Maspalomas, 23 de abril de 2010

EPOC
e
HIPERTENSIÓN PULMONAR

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Hospital de Cruces

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EPOC
e
HIPERTENSIÓN PULMONAR

13:30-14:00 h	**MARCHA POR LA EPOC** (Marcha a pie por el Paseo Marítimo de Meloneras)
14:00-16:00 h	**ALMUERZO DE TRABAJO**
16:00-17:30 h	**MESA REDONDA** COMORBILIDAD EN EPOC

EPOC e Hipertensión Pulmonar

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Hipertensión Pulmonar en la EPOC

1. Es importante ?
2. Por qué se produce ?
3. Cómo se diagnostica ?
4. Cómo se trata ?

Hipertensión Pulmonar en la EPOC

1. Es importante ?

European Heart Journal
doi:10.1093/eurheartj/ehp297

ESC/ERS GUIDELINES

Guidelines for the diagnosis and treatment of pulmonary hypertension

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

Authors/Task Force Members: Nazzareno Galiè (Chairperson) (Italy)*; Marius M. Hoeper (Germany); Marc Humbert (France); Adam Torbicki (Poland); Jean-Luc Vachiery (France); Joan Albert Barbera (Spain); Maurice Beghetti (Switzerland); Paul Corris (UK); Sean Gaine (Ireland); J. Simon Gibbs (UK); Miguel Angel Gomez-Sanchez (Spain); Guillaume Jondeau (France); Walter Klepetko (Austria) Christian Opitz (Germany); Andrew Peacock (UK); Lewis Rubin (USA); Michael Zellweger (Switzerland); Gerald Simonneau (France)

Haemodynamic definitions of pulmonary hypertension[a]

Definition	Characteristics	Clinical group(s)[b]
Pulmonary hypertension (PH)	Mean PAP ≥25 mmHg	All
Pre-capillary PH	Mean PAP ≥25 mmHg PWP ≤15 mmHg CO normal or reduced[c]	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥25 mmHg PWP >15 mmHg CO normal or reduced[c]	2. PH due to left heart disease
Passive	TPG ≤12 mmHg	
Reactive (out of proportion)	TPG >12 mmHg	

2ª causa más frecuente de HTP

Updated clinical classification of pulmonary hypertension (Dana Point, 2008[1])

1 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

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

2 Pulmonary hypertension due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3 Pulmonary hypertension due to lung diseases and/or hypoxaemia
- 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 abnormalities

4 Chronic thromboembolic pulmonary hypertension

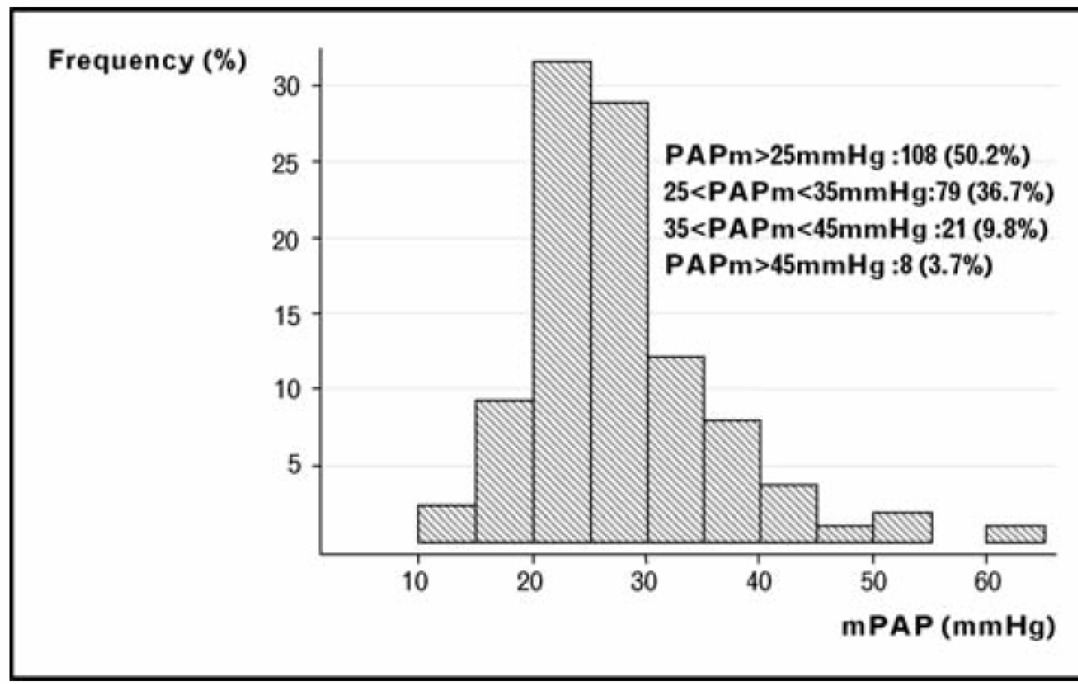
5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Prevalencia

Desconocida (1-3% HTP desproporcionada)

- Scharf
- Chaouat
- Thabut
- Weitzenblum

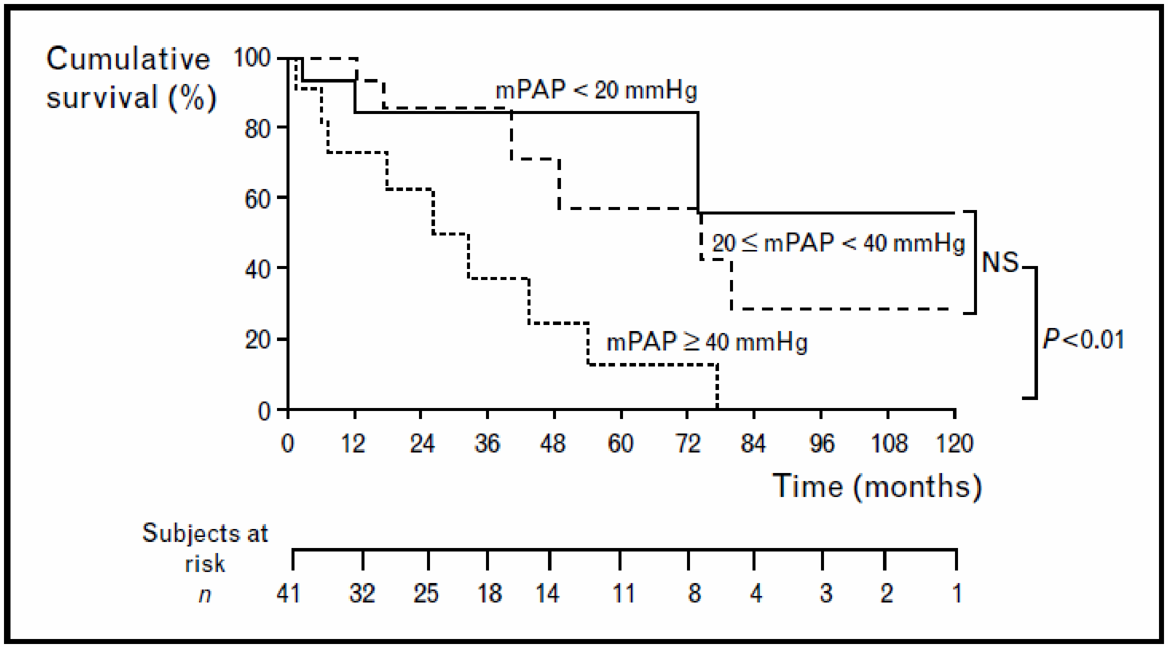
Frequency distributions of mPAP ($n = 215$)



Thabut 2005

Predice mortalidad

Survival of patients with COPD with mPAP≥40 mmHg and no other detectable cause of pulmonary hypertension compared with that of the control group of patients with COPD



Chaouat 2005

……………………………. *y consume muchos recursos*

Hipertensión Pulmonar en la EPOC

1. Es importante ?

2. Por qué se produce ?

Hipoxia

Inflamación

Pérdida de capilares

Table 1 Factors Increasing Pulmonary Vascular Resistance (PVR) in Chronic Respiratory Diseases

Anatomical factors: reduction (destruction, obstruction) of the pulmonary vascular bed
Thromboembolic lesions
Fibrosis
Emphysema
Functional factors
Alvolar hypoxia*
Acute hypoxia (pulmonary vasoconstriction)
Chronic hypoxia (remodeling of the pulmonary vascular bed)
Acidosis, hypercapnia
Hyperviscosity (polycythemia)
Hypervolemia (polycythemia)
Mechanical factors (compression of alveolar vessels)

*Most important factor.

Weitzenblum 2005

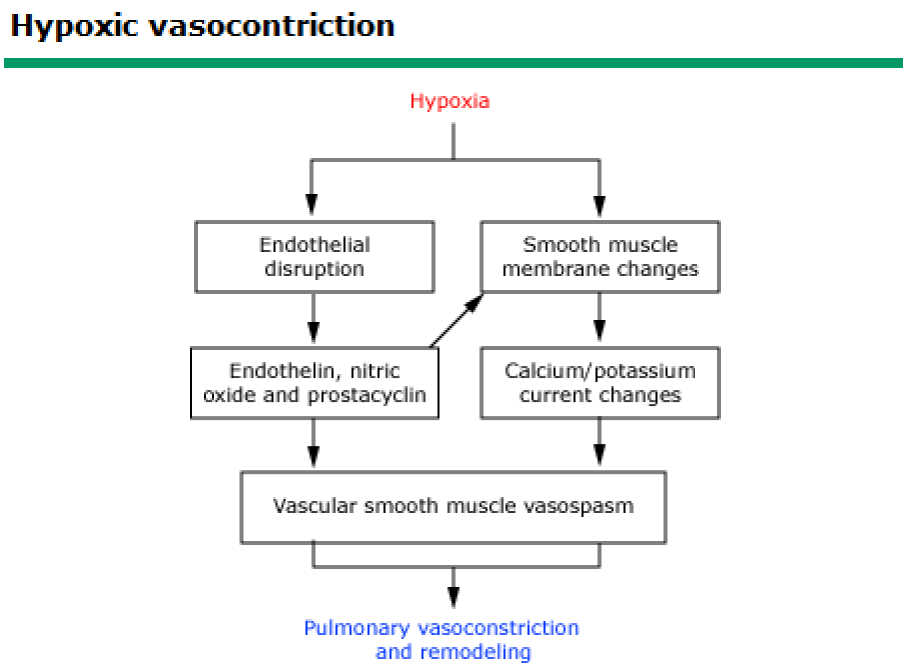
Hipoxia Crónica

Disminución NO

disminución producción NOSe
inactivación por aumento Hb

Cambios potencial de membrana

aumento Ca libre intracelular contracción muscular art. pulmonar



Two possible pathways for producing hyoxic vasoconstriction: one based on smooth muscle membrane changes and the other based on the release of endothelial factors. It is possible that these pathways are not in fact separate.
Adapted from Fishman, AP, in: Pulmonary Disease, Fishman, AP (Ed), McGraw Hill, New York, 1989.

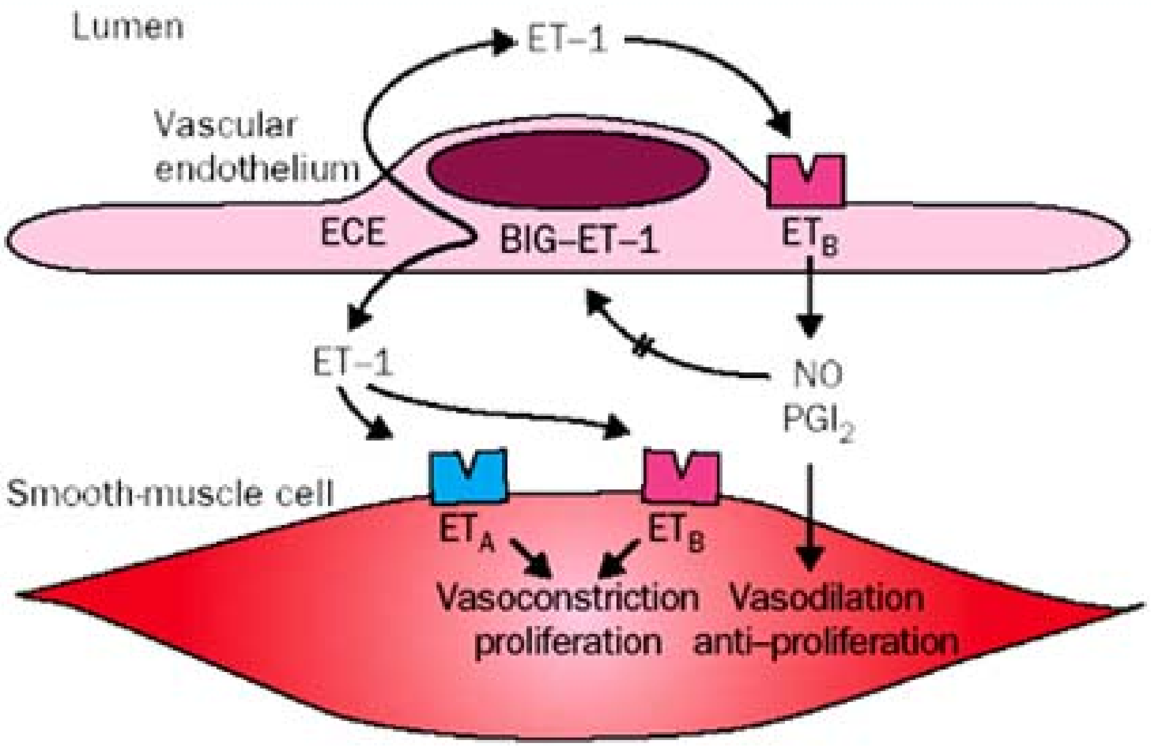
Aumento actividad PLA2c

liberación ac. araquidónico

metabolización eicosanoides vasoactivos

Incremento expresión endotelina

Endothelin system in vascular tissue



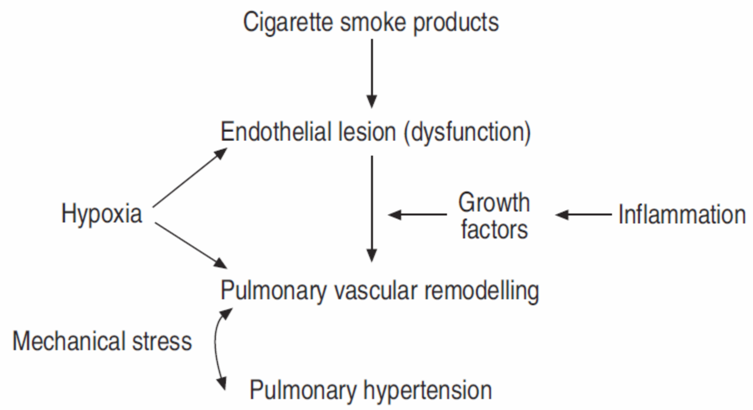
ET: endothelin-1; BIG-ET-1: proendothelin-1; ECE: endothelin-converting enzyme; NO: nitric oxide, PGI2: prostacyclin.

Role for Interleukin-6 in COPD-Related Pulmonary Hypertension

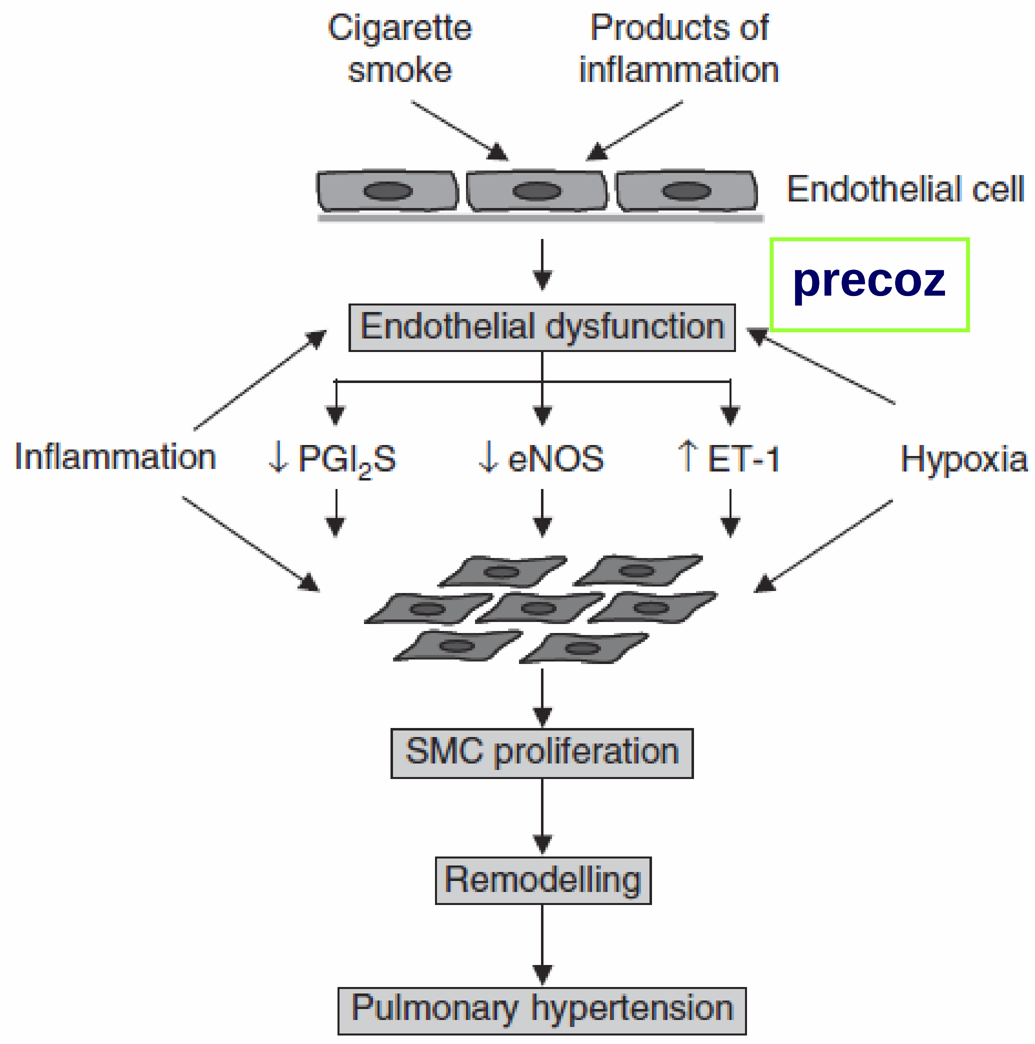
Chaouat 2009

Table 2—*Comparisons of Physiologic Variables and Circulating Cytokine Levels According to the Absence or Presence of PH (PAP ≥ 25 mm Hg) in 148 Patients With COPD*

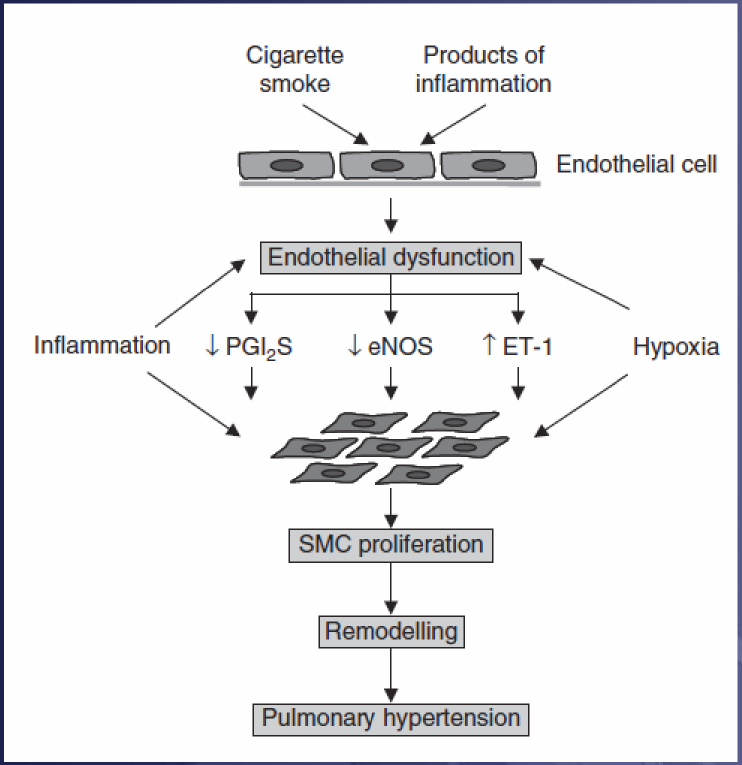
Variables	PAP < 25 mm Hg	PAP ≥ 25 mm Hg	p Value*
Age, yr	63 (56–71)	64 (56–69)	0.509
Gender			
Female	19	11	
Male	71	47	0.751†
BMI, kg/m²	25 (21–28)	26 (21–30)	0.219
Smoking history, pack–yr	50 (39–70)	45 (30–63)	0.199
MRC dyspnea score	3 (3–4)	4 (3–4)	0.302
6–min walking distance, m	370 (245–460) (n = 75)	360 (270–455) (n = 48)	0.825
BODE index	5 (3–6) (75)	4 (3–6) (48)	0.492
FEV_1, % predicted	35 (24–50)	37 (27–49)	0.621
D_{LCO}/VA, % predicted	58 (41–82) (n = 50)	62 (43–79) (n = 34)	0.530
Pa_{O_2}, mm Hg	64 (59–70)	59 (54–67)	0.007‡
Pa_{CO_2}, mm Hg	43 (39–48)	44 (41–44)	0.170
Hb, g/dL	13.6 (12.5–15.0)	14.5 (13.4–15.7)	0.002‡
PAP, mm Hg	21 (17–23)	29 (27–33)	
PWP, mm Hg	7 (5–12)	12 (9–14)	< 0.001‡
Cardiac index, L/min/m²	3.0 (2.5–3.5)	3.0 (2.6–3.3)	0.848
PVR, international units/m²	3.63 (3.01–5.36)	6.11 (4.41–8.25)	< 0.001‡
CT score	16 (8–25) (n = 65)	13 (4–22) (n = 35)	0.439
IL-6, pg/mL	2.4 (1.3–3.8) (n = 48)	3.3 (2.2–4.7) (n = 43)	0.023‡
MCP-1, pg/mL	551 (426–658) (n = 48)	549 (361–786) (n = 43)	0.862
IL-1β, pg/mL	0.68 (0.40–1.27) (n = 48)	0.65 (0.41–1.09) (n = 43)	0.642



Barberá 2003

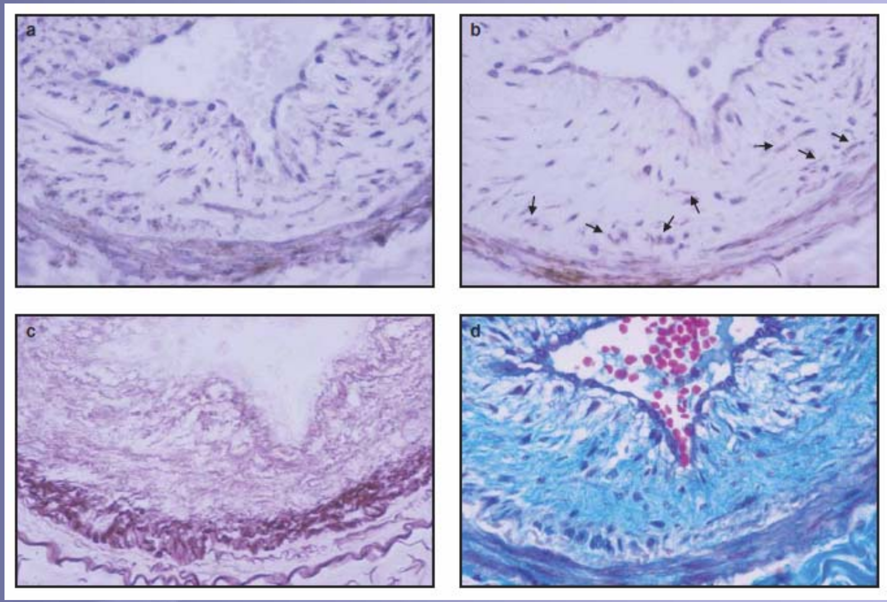


Barberá 2009

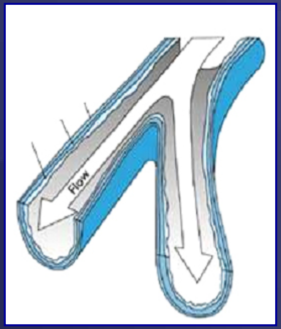


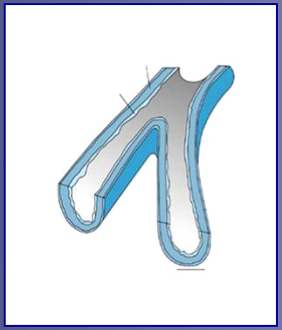
Remodelado vascular

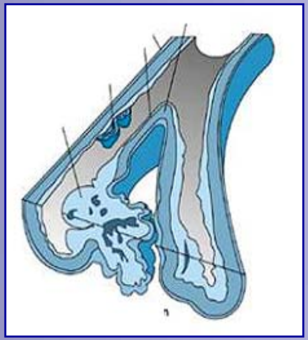
Barberá 2009



Santos 2002







Hipertensión Pulmonar en la EPOC

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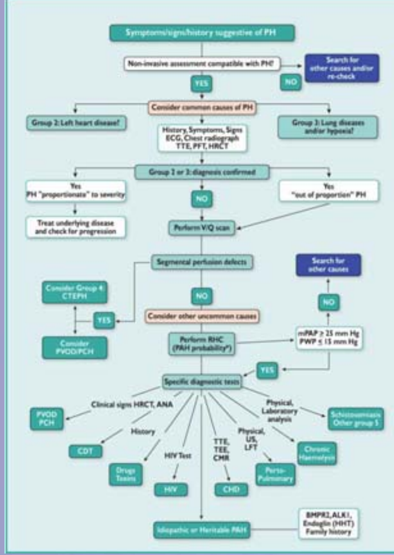
3. Cómo se diagnostica ?

Diagnóstico



Síntomas clínicos: enmascarados

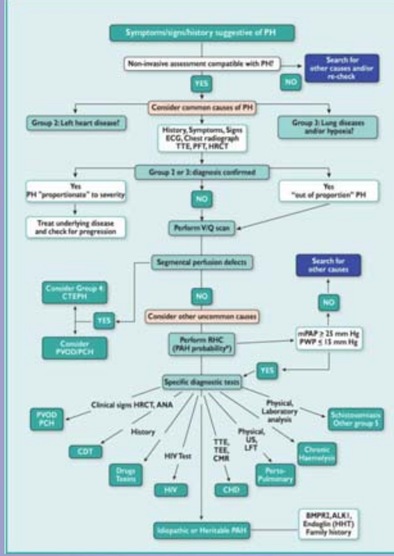
ECG y Rx tórax: baja sensibilidad

Biomarcadores: no disponibles

Exploración Funcional Respiratoria:

- **obstrucción al flujo aéreo**
- **difusión descendida !OJO!**

Diagnóstico



Ecocardiograma

dificultades técnicas

VPN bajo

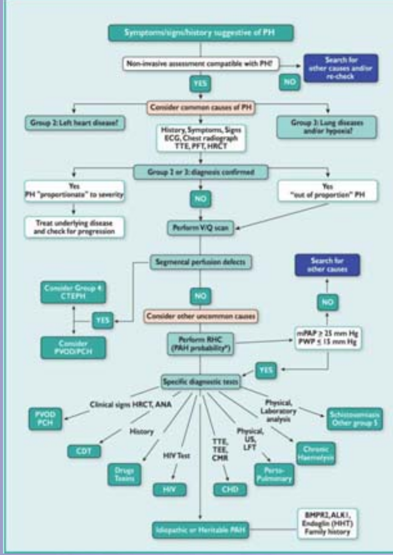
En caso de:

* Disociación entre intensidad de los síntomas y grado de obstrucción

* Disparidad entre obstrucción y difusión

* Sospecha de HAP desproporcionada

Diagnóstico



Cateterismo cardiaco derecho

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Passive	TPG ≤12 mmHg	
Reactive (out of proportion)	TPG >12 mmHg	

*** si PAPs >50 mmHg**

*** fallo cardiaco derecho frecuente**

*** evaluación preoperatoria**

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Tratamiento

Oxigenoterapia Continua Domiciliaria OCD

invierte la progresión de la hipertensión pulmonar

Weitzenblum 1985

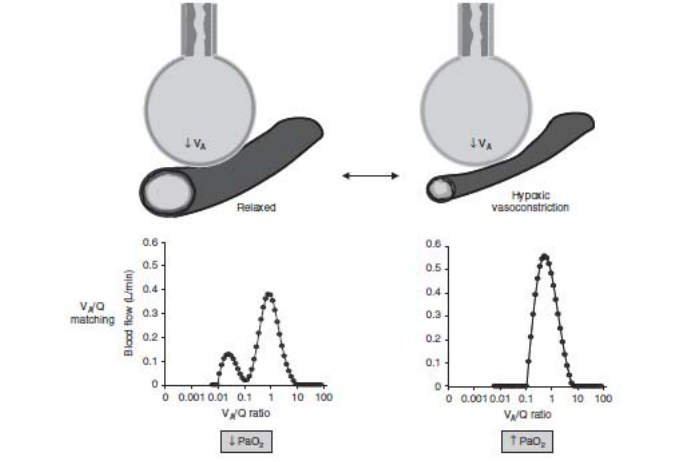
no modifica hemodinámica pulmonar

NOTT 1980

no revierte las lesiones anatomopatológicas

Wilkinson 1988

Tratamiento



OCD

Vasodilatadores

efectividad escasa

empeoran la oxigenación arterial

por inhibición de vasoconstricción pulmonar hipóxica

escasa reducción del tono vascular

escaso incremento del gasto cardiaco

Tratamiento

OCD

Vasodilatadores

Tratamiento de la disfunción endotelial

- inhibidores 5-fosfodiesterasa
- antagonistas receptor endotelina
- prostanoides

En contexto de ensayos clínicos

Table II. New specific therapy for pulmonary arterial hypertension in chronic obstructive pulmonary disease (COPD)

Study	Drug	Design	No. pts	Dose (mg)	Time (mo)	6MWD (m) pre	6MWD (m) post	PAP (mmHg) pre	PAP (mmHg) post	PaO_2 (mmHg) pre	PaO_2 (mmHg) post
Alp et al.[117]	Sildenafil	Uncontrolled	6	50 bid	3	351 ± 49	$433 \pm 52^*$	30 ± 6	$25 \pm 4^*$	NR	NR
Madden et al.[118][a]	Sildenafil	Uncontrolled	7	50 tid	2	107 ± 76	$145 \pm 96^*$	39 ± 10	35 ± 9	NR	NR
Rietema et al.[119]	Sildenafil	Uncontrolled	14	20 tid	3	385 ± 135	394 ± 116	20 ± 9	NR	NR	NR
Stolz et al.[116]	Bosentan	Double-blind, placebo-controlled	30	125 bid	3	331 ± 123	329 ± 94	32 (29–38)[b]	30 (26–34)[b]	65 ± 11	$61 \pm 8^*$

a Four patients had COPD and three idiopathic pulmonary fibrosis.

b Measured by echocardiography; values are median (interquartile range).

bid = twice daily; **NR** = not reported; **PAP** = pulmonary artery pressure; **PaO_2** = partial pressure of arterial oxygen; **pts** = patients; **tid** = three times daily; **6MWD** = distance covered in the 6-minute walk test; * $p < 0.05$ vs pretreatment value.

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Recommendations for PH due to lung diseases

Statement	Class[a]	Level[b]
Echocardiography is recommended as a screening tool for the assessment of PH due to lung diseases	I	C
RHC is recommended for a definite diagnosis of PH due to lung diseases	I	C
The optimal treatment of the underlying lung disease including long-term O_2 therapy in patients with chronic hypoxaemia is recommended in patients with PH due to lung diseases	I	C
Patients with 'out of proportion' PH due to lung diseases should be enrolled in RCTs targeting PAH-specific drugs	IIa	C
The use of PAH-specific drug therapy is not recommended in patients with PH due to lung diseases	III	C

Conclusiones

Hipertensión Pulmonar frecuente en EPOC

Hipertensión ARTERIAL Pulmonar grave infrecuente

Predice mortalidad

Consecuencia de disfunción endotelio pulmonar

Sospecha diagnóstica clínica y ecocardiográfica

Confirmación diagnóstica hemodinámica

Tratamiento con oxigenoterapia

Otros tratamientos no estandarizados

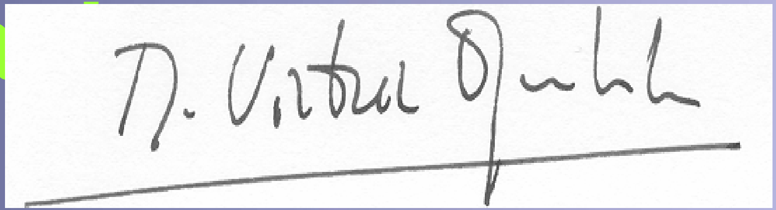
Maspalomas, 23 de abril de 2010

EPOC

e

HIPERTENSIÓN PULMONAR

Muchas Gra



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