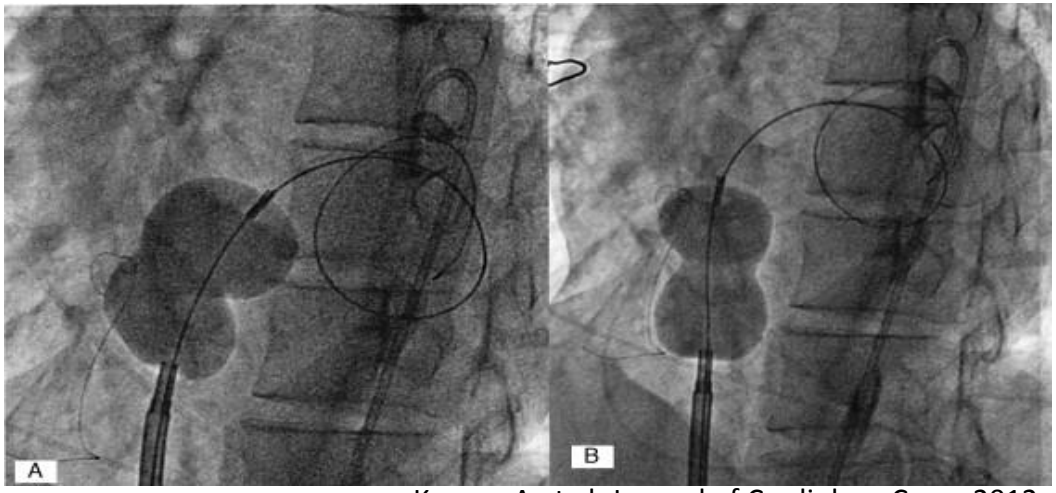
Princípios da septostomia auricular e mecanismos benéficos

Efeitos Hemodinâmicos Agudos da Septostmia Auricular

- ↑ systemic oxygen transport by ↑ cardiac output.
- ↓ in right atrial pressure → ↓ systemic venous congestion thereby improving right heart failure.
- With exercise → ↑ right to left shunting → ↑ oxygen transport although at the expense of the systemic arterial oxygen saturation.
- ↑ right ventricular coronary perfusion due to a ↓ in right heart filling pressures.

Because the pulmonary vascular bed is unaffected by the procedure, the long term effects of an AS must be considered palliative.

Barst RJ. Thorax 2000

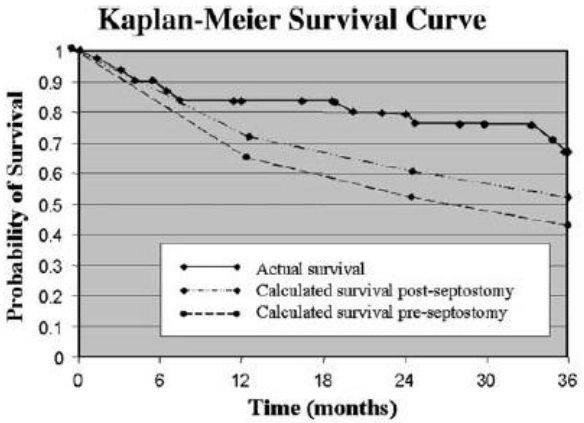


Kapoor A et al. Journal of Cardiology Cases 2012

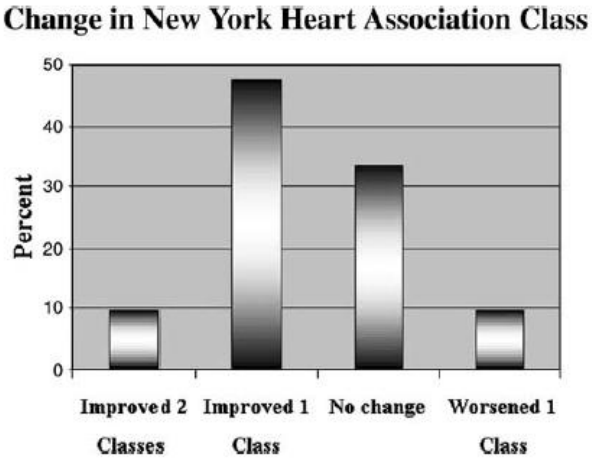
INTERVENÇÃO COMO PALIAÇÃO- SEPTOSTOMIA

Follow up and outcome

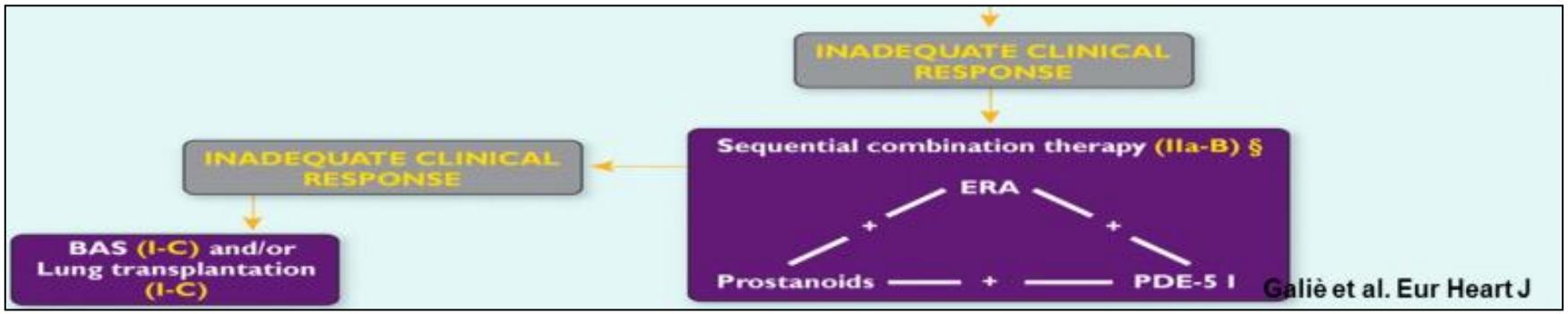
- Greatest relief is from syncope.
- Functional class improvement in >50% .
- One year survival benefit(75-90% vs the 40% natural history survival)
- Late deterioration can occur as ASD gets closed.



Kaplan-Meier survival curve for patients surviving >30 days



Law MA, et al. Am Heart J 2007



Galiè et al. Eur Heart J

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DESENERVAÇÃO DAS ART. PULMONARES

- Stepwise balloon distention of the MPA → step ↑ in pulmonary artery pressure downstream from the balloon.
- This elevation in pressure occurs in the absence of any significant change in right ventricular end-diastolic pressure, aortic pressure, left atrial pressure, and cardiac output. Therefore, the pulmonary vascular resistance rises significantly.

Laks MM, et al. Chest 1975

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 62, No. 12, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.05.075

Pulmonary Artery Denervation to Treat Pulmonary Arterial Hypertension

The Single-Center, Prospective, First-in-Man PADN-1 Study (First-in-Man Pulmonary Artery Denervation for Treatment of Pulmonary Artery Hypertension)

Shao-Liang Chen, MD,*† Feng-Fu Zhang, MD,* Jing Xu, MD,* Du-Jiang Xie, MD,* Ling Zhou, MD,* Thach Nguyen, MD,‡ Gregg W. Stone, MD§

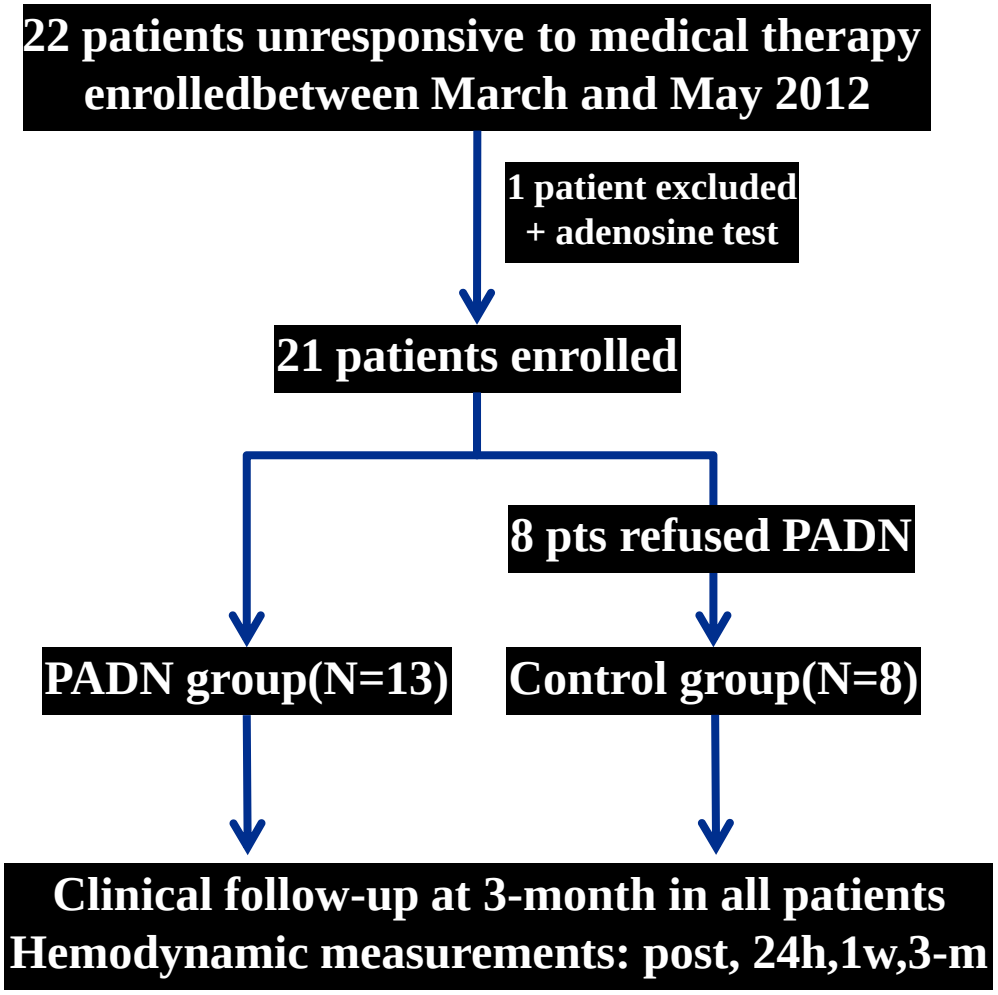
Nanjing, China; Hobart, Indiana; and New York, New York

DESENERVAÇÃO DAS ART. PULMONARES

Design

- **OBJECTIVE: first-in man study to test the safety and efficacy of PADN by inducing local injury/destruction to the baroreceptor or sympathetic nervous fibers in patients with IPAH who did not respond optimally to current medical therapy.**

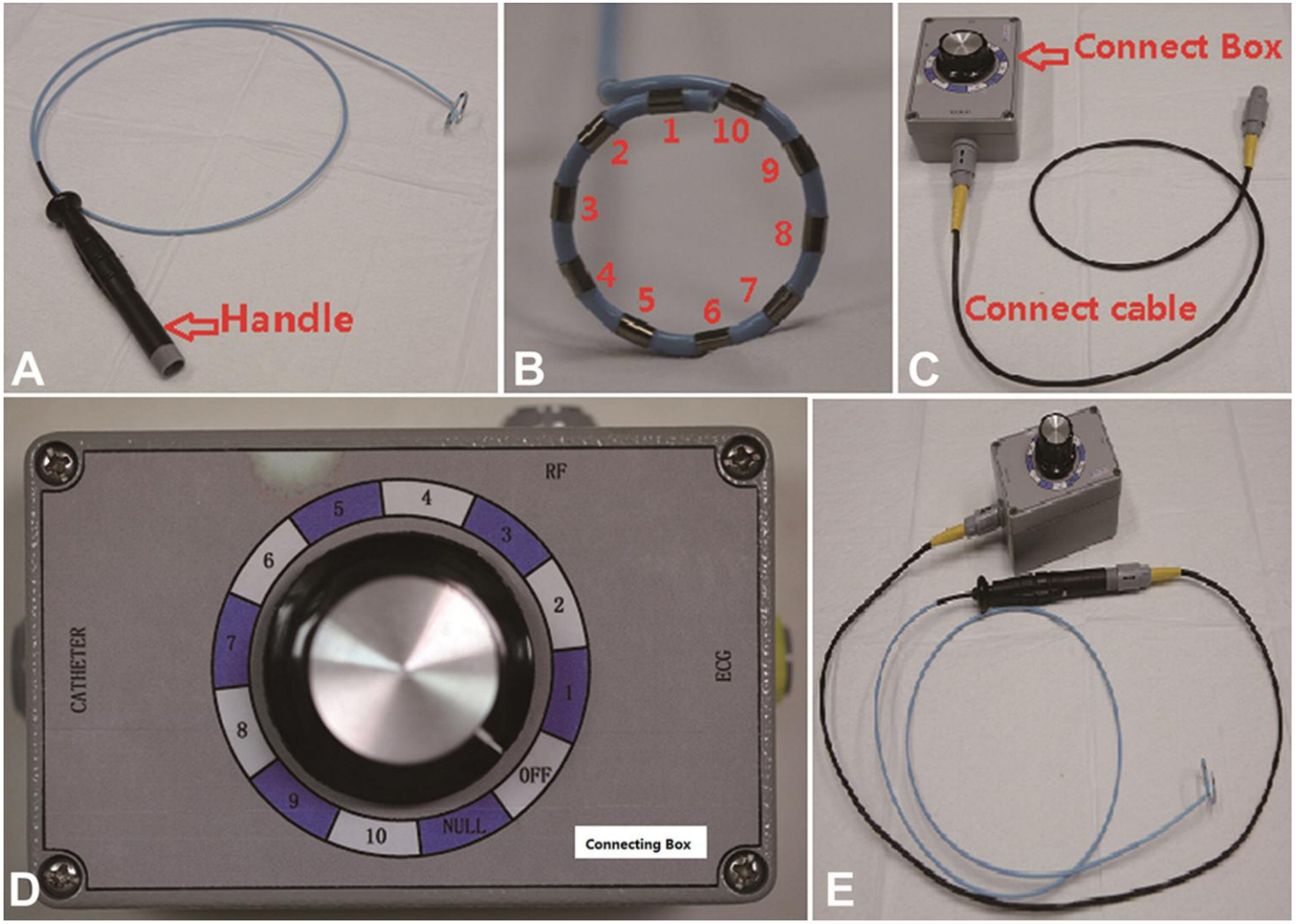
- **ENDPOINTS. The primary endpoints were improvement of functional capacity by the 6MWT and mean PAP at 3 months.**
- Clinical adverse events (including PA perforation/ dissection, acute thrombus formation in the PA, all-cause death, rehospitalization due to PAH, and lung transplantation) served as secondary endpoints and were assessed by an independent event committee.



Chen SL et al. J Am Coll Cardiol 2013;62:1092–100

DESENERVAÇÃO DAS ART. PULMONARES

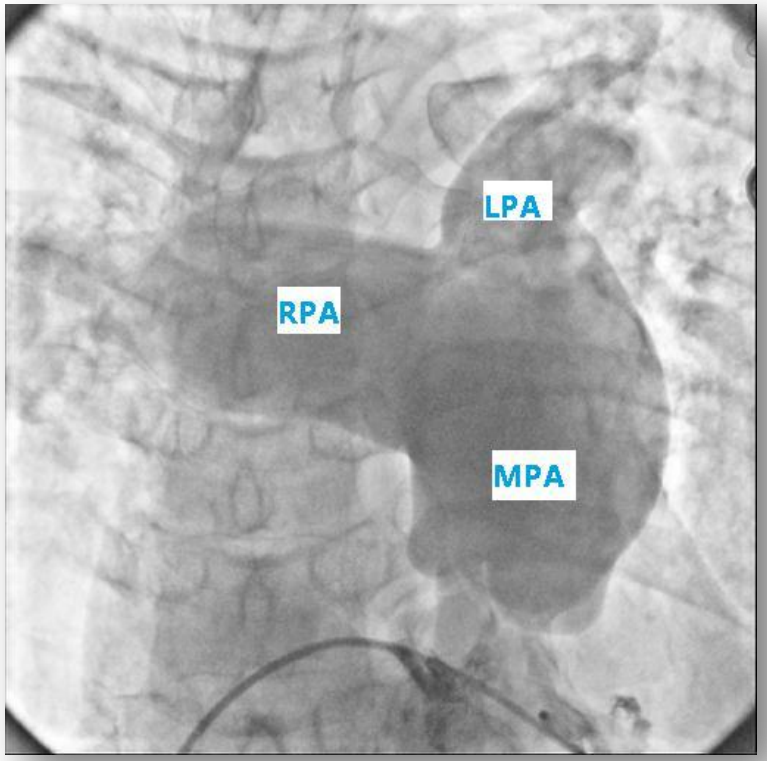
PADN system



Chen SL et al. J Am Coll Cardiol 2013;62:1092–100

DESENERVAÇÃO DAS ART. PULMONARES

PADN procedure



- Baseline PA angiography was performed
- 8-F long sheath through the femoral vein direction, the circular tip would be Position the tip of the catheter at the ostium of the left PA (3 positions)

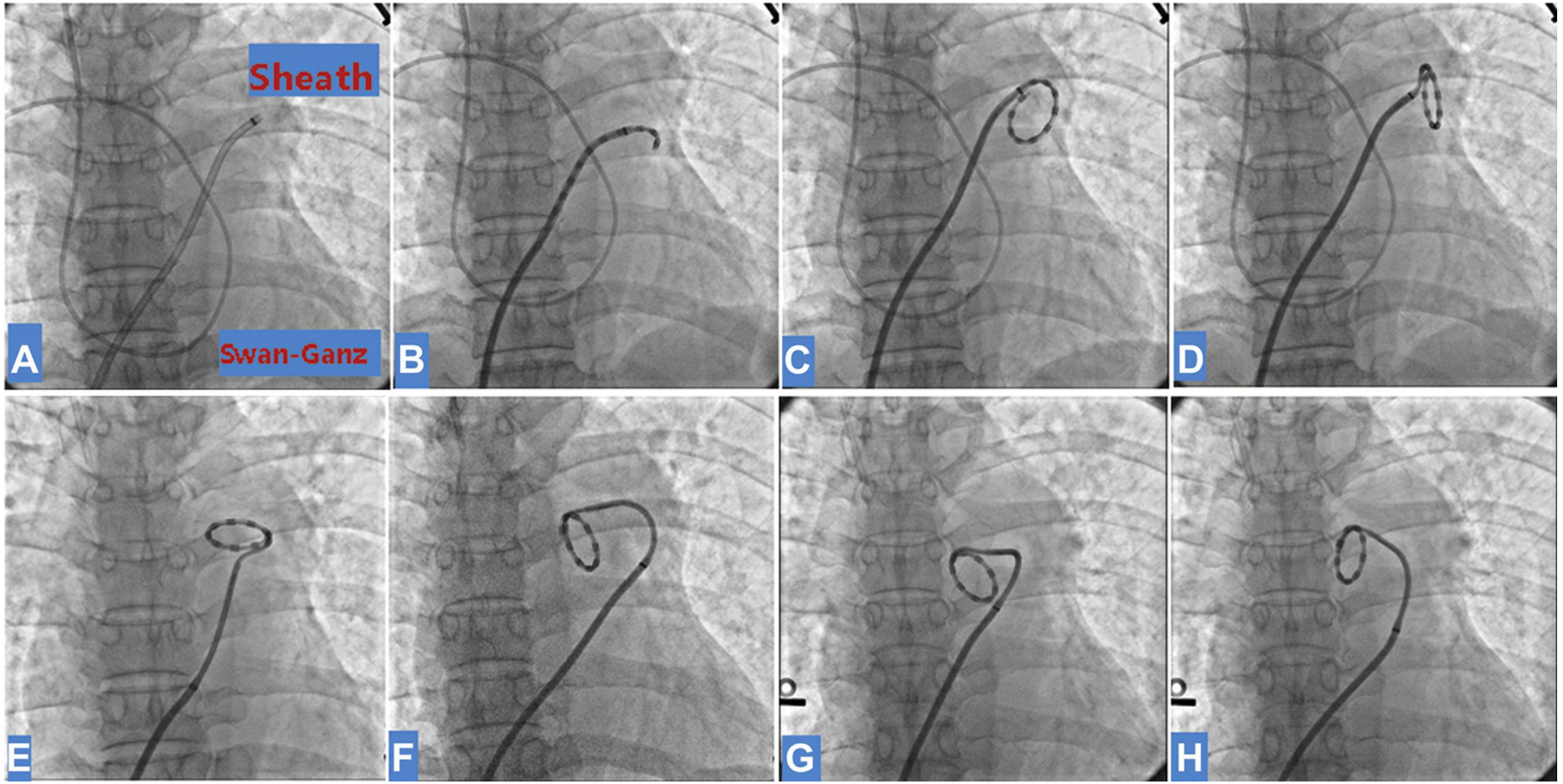
- 3 criteria were used to ensure tightly contact:
  1) strong manual resistance;
  2) inability to advance distally;
  3) angiographic confirmation.

temperature > 50 ºC, energy 10 W, and time 60 s

Chen SL et al. J Am Coll Cardiol 2013;62:1092–100

DESENERVAÇÃO DAS ART. PULMONARES

PADN procedure



Chen SL et al. J Am Coll Cardiol 2013;62:1092–100

DESENERVAÇÃO DAS ART. PULMONARES

Table 2 Echocardiographic Measurements in 2 Groups

		Following PADN					
	Before	Post	24 H	1 Week	1 Month	2 Months	3 Months
SPAP, mm Hg							
PADN group	86 ± 5*	70 ± 4	70 ± 6	70 ± 6	69 ± 6	71 ± 6	72 ± 7
Control group	86 ± 8*	—	84 ± 9*	84 ± 8*	85 ± 9*	83 ± 7*	83 ± 9*
MPAP, mm Hg							
PADN group	38 ± 6†	24 ± 5	24 ± 4	25 ± 5	23 ± 4	26 ± 5	26 ± 6*
Control group	37 ± 7*	±	36 ± 5*	36 ± 5*	37 ± 5*	35 ± 5*	35 ± 6*
Tei							
PADN group	0.7 ± 0.04§	0.5 ± 0.04‡	0.4 ± 0.04	0.5 ± 0.04‡	0.4 ± 0.05	0.4 ± 0.04	0.5 ± 0.04‡
Control group	0.7 ± 0.04	—	0.7 ± 0.04§	0.7 ± 0.04§	0.7 ± 0.05§	0.7 ± 0.05§	0.7 ± 0.06§
Pericardial-effusion depth, mm							
PADN group	3.5 ± 0.8*	2.7 ± 0.5	2.8 ± 0.7	2.4 ± 0.5	1.4 ± 0.5	0.7 ± 0.2	0.7 ± 0.4
Control group	3.5 ± 0.7*	—	3.3 ± 0.9*	3.4 ± 0.7*	3.4 ± 0.7*	3.4 ± 0.7*	3.4 ± 0.7*
PA compliance							
PADN group	0.2 ± 0.1*	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
Control group	0.2 ± 0.1*	—	0.2 ± 0.1*	0.2 ± 0.1*	0.2 ± 0.1*	0.2 ± 0.1*	0.2 ± 0.1*

Values are mean ± SD. *$p < 0.001$, compare with following PADN. †$p < 0.04$, compared with following PADN. ‡$p < 0.001$, compared with before PADN. §$p < 0.03$, compared with following PADN at 24 h, 1 month, and 2 months.

MPAP = mean pulmonary artery pressure; PA = pulmonary artery; PADN = pulmonary artery denervation; SPAP = systolic pulmonary artery pressure; Tei = tricuspid excursion index.

Chen SL et al. J Am Coll Cardiol 2013;62:1092–100

DESENERVAÇÃO DAS ART. PULMONARES

Table 3 Hemodynamic Measurements by Right Heart Catheterization

		Following PADN		
	Before Intervention	Post	24 H	3 Months
SPAP, mm Hg				
PADN group	86 ± 8*	72 ± 5	70 ± 5	71 ± 6
Control group	86 ± 7*	—	—	86 ± 7*
MPAP, mm Hg				
PADN group	55 ± 5*	39 ± 7	36 ± 5	36 ± 5
Control group	53 ± 5*	—	—	50 ± 5*
PVR, dyne · s · cm^{-5}				
PADN group	1,883 ± 281	1,150 ± 208†	876 ± 154‡	763 ± 162§
Control group	1,877 ± 275	—	—	1,847 ± 239‖
RVP, mm Hg				
PADN group	85 ± 7‡	71 ± 6	70 ± 5	69 ± 6
Control group	86 ± 8‡	—	—	85 ± 7‡
RAP, mm Hg				
PADN group	4 ± 2	5 ± 2	5 ± 3	5 ± 2
Control group	5 ± 2	—	—	5 ± 2
PAOP, mm Hg				
PADN group	8 ± 2	8 ± 3	8 ± 4	8 ± 3
Control group	7 ± 3	—	—	7 ± 4
TPG, mm Hg				
PADN group	36 ± 6*	30 ± 5	27 ± 4	28 ± 5
Control group	42 ± 6*	—	—	34 ± 6*
Cardiac output (l/min · m^2)				
PADN group	2.0 ± 0.2	2.6 ± 0.1	2.8 ± 0.2	2.8 ± 0.3
Control group	2.1 ± 0.1	2.1 ± 0.2	2.1 ± 0.1	2.2 ± 0.2
PA O_2 saturation, %				
PADN group	42 ± 7*	51 ± 6	51 ± 6	52 ± 7
Control group	42 ± 5	43 ± 5	43 ± 5	43 ± 6

Values are mean ± SD. *$p < 0.001$, compared with following PADN. †$p < 0.05$, compared with before PADN. ‡$p < 0.003$, compared with following PADN. §$p < 0.001$, compared with before PADN. ‖$p < 0.001$, compared with 3 months in following PADN.

PAOP = pulmonary artery occlusive pressure; PVR = pulmonary vessel resistance; RAP = right atrial pressure; RVP = right ventricular pressure; TPG = transpulmonary pressure gradient; other abbreviations as in Table 2.

Chen SL et al. J Am Coll Cardiol 2013;62:1092–100

DESENERVAÇÃO DAS ART. PULMONARES

Table 4 Assessment of Functional Capacity

		Following PADN				
	Before	24 H	1 Week	1 Month	2 Months	3 Months
6MWD, m						
PADN group	324 ± 21	—	390 ± 33	459 ± 42*	487 ± 47*	491 ± 38*
Control group	358 ± 30	—	361 ± 36	365 ± 38†	362 ± 39‡	364 ± 38†
WHO class						
PADN group	3.6 ± 0.8†	—	2.3 ± 1	1.7 ± 0.9	1.6 ± 0.7	1.6 ± 0.8
Control group	3.5 ± 0.9†	—	3.5 ± 0.8†	3.5 ± 0.8†	3.5 ± 0.9†	3.2 ± 0.4†
Class ≥3						
PADN group	6 (46)†	—	1 (7.6)	1 (7.6)	1 (7.6)	1 (7.6)
Control group	4 (50)†	—	4 (50)†	4 (50)†	4 (50)†	4 (50)†
BORG index						
PADN group	3.4 ± 0.3	—	3.0 ± 0.4	3.0 ± 0.3	2.3 ± 0.4*	2.3 ± 0.4*
Control group	3.5 ± 0.4	—	3.5 ± 0.3	3.3 ± 0.4	3.2 ± 0.3†	3.3 ± 0.3†
Class ≥3						
PADN group	8 (62)†	—	3 (23)	3 (23)	3 (23)	3 (23)
Control group	4 (50)†	—	4 (50)†	4 (50)†	4 (50)†	4 (50)†
NT-BNP, pg/ml						
PADN group	2,005 ± 442‡	1,502 ± 419	1,234 ± 322	910 ± 205	837 ± 204	822 ± 201
Control group	1,993 ± 407‡	2,020 ± 435‡	1,992 ± 387‡	1,990 ± 418‡	2,001 ± 411‡	1,988 ± 422‡
All-cause death						
PADN group	—	0	0	0	1 (7.6)	1 (7.6)
Control group	—	0	0	0	1 (12.5)	1 (12.5)
Rehospitalization						
PADN group	—	0	0	0	0	0
Control group	—	0	5 (62.5)§	5 (62.5)§	5 (62.5)§	5 (62.5)§
Lung transplantation						
PADN group	—	0	0	0	0	0
Control group	—	0	0	0	0	0

Values are mean ± SD or n (%). *$p < 0.010$, compared with before PADN. †$p < 0.010$, compared with following PADN. ‡$p < 0.001$, compared with following PADN. §$p < 0.001$, compared with following PADN.
6 MWD = 6-min walk distance; BORG = BORG dyspnea scoring; NT-BNP = N-terminal brain natriuretic peptide; PADN = pulmonary artery denervation; WHO = World Health Organization.

Chen SL et al. J Am Coll Cardiol 2013;62:1092–100

TRATAMENTO COM CÉLULAS ESTAMINAIS

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 49, No. 14, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.12.037

Pulmonary Vascular Disease

Transplantation of Autologous Endothelial Progenitor Cells May Be Beneficial in Patients With Idiopathic Pulmonary Arterial Hypertension

A Pilot Randomized Controlled Trial

Xing-Xiang Wang, MD, PHD, Fu-Rong Zhang, MD, Yun-Peng Shang, MD, PHD, Jun-Hui Zhu, MD, Xu-Dong Xie, MD, PHD, Qian-Min Tao, MD, Jian-Hua Zhu, MD, Jun-Zhu Chen, MD

Hangzhou, China

A variety of evidence suggests that endothelial progenitor cells (EPCs) constitute one aspect of the endothelial repair process.

Experimental data have suggested that transplantation of EPCs attenuated monocrotaline-induced pulmonary hypertension in the rat model.

Wang XX et al. J Am Coll Cardiol 2007;49:1566–71

TRATAMENTO COM CÉLULAS ESTAMINAIS

Prospective, randomized trial comparing the effects of EPC transplantation plus conventional therapy with those of conventional therapy alone in patients with IPAH.

The primary end-point was change in the 6-min walk distance using a standardized protocol.

31 patients, 16 were randomized to conventional therapy (conventional therapy group) and 15 to cell infusion plus conventional therapy (cell infusion group).

Table 3 Changes in the Exercise Capacity and Hemodynamic Variables From Baseline to Week 12*

	Change From Baseline			
	Cell Infusion	Conventional Therapy	Mean Difference	95% Confidence Interval
6-min walk distance (m)	48.2 ± 17.1	5.7 ± 20.3	42.5	28.7 to 56.3
Mean pulmonary artery pressure (mm Hg)	−4.5 ± 3.4	−0.4 ± 2.4	−4.0	−6.2 to −1.9
Pulmonary vascular resistance (dyne-s-cm^{-5})	−185.4 ± 150.8	−27.8 ± 98.0	−157.6	−250 to −65
Cardiac output (l/min)	0.38 ± 0.43	0.06 ± 0.30	0.32	0.05 to 0.59

*Changes from baseline are presented as mean ± SD; 95% confidence intervals are for comparisons between the 2 groups. A confidence interval that does not contain zero indicates statistical significance.

Wang XX et al. J Am Coll Cardiol 2007;49:1566–71

NOVAS ESTRATÉGIAS DE TRATAMENTO

- **A desenervação das artérias pulmonares parece ser uma técnica percutânea promissora no tratamento da HTP**

- **No entanto existem dúvidas metodológicas e de integração dos resultados na fisiopatologia da doença que levam a que se tenha de confirmar estes resultados iniciais em estudos aleatorizados de maior dimensão.**

- **No tratamento com células estaminais não foram até agora replicados os resultados iniciais em grandes séries pelo que permanece uma técnica experimental.**

INTERVENÇÃO NA HIPERTENSÃO PULMONAR

Intervenção no Diagnóstico e Prognóstico

Intervenção como paliação/ ponte para transplante

Intervenção como tratamento de doentes com Hipertensão Pulmonar Tromboembólica Crónica

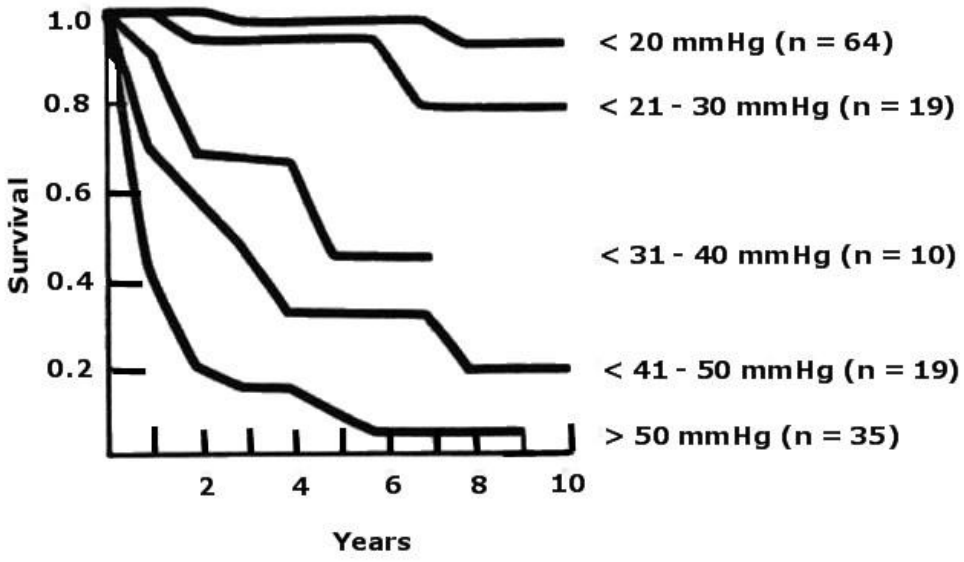
Novas estratégias de tratamento

-Desenervação das artérias pulmonares

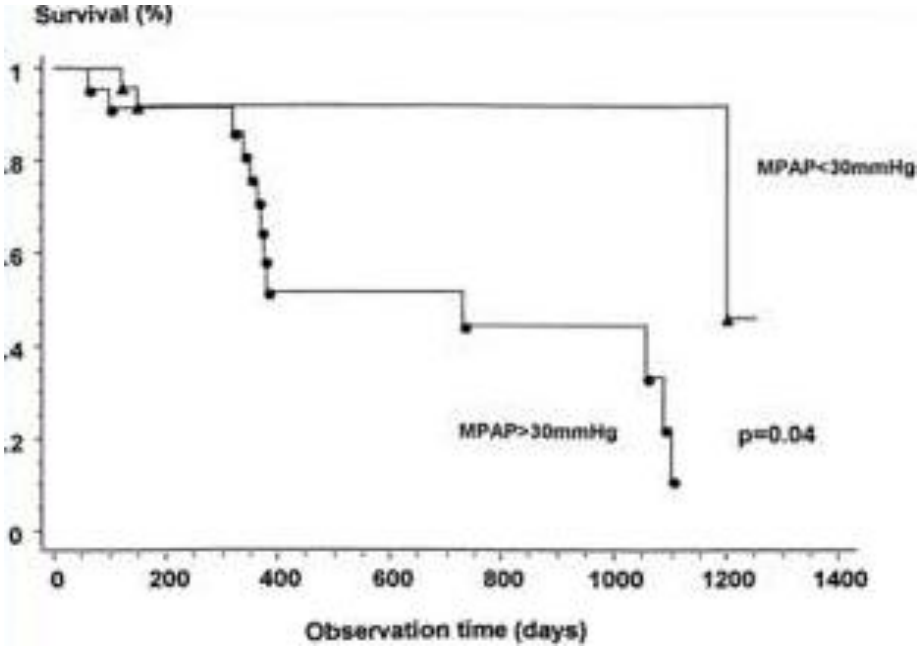
- Tratamento com células estaminais

INTERVENÇÃO NA HTP TE CRONICA

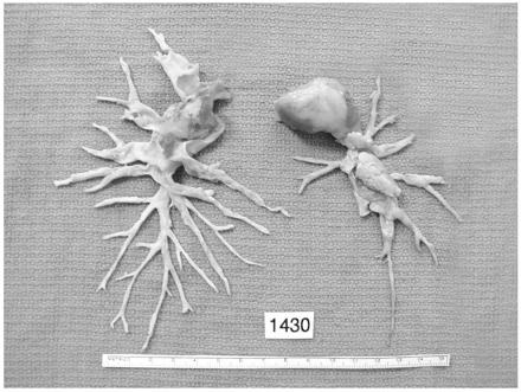
CTEPH: Survival without intervention

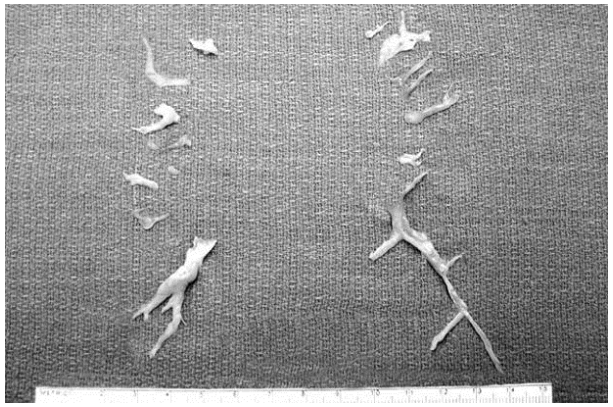


Riedel M et al. Chest 1982



Lewczuk J et al. Chest 2001





INTERVENÇÃO NA HTP TE CRONICA

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

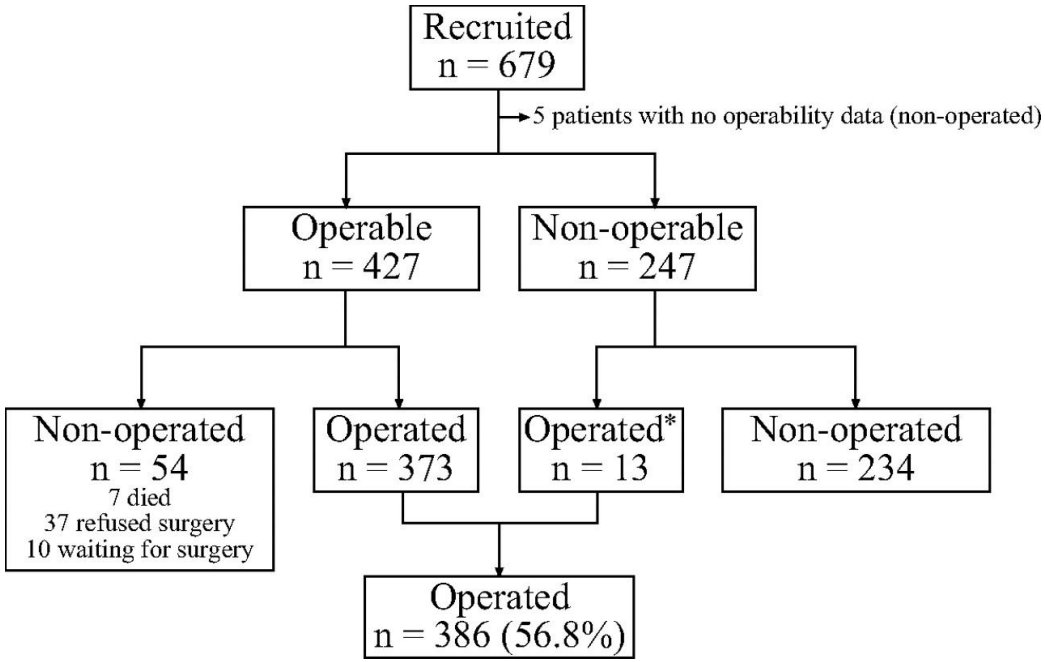
American Heart Association

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) : Results From an International Prospective Registry

679 pts included from Europe and Canada

Prospective registry

The largest contemporary population of patients with CTEPH, including newly diagnosed operable and nonoperable cases

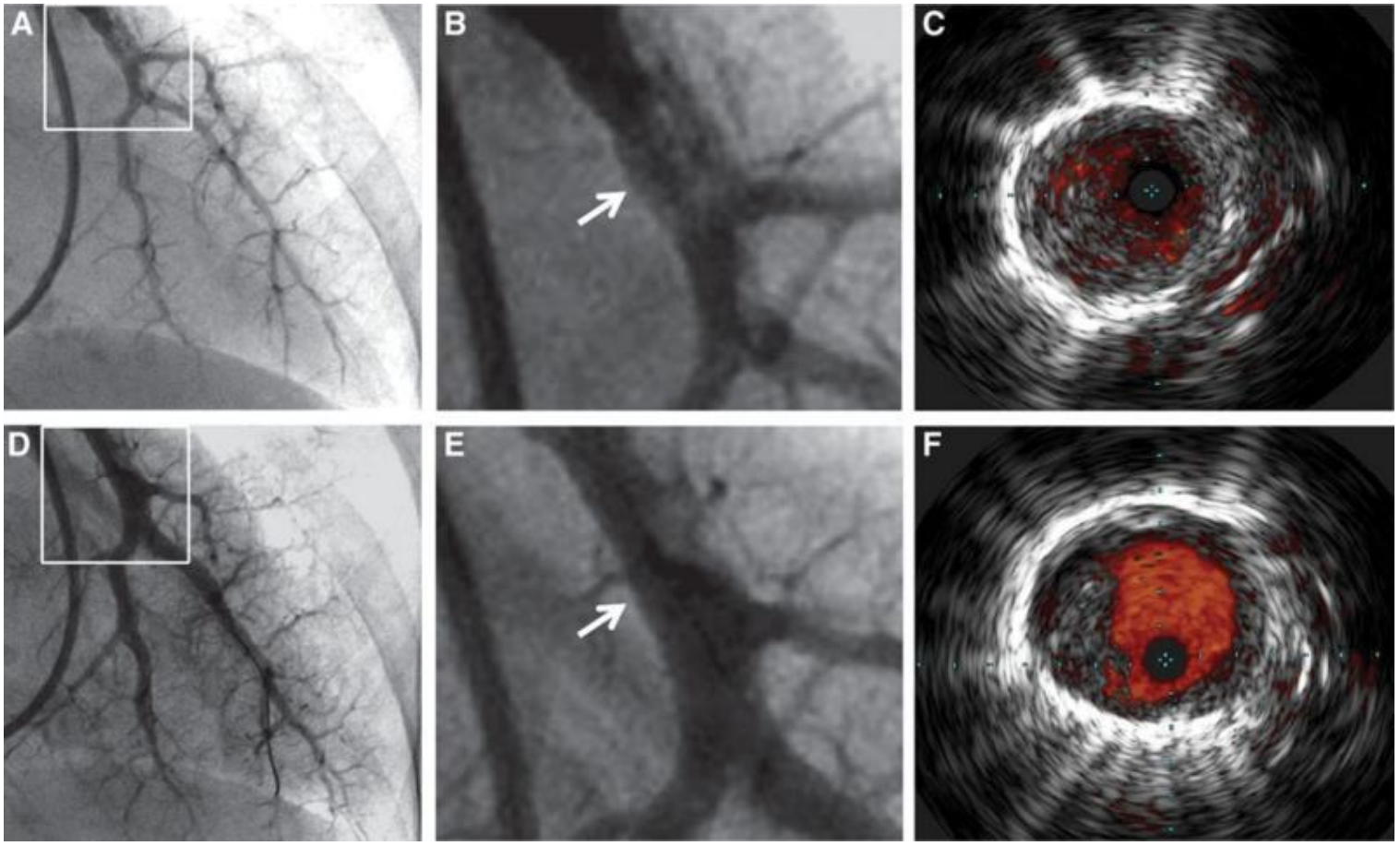


Pepke-Zaba J et al. Circulation 2011

INTERVENÇÃO NA HTP TE CRONICA

- 68 consecutive pts with inoperable CTEPH who underwent BPA between November 2004 and September 2011 were enrolled in this study.
- 4 (2-8) sessions/patient; 3 (1-14) vessels/session.

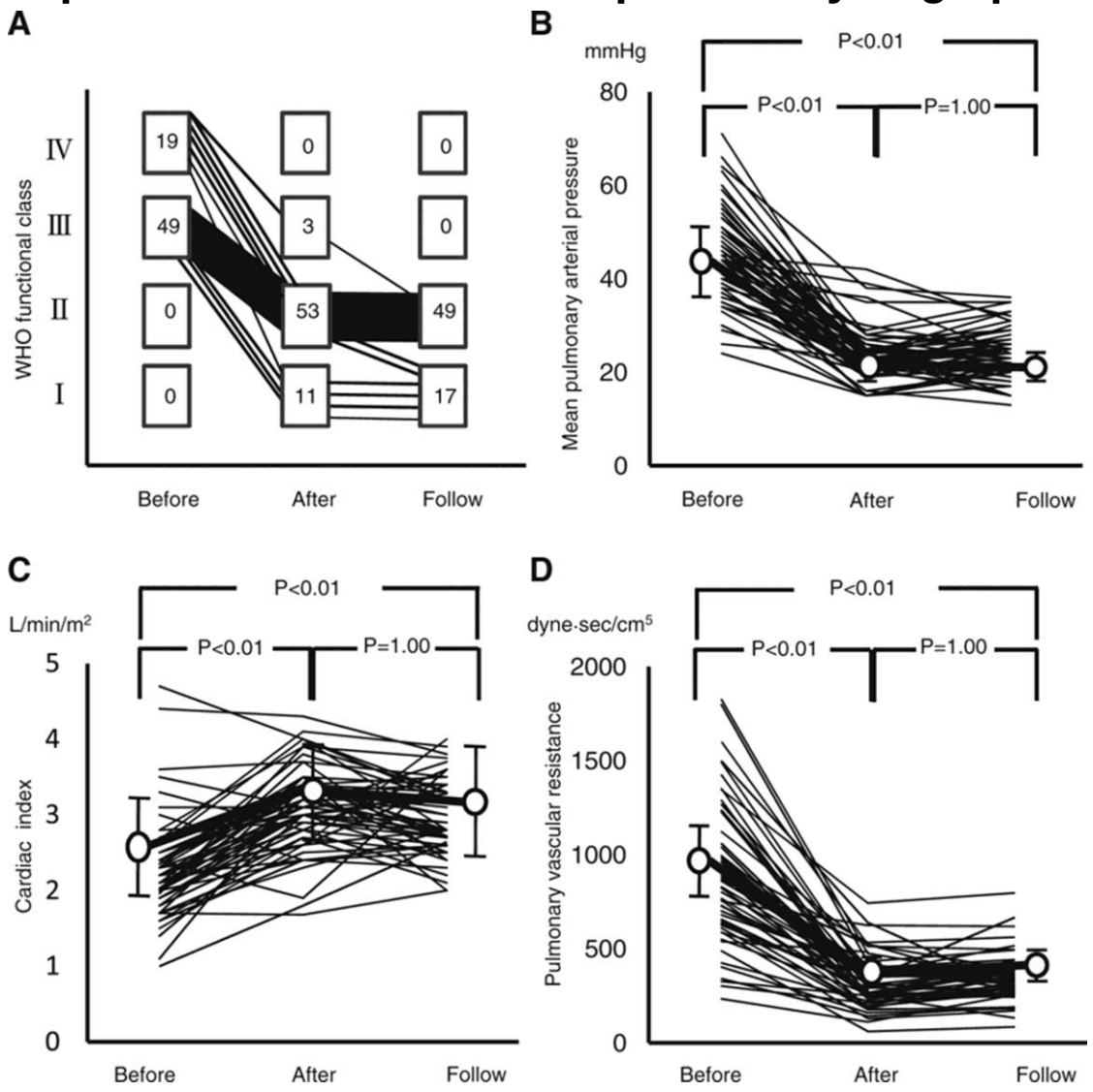
Representative angiographic and IVUS images of balloon pulmonary angioplasty (BPA)



Mizoguchi H et al. Circ Cardiovasc Interv. 2012

INTERVENÇÃO NA HTP TE CRONICA

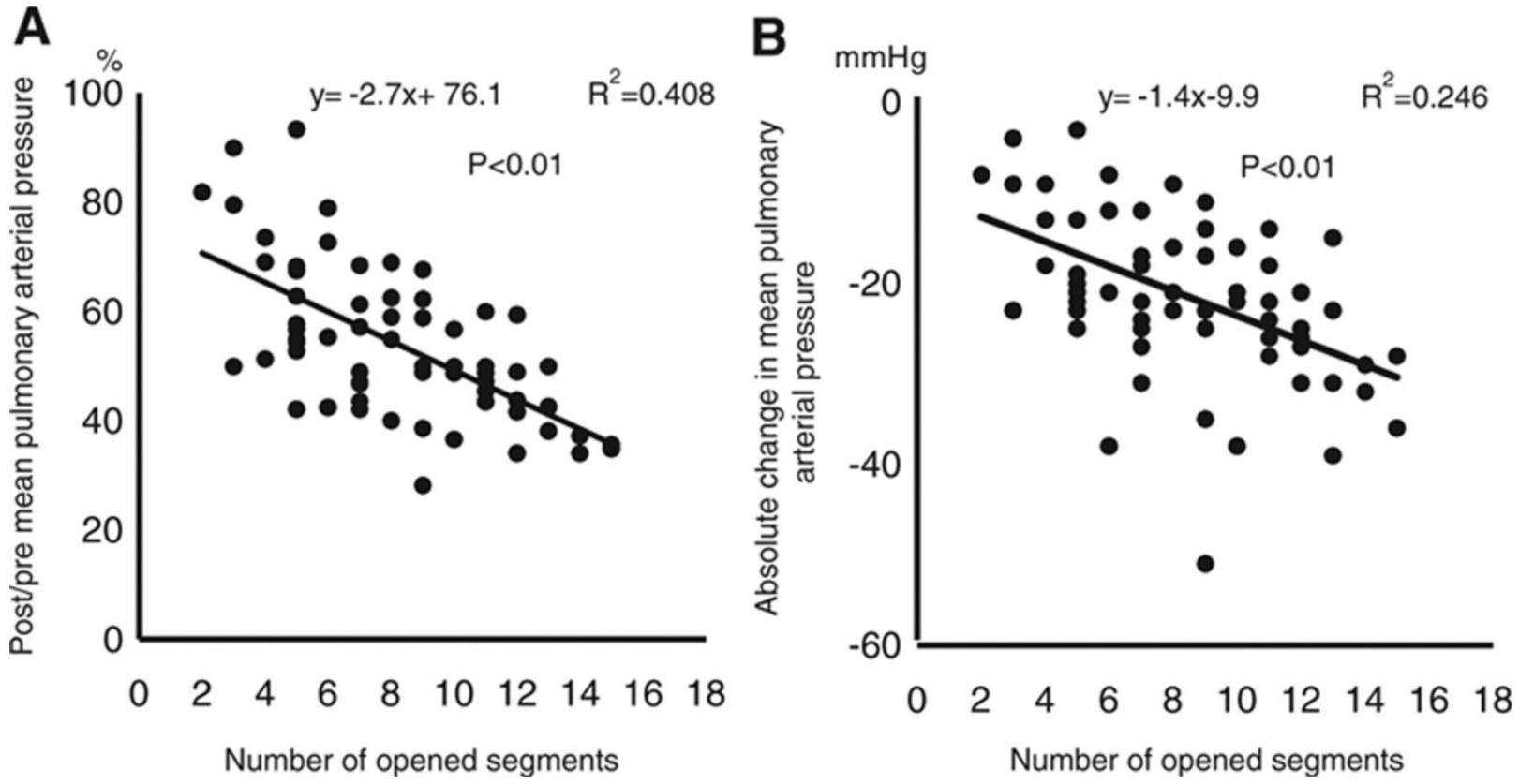
Change in parameters after balloon pulmonary angioplasty (BPA)



Mizoguchi H et al. Circ Cardiovasc Interv. 2012

INTERVENÇÃO NA HTP TE CRONICA

Correlation between the number of opened segments and the decrease in mean PAP



Mizoguchi H et al. Circ Cardiovasc Interv. 2012

INTERVENÇÃO NA HTP TE CRONICA

- **Dado os bons resultados iniciais e a escassez de terapêuticas eficazes e duradouras em doentes com HTP Tromboembólica Crónica a Angioplastia das Artérias Pulmonares parece uma alternativa a considerar no tratamento de doentes inoperáveis.**

- **Desconhece-se o papel relativo entre esta técnica de intervenção vs terapêutica farmacológica.**