Πνευμονική Υπέρταση

Παθοφυσιολογικοί Μηχανισμοί

Σ. Ορφανός

Β' Κλινική Εντατικής Θεραπείας

&

Διακλινικό Ιατρείο Πνευμονικής Υπέρτασης

Π.Γ.Ν ΑΤΤΙΚΟΝ

Disclosures

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- **Bayer**
- **ELPEN**
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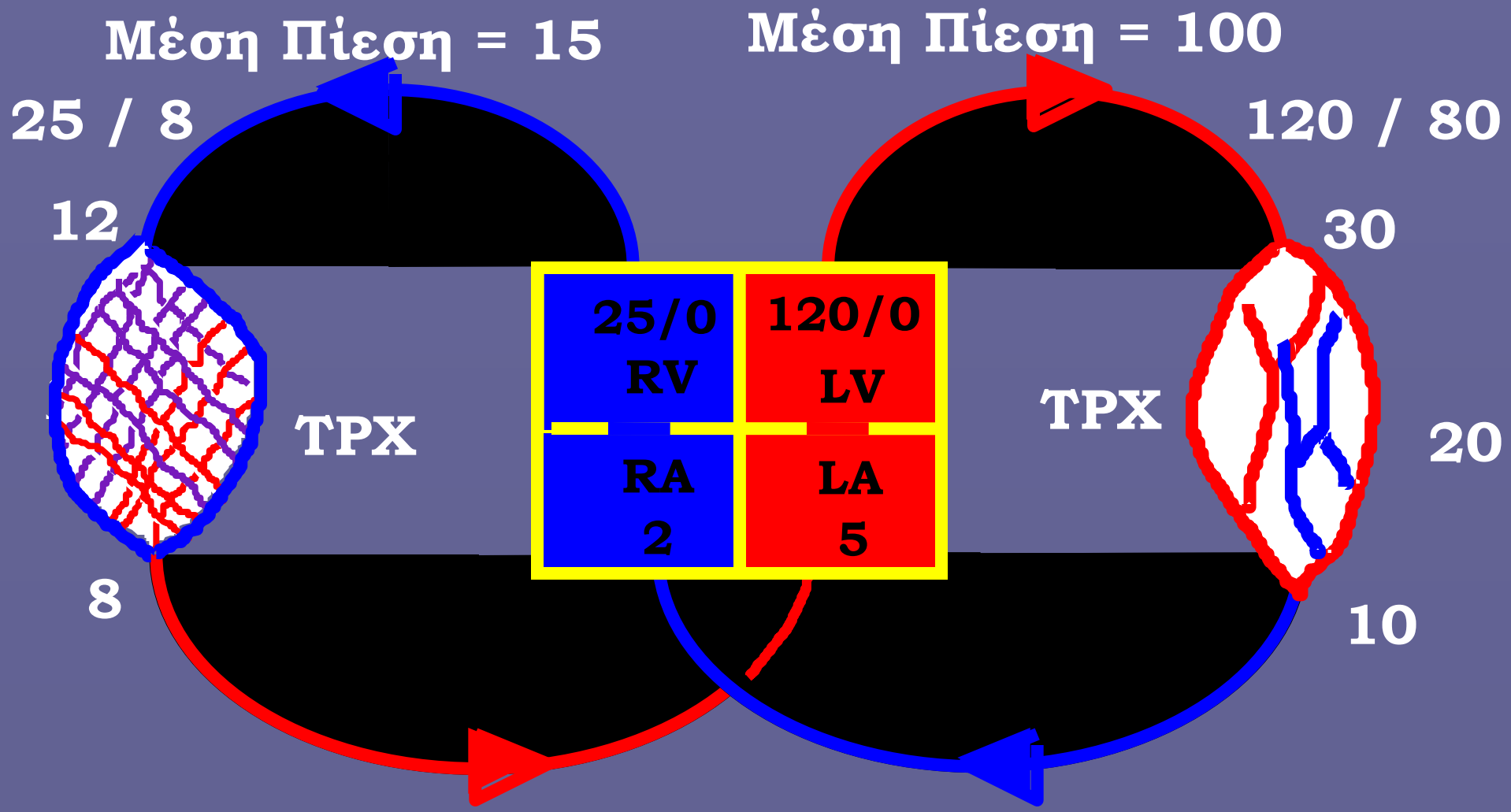
- **Galenica**
- **GSK**
- **MSD**
- **Pharmaserve Lilly**
- **PharmaSwiss**
- **Pfizer**
- **United Therapeutics**

Φυσιολογία
Πνευμονικής Κυκλοφοριας



5TH

WORLD SYMPOSIUM ON PULMONARY HYPERTENSION

NICE ACROPOLIS, Nice

February 27-28 / March 1, 2013

European Heart Journal Advance Access published September 15, 2015

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)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

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EHJ & ERJ, 2015

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Definitions and Diagnosis of Pulmonary Hypertension

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Hannover, Germany; Amsterdam, the Netherlands; Sheffield and London, United Kingdom; Rochester, Minnesota; Ann Arbor, Michigan; Warsaw, Poland; Montreal, Quebec, Canada; Bologna, Italy; Tokyo, Japan; Dallas, Texas; and Denver, Colorado

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure ≥25 mm Hg at rest, measured during right heart catheterization. There is still insufficient evidence to add an exercise criterion to this definition. The term pulmonary arterial hypertension (PAH) describes a subpopulation of patients with PH characterized hemodynamically by the presence of pre-capillary PH including an end-expiratory pulmonary artery wedge pressure (PAWP) ≤15 mm Hg and a pulmonary vascular resistance >3 Wood units. Right heart catheterization remains essential for a diagnosis of PH or PAH. This procedure requires further standardization, including uniformity of the pressure transducer zero level at the midthoracic line, which is at the level of the left atrium. One of the most common problems in the diagnostic workup of patients with PH is the distinction between PAH and PH due to left heart failure with preserved ejection fraction (HFpEF). A normal PAWP does not rule out the presence of HFpEF. Volume or exercise challenge during right heart catheterization may be useful to unmask the presence of left heart disease, but both tools require further evaluation before their use in general practice can be recommended. Early diagnosis of PAH remains difficult, and screening programs in asymptomatic patients are feasible only in high-risk populations, particularly in patients with systemic sclerosis, for whom recent data suggest that a combination of clinical assessment and pulmonary function testing including diffusion capacity for carbon monoxide, biomarkers, and echocardiography has a higher predictive value than echocardiography alone. (J Am Coll Cardiol 2013;62: D42–50) © 2013 by the American College of Cardiology Foundation

PULMONARY HYPERTENSION

WHAT IS IT?

• ELEVATED PULMONARY ARTERIAL PRESSURE
(≥25 mm Hg mean, at rest)

PULMONARY ARTERIAL HYPERTENSION

RESULTS FROM

• ABNORMAL PULMONARY VASCULAR RESISTANCE

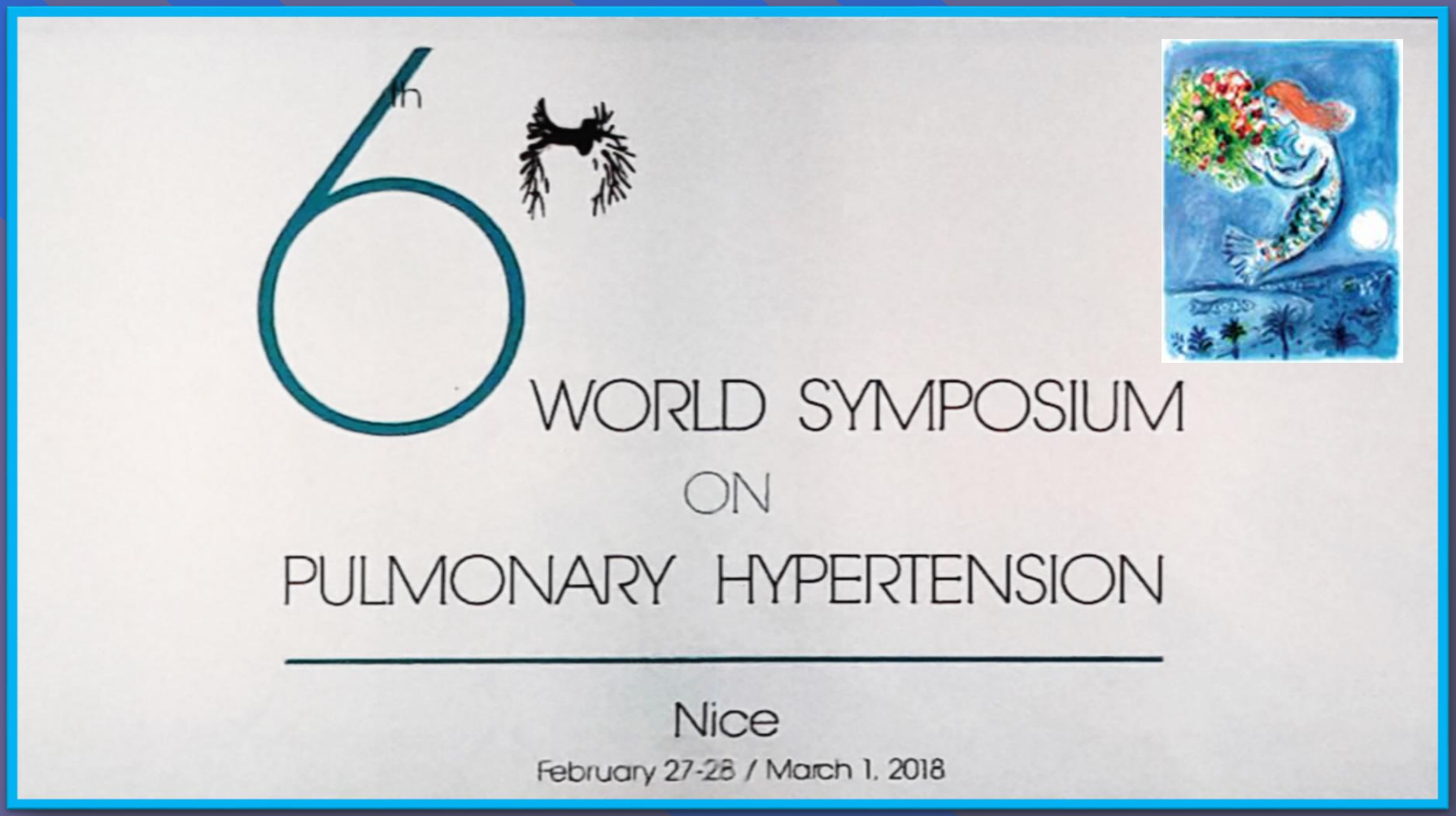
(PVR > 3 WU)
DUE TO

• PULMONARY VASCULAR REMODELLING AND CONSTRICTION

Left Heart Disease excluded: PAWP ≤ 15 mm Hg

PH is defined as an increase in mean pulmonary arterial pressure (PAPm) $\geq$25 mmHg at rest as assessed by right heart catheterization (RHC).[1] Available data have shown that the normal PAPm at rest is 14 $\pm$ 3 mmHg with an upper limit of normal of approximately 20 mmHg.[1,2] The clinical significance of a PAPm between 21 and 24 mmHg is unclear. Patients presenting with a pulmonary artery pressure (PAP) in this range should be carefully followed when they are at risk for developing PAH [e.g. patients with connective tissue disease (CTD) or family members of patients with heritable PAH (HPAH)].[1]

EHJ & *ERJ*, 2015
European Heart Journal
doi:10.1093/eurheartj/ehv317



Παρουσιάζονται διαφάνειες με Ανεπίσημα δεδομένα που παρουσίασαν οι Task Forces στο έκτο World Symposium!

Δεν ισχύει κάτι από αυτά προ δημοσιεύσεως στο αντίστοιχο statement paper , στα τέλη του 2018!

TF 4: PH Haemodynamic definitions

1. Should we redefine pulmonary hypertension (PH) and pre-capillary pulmonary pulmonary hypertension?

- **A mean PAP>20 mmHg should be considered as upper normal value**

It is not defining a disease but it is only abnormal increase of PAP pressure

- **Pre-capillary pulmonary hypertension could be defined as**

mean PAP> 20 mm Hg, PAWP < 15 mm Hg and PVR > 3 WU

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Updated Clinical Classification of Pulmonary Hypertension

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Le Kremlin-Bicêtre and Paris, France; London, United Kingdom; Edmonton, Alberta, Canada; Sydney, Australia; Marburg, Germany; Madrid, Spain; Kerala, India; Boston, Massachusetts; Chicago, Illinois; Graz, Austria; Nashville, Tennessee; and São Paulo, Brazil

In 1998, a clinical classification of pulmonary hypertension (PH) was established, categorizing PH into groups which share similar pathological and hemodynamic characteristics and therapeutic approaches. During the 5th World Symposium held in Nice, France, in 2013, the consensus was reached to maintain the general scheme of previous clinical classifications. However, modifications and updates especially for Group 1 patients (pulmonary arterial hypertension [PAH]) were proposed. The main change was to withdraw persistent pulmonary hypertension of the newborn (PPHN) from Group 1 because this entity carries more differences than similarities with other PAH subgroups. In the current classification, PPHN is now designated number 1. Pulmonary hypertension associated with chronic hemolytic anemia has been moved from Group 1 PAH to Group 5, unclear/multifactorial mechanism. In addition, it was decided to add specific items related to pediatric pulmonary hypertension in order to create a comprehensive, common classification for both adults and children. Therefore, congenital or acquired left-heart inflow/outflow obstructive lesions and congenital cardiomyopathies have been added to Group 2, and segmental pulmonary hypertension has been added to Group 5. Last, there were no changes for Groups 2, 3, and 4.
(J Am Coll Cardiol 2013;62:D34–41) © 2013 by the American College of Cardiology Foundation

Table 1 Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
   1.2.1 BMPR2
   1.2.2 ALK-1, ENG, **SMAD9**, **CAV1**, **KCNK3**
   1.2.3 Unknown
   1.3 Drug and toxin induced
   1.4 Associated with:
   1.4.1 Connective tissue disease
   1.4.2 HIV infection
   1.4.3 Portal hypertension
   1.4.4 Congenital heart diseases
   1.4.5 Schistosomiasis

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

1′′. Persistent pulmonary hypertension of the newborn (PPHN)

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

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

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1 Hematologic disorders: **chronic hemolytic anemia**, 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: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

Table 7 Updated risk level of drugs and toxins known to induce pulmonary arterial hypertension

Definite	Likely	Possible
• Aminorex • Fenfluramine • Dexfenfluramine • Toxic rapeseed oil • Benfluorex • Selective serotonin reuptake inhibitors[a]	• Amphetamines • Dasatinib • L-tryptophan • Methamphetamines	• Cocaine • Phenylpropanolamine • St John's Wort • Amphetamine-like drugs • Interferon α and β • Some chemotherapeutic agents such as alkylating agents (mytomycine C, cyclophosphamide)[b]

[a]Increased risk of persistent pulmonary hypertension in the newborns of mothers with intake of selective serotonin reuptake inhibitors.
[b]Alkylating agents are possible causes of pulmonary veno-occlusive disease.

EHJ & ERJ, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv317

CLINICAL CLASSIFICATION OF PH

1. Pulmonary Arterial Hypertension

1.1 Idiopathic PAH
1.2 PAH with vasoreactivity (Table 1)
1.3 Heritable PAH (Table 2)
1.4 Drugs and toxins induced (Table 3)
1.5 Associated with:
- 1.5.1 Connective tissue disease
- 1.5.2 HIV infection
- 1.5.3 Portal hypertension
- 1.5.4 Congenital heart disease (Table 4)
- 1.5.5 Schistosomiasis

1.6 PAH with overt signs of venous/capillaries (PVOD/PCH) involvement (Table 5)
1.7 Persistent PH of the Newborn syndrome (Table P1)

2. PH due to left heart disease

2.1 PH due to heart failure with preserved E.F
2.2 PH due to heart failure with reduced E.F
2.3 Valvular heart disease
2.4 Congenital post-capillary obstructive lesions (Table P2)

3. PH due to lung diseases and/or hypoxia (Table 6)

3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders (Table P3)

4. PH due to pulmonary artery obstruction

4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions (Table 7)

5. PH with unclear mechanisms (Table 8)

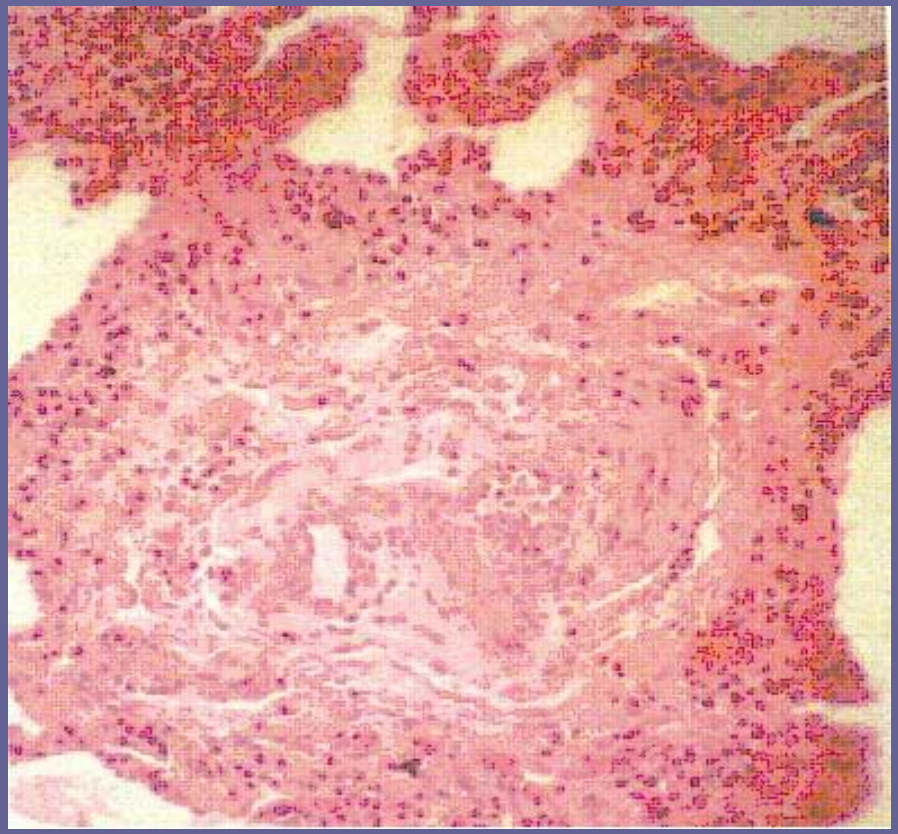
5.1 Haematologic disorders
5.2 Systemic disorders
5.3 Others
5.4 Complex congenital heart disease (Table P4)

PAH with overt signs of venous and capillary (PVOD/PCH) involvement

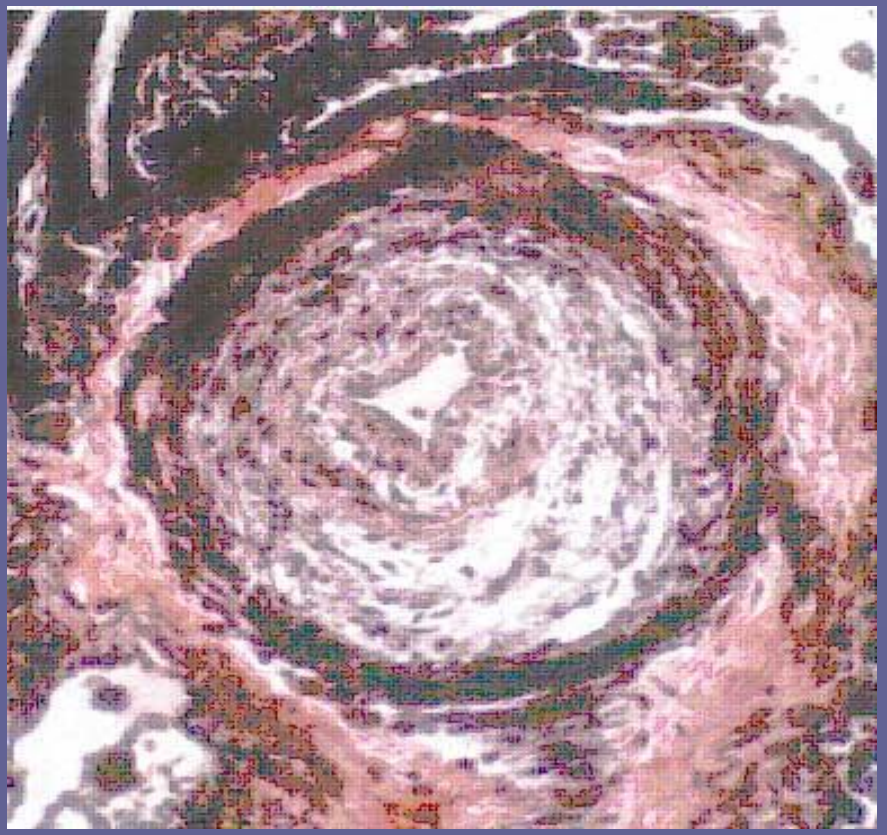
Gighna, Eur Respir J 2016
Nossent, JHLT 2017

ΠΑΥ: νόσος υπερπλασίας και απόφραξης

Plexiform lesion

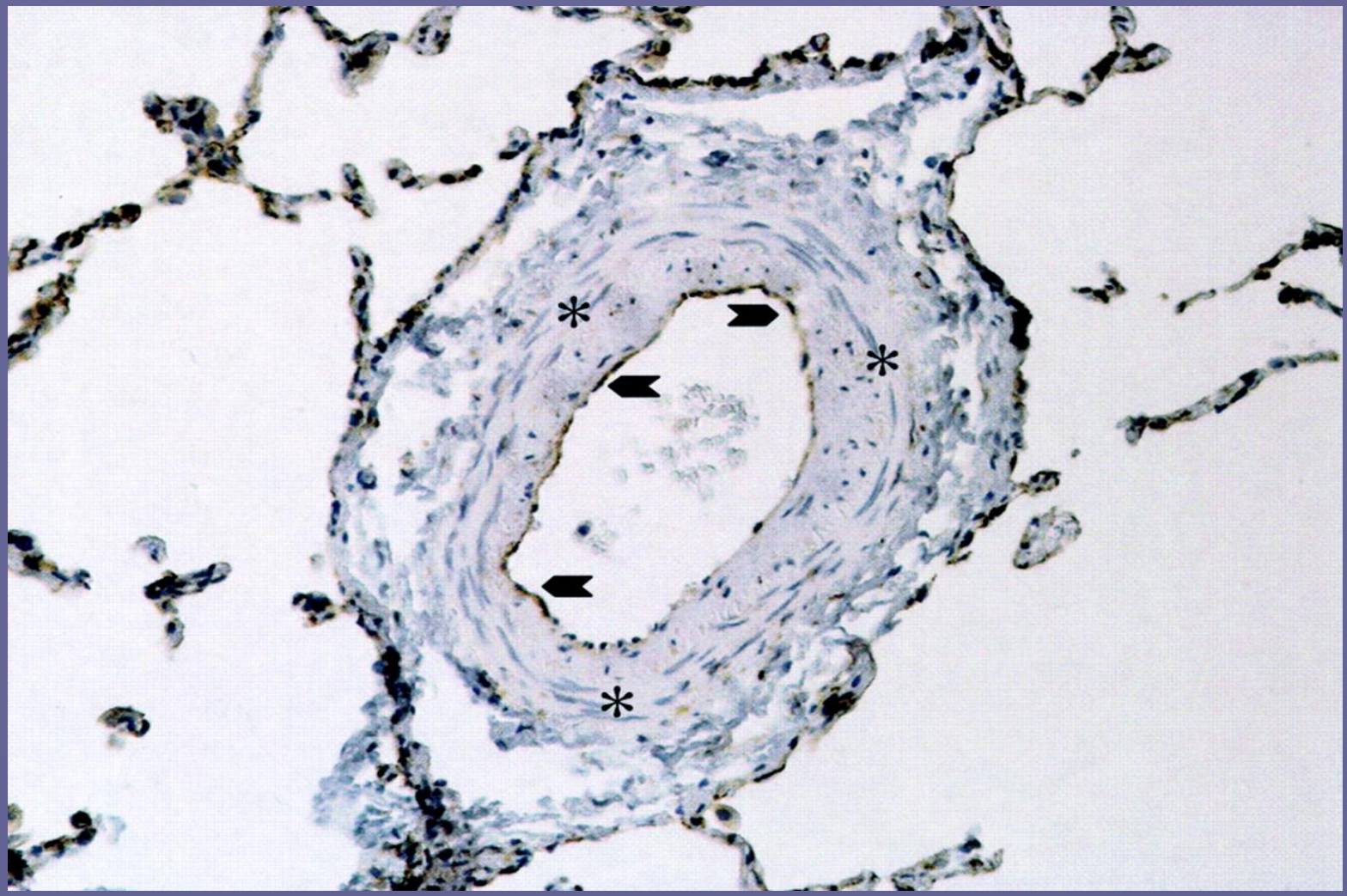


Occlusion of pulmonary artery



Fishman. Physiol Res 2000

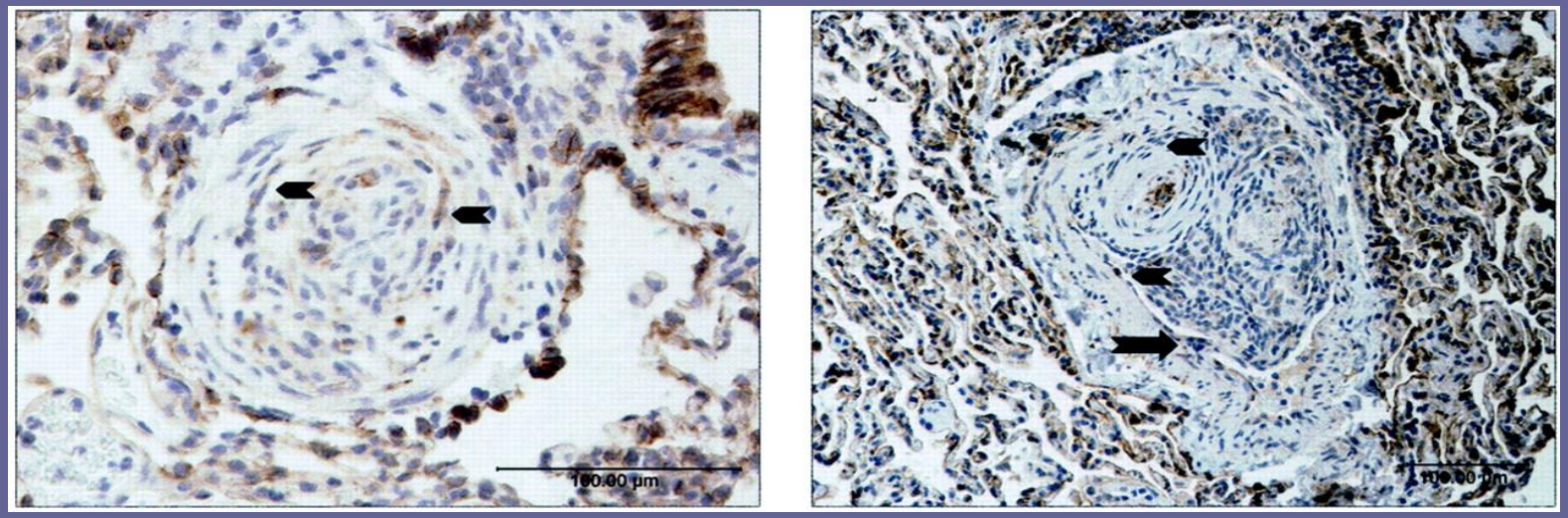
The principal lesion in idiopathic pulmonary arterial hypertension involves intermediate- and large-sized pulmonary arteries/arterioles, with medial and adventitial hypertrophy/hyperplasia



Stevens, T. Chest 2005;128:558S-564S

CHEST
The Cardiopulmonary and Critical Care Journal

Lumen-occluding plexiform lesions are seen in severe pulmonary hypertension



Stevens, T. Chest 2005;128:558S-564S

Modern Age Pathology of Pulmonary Arterial Hypertension

Elvira Stacher[1,2,3], Brian B. Graham[3], James M. Hunt[3], Aneta Gandjeva[3], Steve D. Groshong[4], Vallerie V. McLaughlin[5], Marsha Jessup[5], William E. Grizzle[6], Michaela A. Aldred[7], Carlyne D. Cool[3], and Rubin M. Tuder[3]

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of Pathology, National Jewish Hospital, Denver, Colorado; [5]University of Michigan Health System, Cardiovascular Center, Ann
[6]Department of Pathology, University of Alabama, Birmingham, Alabama; and [7]Genomic Medicine Institute and Taussig Cancer
Clinic and Department of Genetics, Case Western Reserve University School of Medicine, Cleveland, Ohio

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Severe pulmonary arterial hypertension is associated with distinct and pronounced pulmonary vascular and nonvascular lung pathology. The last reports of the pathology of severe pulmonary hypertension date back approximately 2 decades, well before use of current therapies for the disease.

What This Study Adds to the Field

The current work systematically examines the largest assortment of lungs collected from transplanted patients with idiopathic and associated pulmonary arterial hypertension in the past 2 decades. Our study reveals that in patients with advanced disease, there is a distinct spectrum of pulmonary vascular and nonvascular pathologies, including localized interstitial and perivascular inflammation. In this set of patients, who were enrolled for lung transplantation while being treated with the modern armamentarium of drug therapies, the appearance of classical pulmonary vascular lesions related to the disease was unaffected. Our results provide a unique insight into the spectrum of these pathological alterations, which can inform future translational work.

Am J Respir Crit Care Med Vol 186, Iss. 3, pp 261–272, Aug 1, 2012

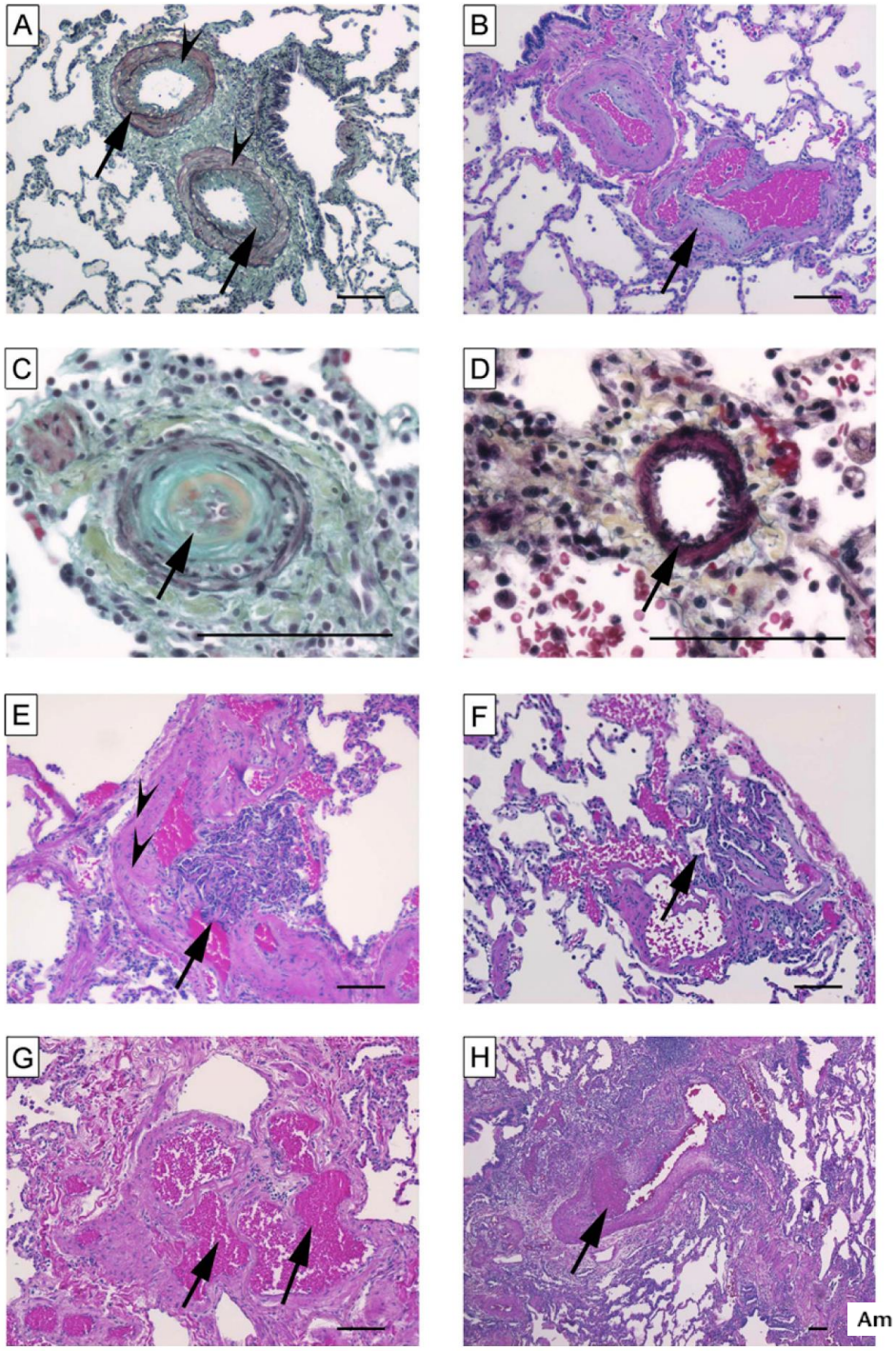


Figure 5. Characteristic histopathological findings encountered in idiopathic pulmonary arterial hypertension–like pattern. (*A*) Intima (*arrows*) and media (*arrowheads*) thickening (Russel-Movat pentachrome stain). (*B*) Cushion-like eccentric intima thickening (*arrow*) in pulmonary arteries (hematoxylin and eosin [H&E]). (*C*) Concentric "onion-skin–like" (*arrow*) intima thickening with subtotal luminal occlusion (Russel-Movat pentachrome stain). (*D*) Muscularization of small artery (*arrow*) (Russel-Movat pentachrome stain). (*E*) Plexiform lesion (*arrow*) fed by muscular artery (*arrowheads*) (H&E). (*F*) Subpleural plexiform lesion (*arrow*) (H&E). (*G*) Angiomatoid lesion consisting of dilated vessels (*arrows*) (H&E). (*H*) Recent thrombus (*arrow*) (H&E). Scale bars = 100 μm.

ΠΑΘΟΦΥΣΙΟΛΟΓΙΑ ΠΑΥ

Πολύπλοκη και πολυπαραγοντική

Αγγειοσύσπαση

Θρόμβωση (αιμοπετάλια)

Αγγειοδραστικές ουσίες, αυξητικοί παράγοντες,

φλεγμονώδεις μεταβιβαστές, συστατικά πήξης

Remodeling

ΓΕΝΕΤΙΚΕΣ ΑΝΩΜΑΛΙΕΣ

πρώτη που ανιχνεύτηκε: BMPR2: αναστολή υπερπλασίας – λεία μυική ίνα

ΕΝΔΟΘΗΛΙΑΚΟ ΚΥΤΤΑΡΟ

4. Pathophysiology

PAH may be idiopathic or secondary to various conditions, but regardless of the underlying aetiology, patients exhibit similar pathological changes which include enhanced pulmonary arteriole contractility, endothelial dysfunction, remodelling and proliferation of both endothelial and smooth muscle cells, and in situ thrombi [5]. The physiological outcome of these disturbances is the partial occlusion of small pulmonary arteries, eventuating in increased PVR, subsequent right ventricular failure and death [5].

Underpinning these progressive pulmonary vascular defects is the disruption of three key signalling pathways outlined in Figure 1: nitric oxide (NO), prostacyclin (PGI_2) and thromboxane A_2 (TXA_2), and endothelin-1 (ET-1) [26]. Broadly speaking, PAH is caused by impaired vasodilation from reduced PGI_2 production (cyclooxygenase-2 dysregulation) and NO synthase (eNOS) function, with concurrent vasoconstrictive and mitogenic effects of an upregulated ET-1 signalling system [26,27]. A mechanistic understanding of these three pathways has prompted rapid development in the quantity and efficacy of targeted pharmacological therapies for PAH.

Endothelial damage is a key initial event in PAH. Although the mechanisms that mediate this damage are largely unknown, insults such as chronic hypoxia, inflammation, viral infection, mechanical stretch or shear stress, can activate the endothelial apparatus and induce cell apoptosis [11]. The death of ECs leads to the appearance of apoptotic-resistant and hyper-proliferative ECs,

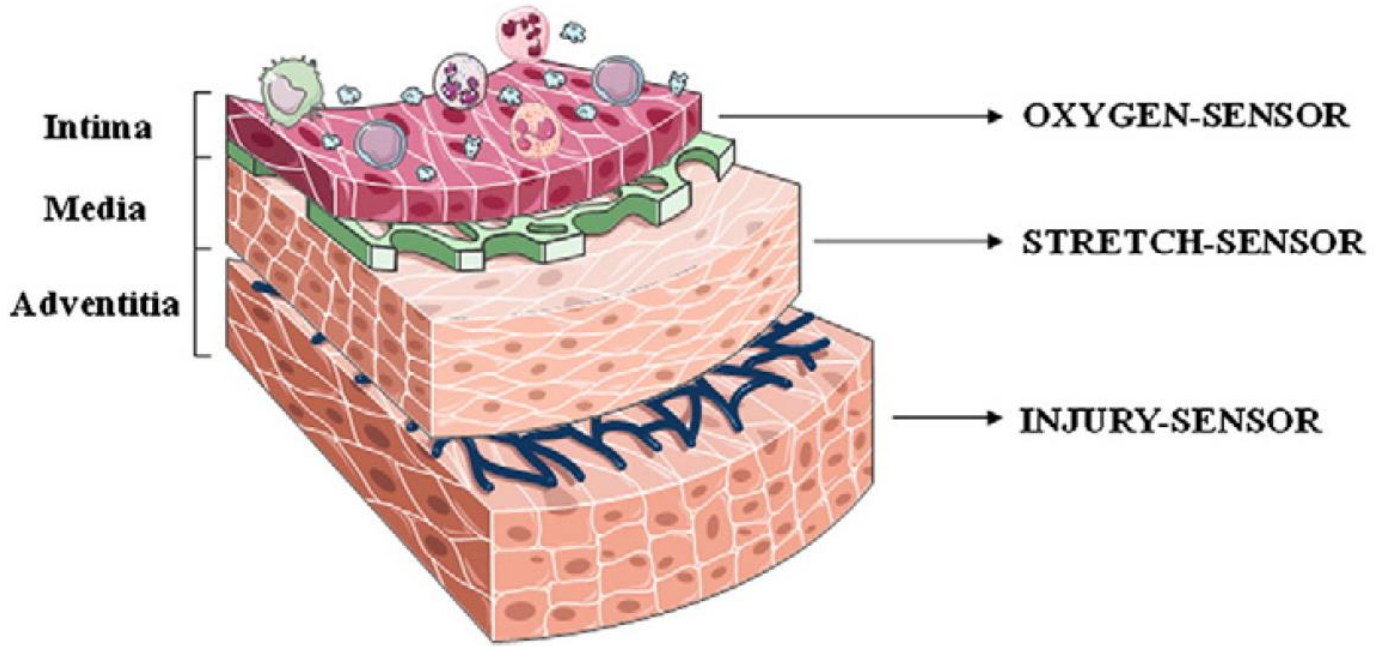
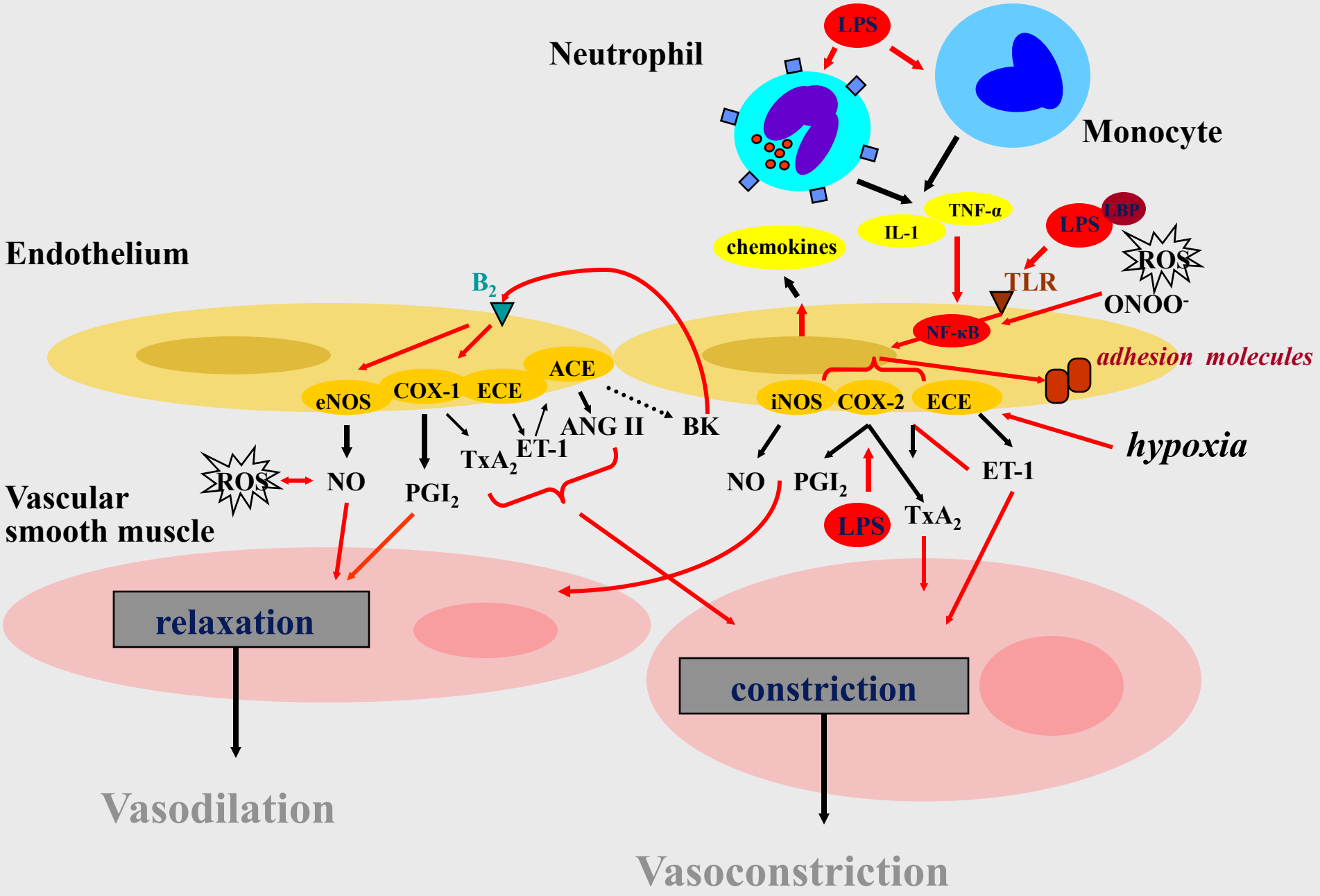
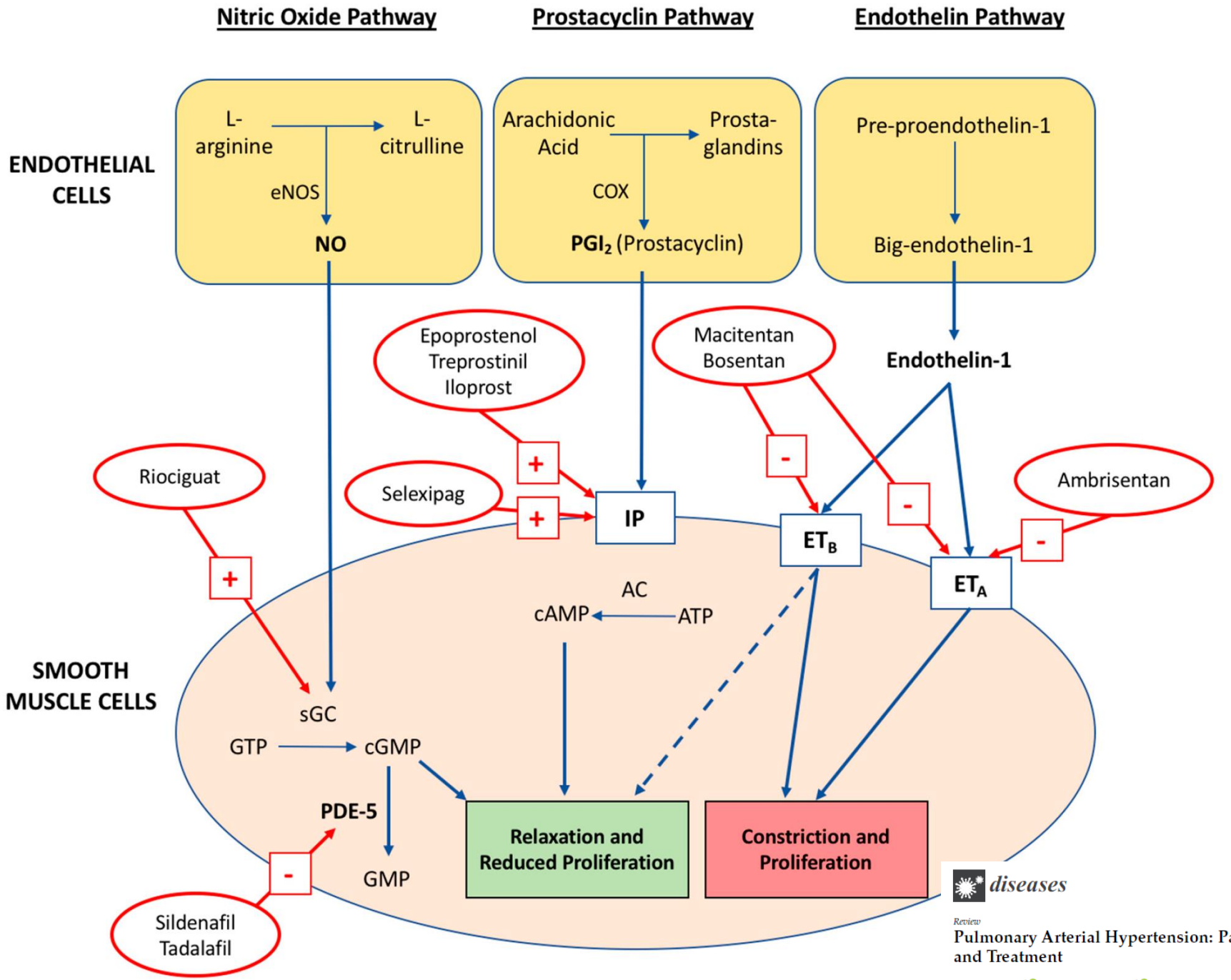


Fig. 1. "Sensing" mechanisms in the different layers of the pulmonary artery wall. Endothelial cells of the intima are equipped with mechanisms to sense differences in the oxygen supply. Medial smooth muscle cells have multiple stretch-sensing mechanisms that participate in the modulation of their functions. Fibroblasts, present in the adventitia, are considered the principal injury-sensing cells.



Intensive Care Med 2004; 30:1702-14

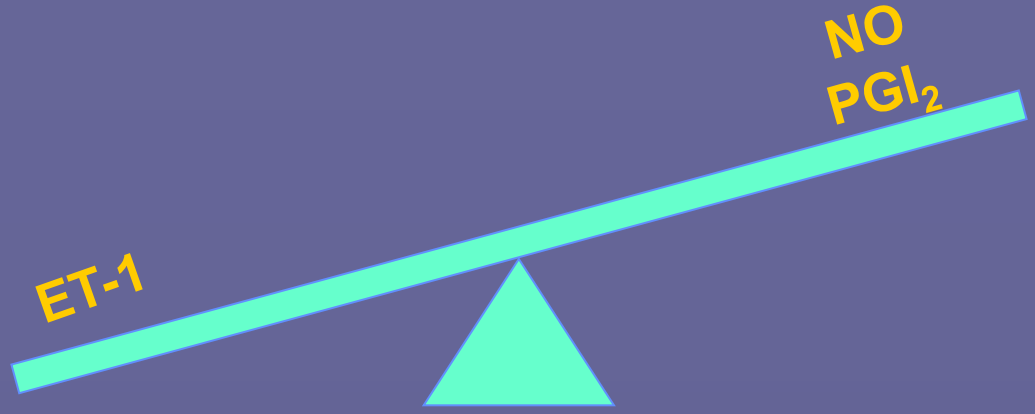


diseases
Review

Pulmonary Arterial Hypertension: Pathophysiology and Treatment

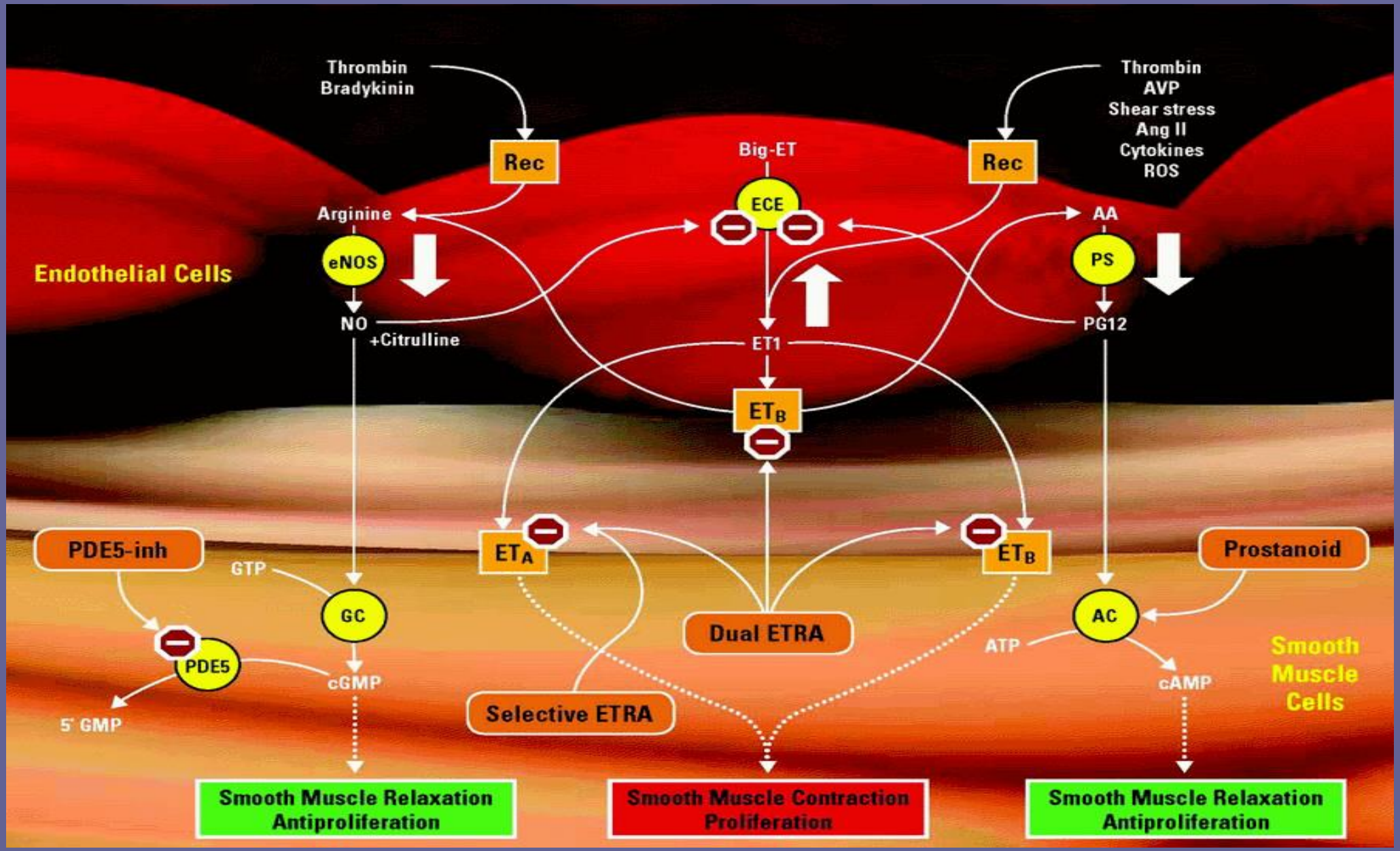
Norris S. H. Lan [1], Benjamin D. Massam [1], Sandeep S. Kulkarni [1] and Chim C. Lang [2,*]

Ενδοθηλιακή Δυσλειτουργία επί ΠΑΥ



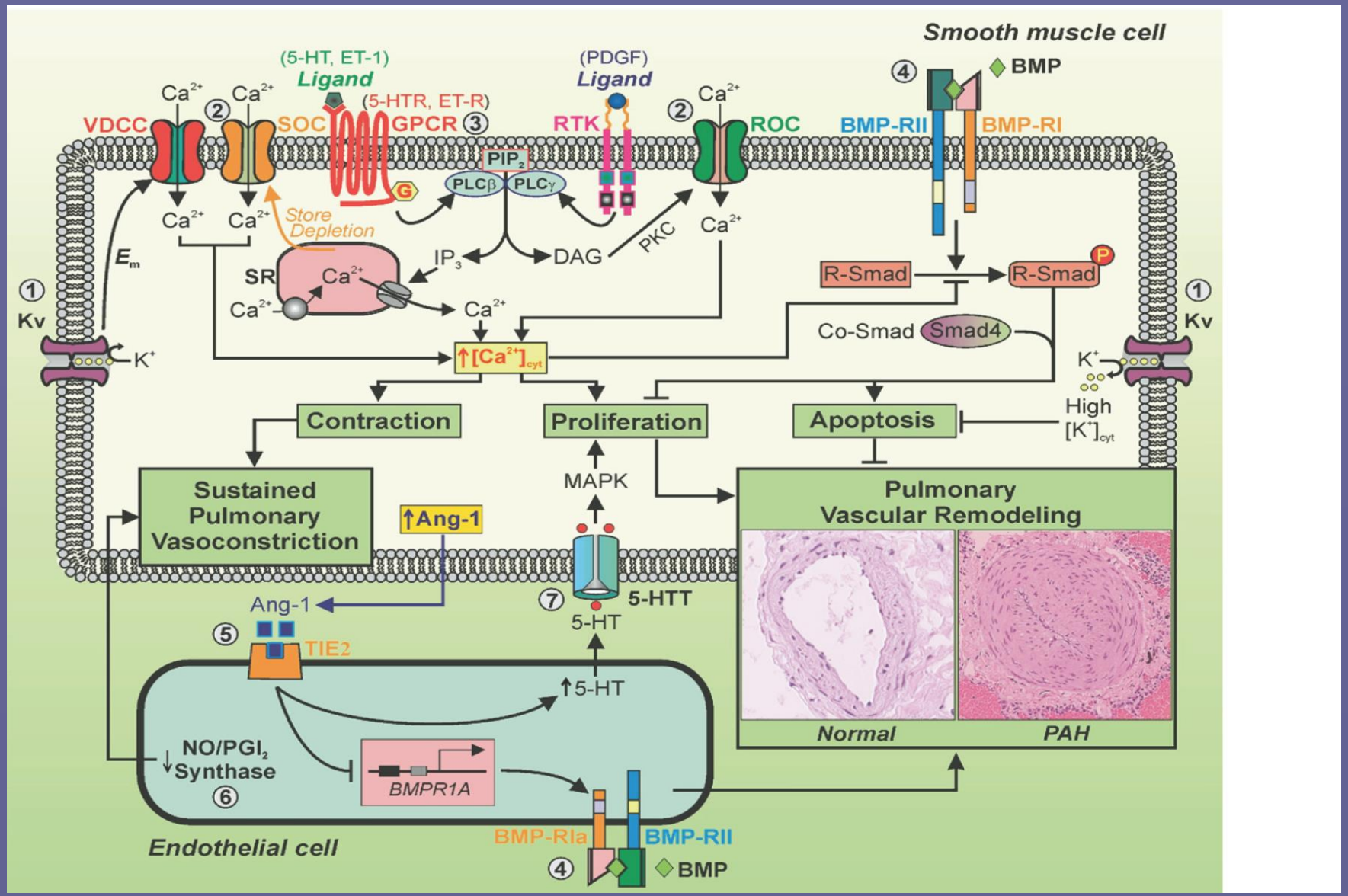
- **ET-1 is elevated (+)**
  - Vasoconstriction
  - Cell proliferation / Hypertrophy
- **NO and PGI_2 are reduced (-)**
  - Vasodilation
  - Anti-proliferation
  - Anti-inflammation

Spieker LE et al. J Am Coll Cardiol. 2001;37:1493-1505.
Luscher TF and Barton M. Circulation. 2000;102:2434-2440.
Albrecht EW et al. J Pathol. 2003;199:8-17.
Hankins SR and Horn EM. Curr Cardiol Rep. 2000;2:244-251.

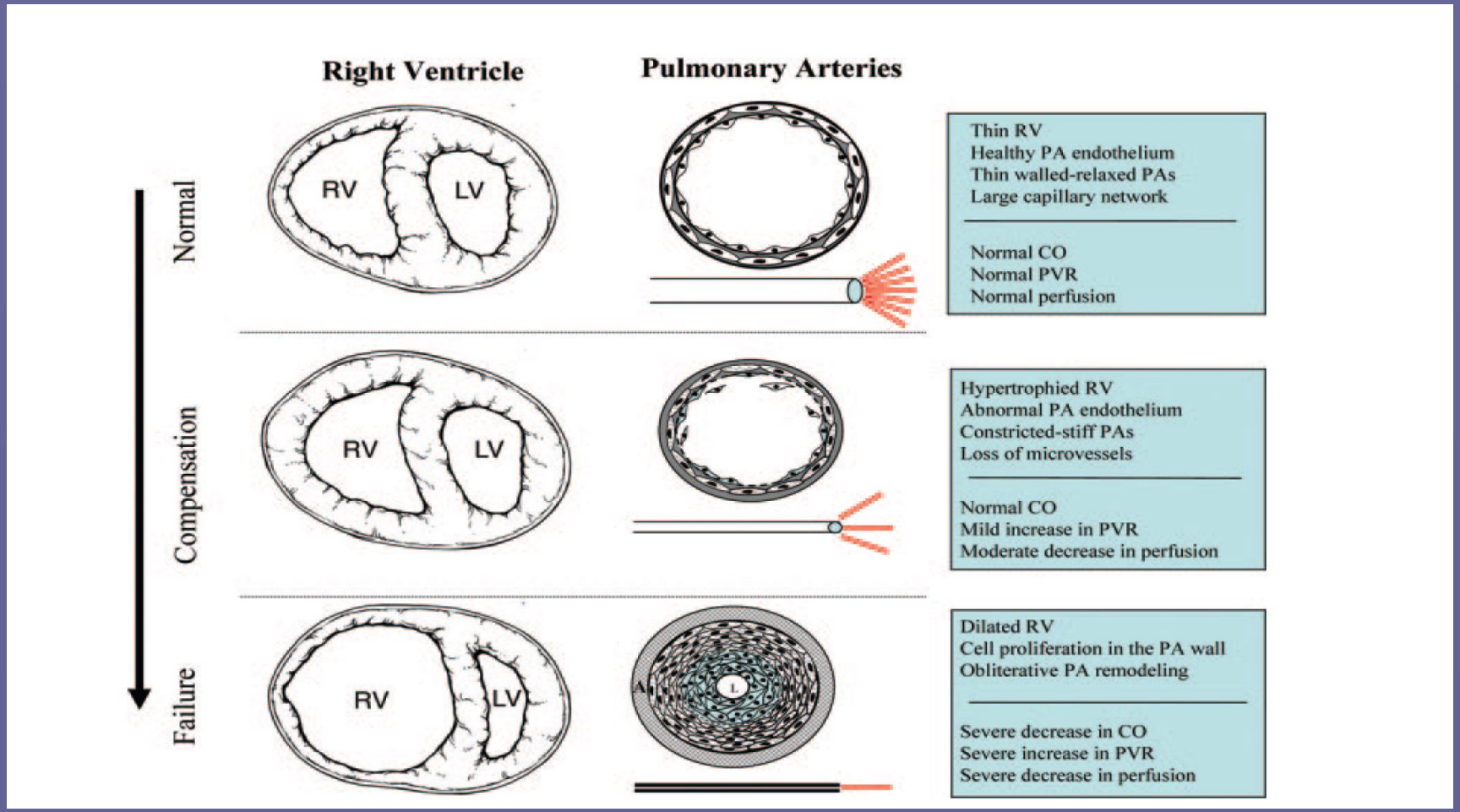


McLaughlin & McGoon *Circulation* 2006, 114:1417-1431

Pathways in the pathogenesis of PH



Progression of vascular disease



Hunter C. Champion, Evangelos D. Michelakis and Paul M. Hassoun

Circulation 2009;120;992-1007

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Right Heart Adaptation to Pulmonary Arterial Hypertension

Physiology and Pathobiology

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Amsterdam and Maastricht, the Netherlands; Stanford and Torrance, California; Dallas, Texas; Philadelphia, Pennsylvania; Brussels, Belgium; Nashville, Tennessee; Chemin Sainte-Foy, Québec, Canada; Otwock, Poland; Richmond, Virginia; and Baltimore, Maryland

Survival in patients with pulmonary arterial hypertension (PAH) is closely related to right ventricular (RV) function. Although pulmonary load is an important determinant of RV systolic function in PAH, there remains a significant variability in RV adaptation to pulmonary hypertension. In this report, the authors discuss the emerging concepts of right heart pathobiology in PAH. More specifically, the discussion focuses on the following questions. 1) How is right heart failure syndrome best defined? 2) What are the underlying molecular mechanisms of the failing right ventricle in PAH? 3) How are RV contractility and function and their prognostic implications best assessed? 4) What is the role of targeted RV therapy? Throughout the report, the authors highlight differences between right and left heart failure and outline key areas of future investigation. (J Am Coll Cardiol 2013;62:D22–33) © 2013 by the American College of Cardiology Foundation

JACC Vol. 62, No. 25, Suppl D, 2013
December 24, 2013:D22–33

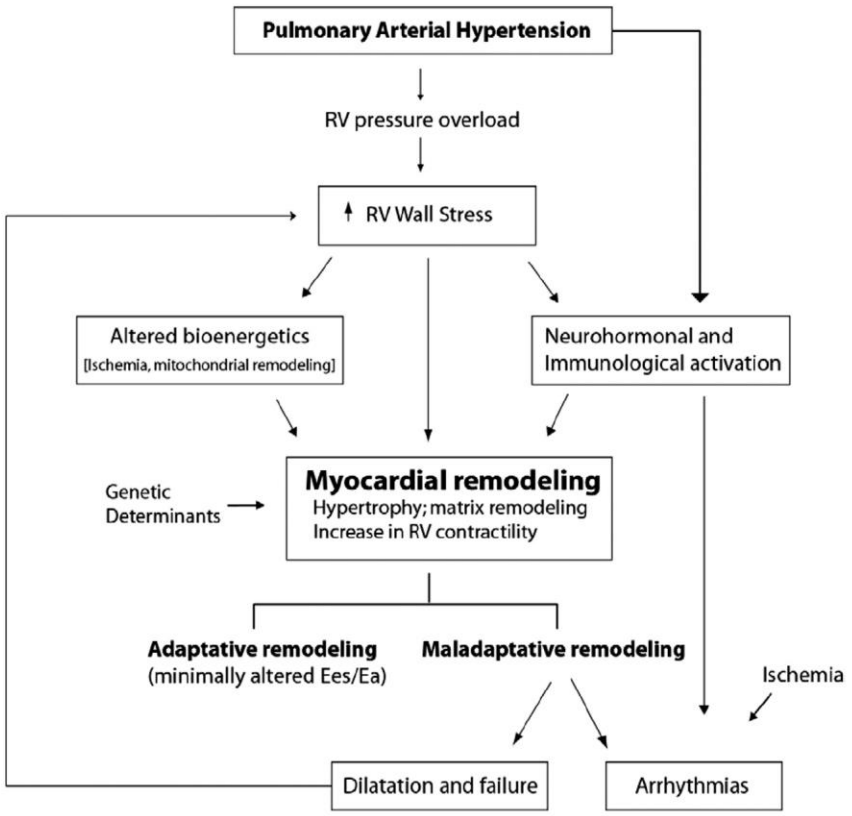
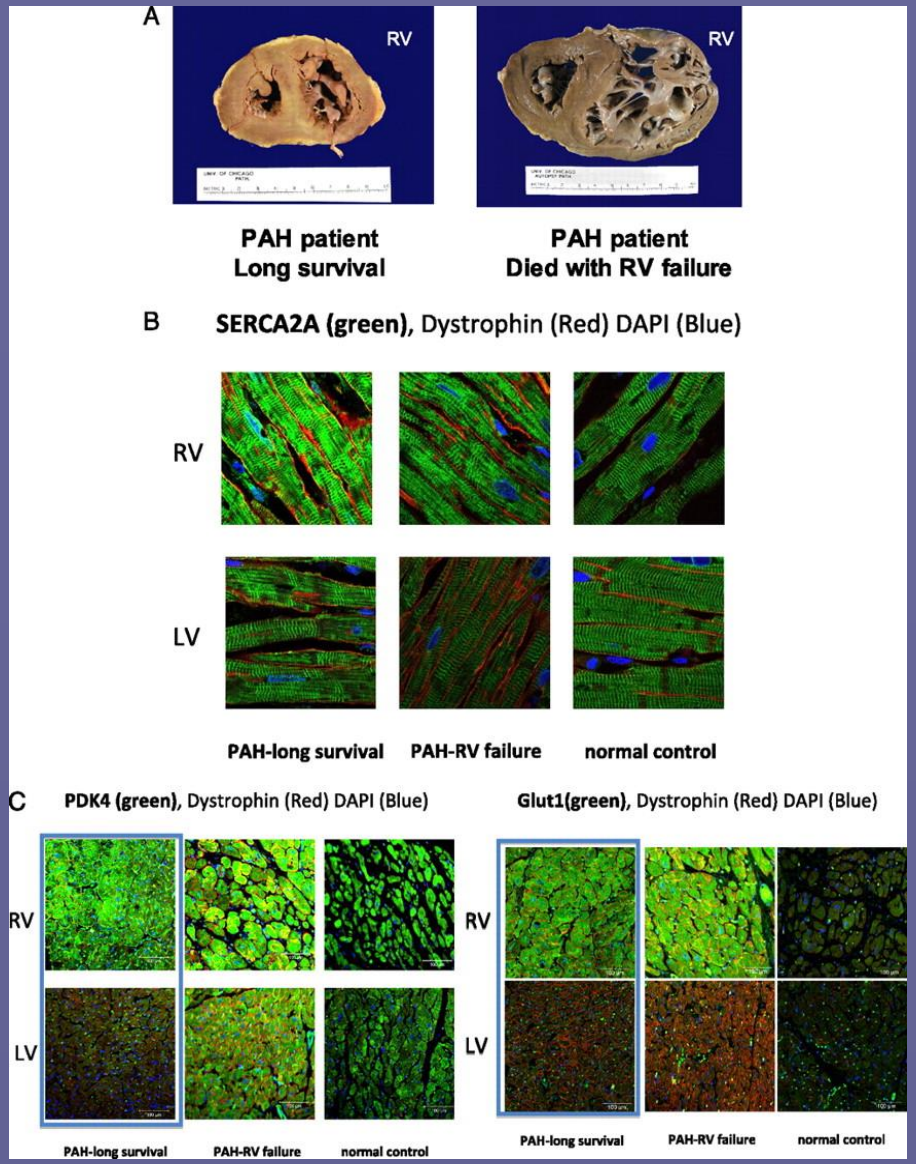


Figure 1 Pathophysiology of RV Dysfunction in PAH

Increased right ventricular (RV) wall stress, neurohormonal activation, inflammation, and altered bioenergetics contribute to RV remodeling in pulmonary arterial hypertension (PAH). Adaptive remodeling is associated with minimally altered ventriculoarterial coupling. Progressive RV dilation with maladaptive remodeling further contributes to RV stress. Adapted, with permission, from Champion et al. (5), Benza et al. (8), and Rudski et al. (99).



CHEST
The Cardiopulmonary and Critical Care Journal

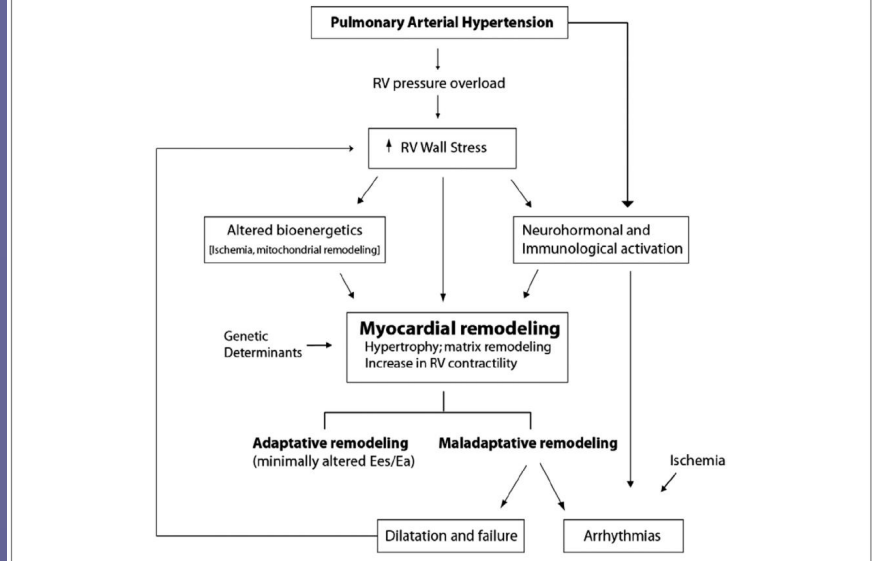
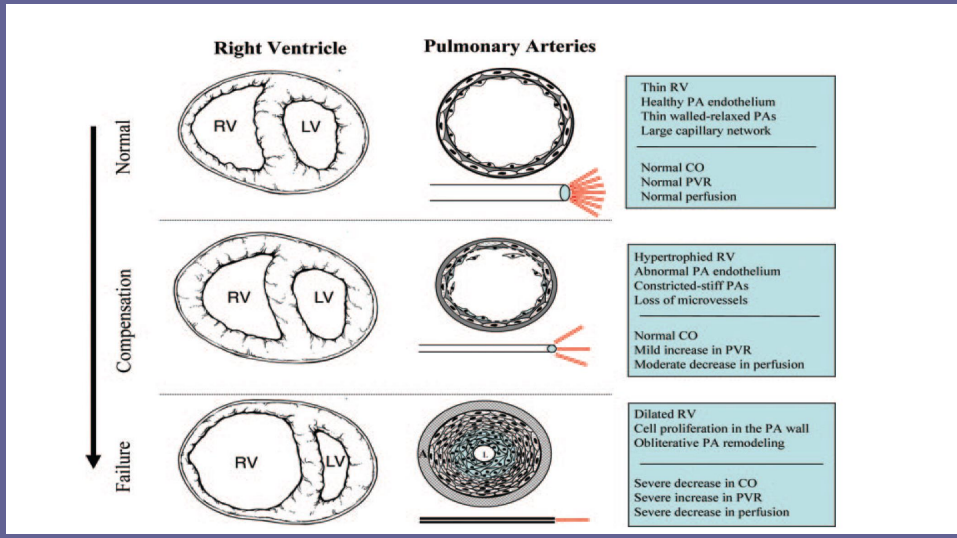
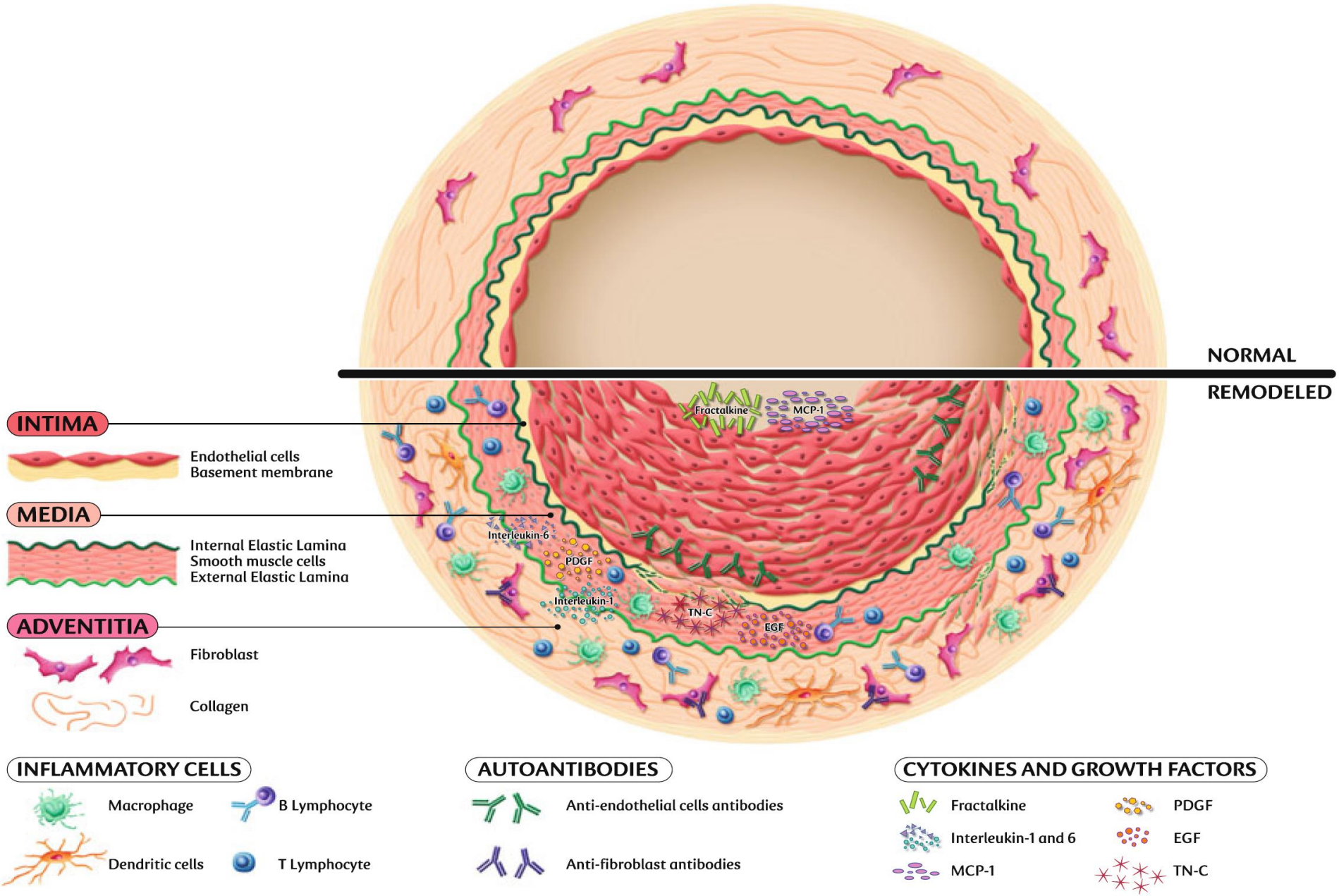


Figure 1 Pathophysiology of RV Dysfunction in PAH

Increased right ventricular (RV) wall stress, neurohormonal activation, inflammation, and altered bioenergetics contribute to RV remodeling in pulmonary arterial hypertension (PAH). Adaptive remodeling is associated with minimally altered ventriculoarterial coupling. Progressive RV dilation with maladaptive remodeling further contributes to RV stress. Adapted, with permission, from Champion et al. (5), Benza et al. (8), and Rudski et al. (99).



Circulation 2009;120:992-1007



Kherbeck et al *Clin Rev Allergy Immunol* 2011

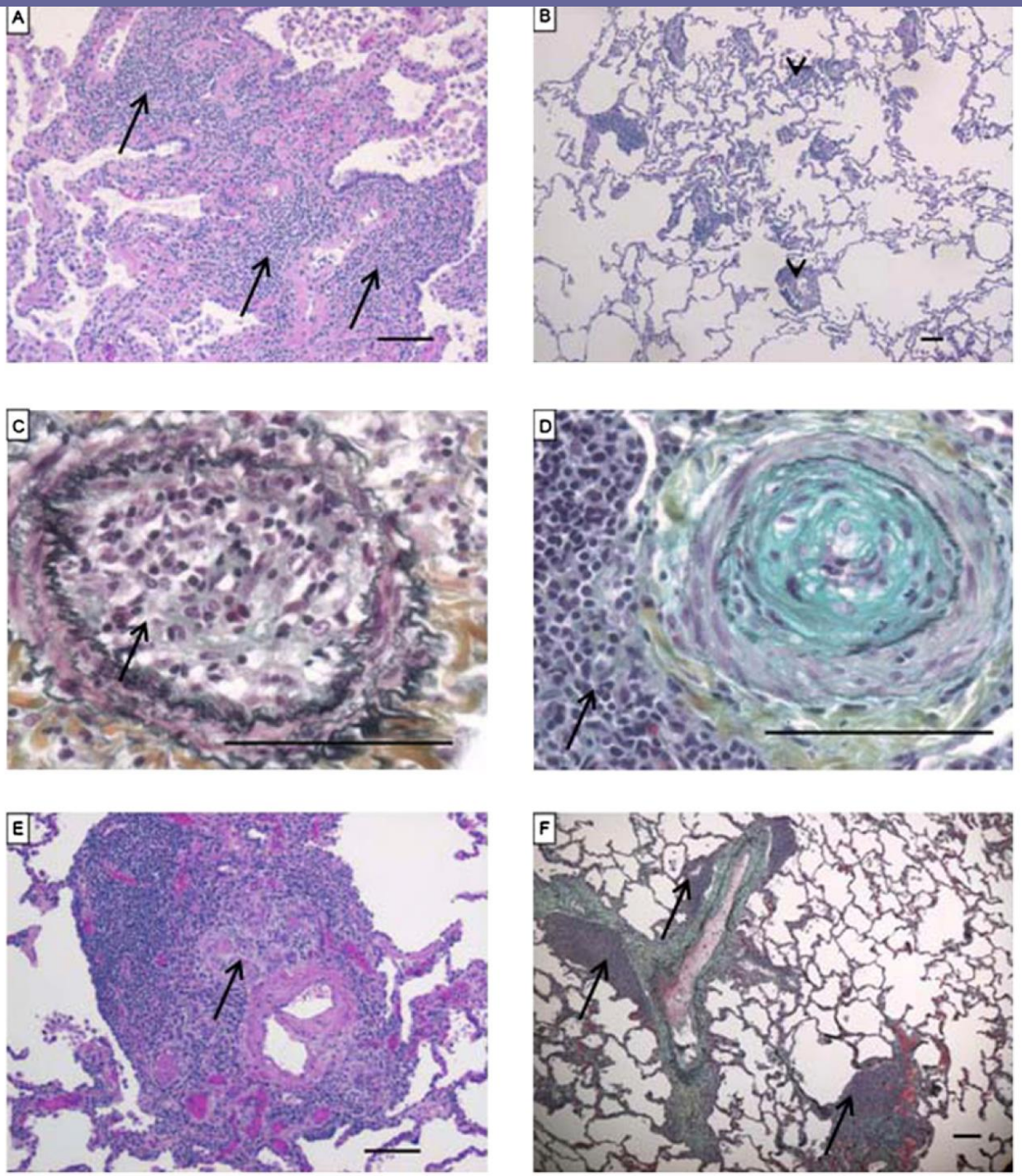


Figure 11. Examples of inflammation in pulmonary arterial hypertension (PAH) lungs. (*A*) Diffuse pronounced interstitial inflammation (*arrows*) (hematoxylin and eosin [H&E]). (*B*) Localized moderate perivascular inflammation (*arrowheads*) (H&E). (*C*) Occluded artery with dense inflammatory infiltrate (*arrow*) (Russel-Movat pentachrome stain). (*D*) Artery with concentric intima proliferation, neighbored by a dense inflammatory infiltrate (*arrow*) (Russel-Movat pentachrome stain). (*E*) Artery with plexiform lesion (*arrow*), embedded in inflammatory infiltrate (H&E). (*F*) Arteries focally cuffed by dense inflammation (*arrows*) (Russel-Movat pentachrome stain). Scale bars = 100 μm.

CLINICAL CLASSIFICATION OF PH

1. Pulmonary Arterial Hypertension

1.1 Idiopathic PAH
1.2 PAH with vasoreactivity (Table 1)
1.3 Heritable PAH (Table 2)
1.4 Drugs and toxins induced (Table 3)
1.5 Associated with:
- 1.5.1 Connective tissue disease
- 1.5.2 HIV infection
- 1.5.3 Portal hypertension
- 1.5.4 Congenital heart disease (Table 4)
- 1.5.5 Schistosomiasis

1.6 PAH with overt signs of venous/capillaries (PVOD/PCH) involvement (Table 5)
1.7 Persistent PH of the Newborn syndrome (Table P1)

2. PH due to left heart disease

2.1 PH due to heart failure with preserved E.F
2.2 PH due to heart failure with reduced E.F
2.3 Valvular heart disease
2.4 Congenital post-capillary obstructive lesions (Table P2)

3. PH due to lung diseases and/or hypoxia (Table 6)

3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders (Table P3)

4. PH due to pulmonary artery obstruction

4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions (Table 7)

5. PH with unclear mechanisms (Table 8)

5.1 Haematologic disorders
5.2 Systemic disorders
5.3 Others
5.4 Complex congenital heart disease (Table P4)

Vasodilator responsiveness in idiopathic pulmonary arterial hypertension: identifying a distinct phenotype with distinct physiology and distinct prognosis

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Abstract

Within the cohort of patients suffering from idiopathic pulmonary arterial hypertension (IPAH) is a group that responds dramatically (VR-PAH) to an acute vasodilator challenge and that has excellent long-term hemodynamic improvement and prognosis on high dose calcium channel blockers compared with vasodilator non-responders (VN-PAH). For the purposes of diagnosing VR-PAH, there is to date no test to replace the acute vasodilator challenge. However, recent studies have identified markers that may aid in the identification of VR-PAH, including peripheral blood lymphocyte RNA expression levels of desmogelin-2 and Ras homolog gene family member Q, and plasma levels of provirus integration site for Moloney murine leukemia virus. Genome wide-array studies of peripheral blood DNA have demonstrated differences in disease specific genetic variants between VR-PAH and NR-PAH, with particular convergence on cytoskeletal function pathways and Wnt signaling pathways. These studies offer hope for future non-invasive identification of VR-PAH, and insights into pathogenesis that may lead to novel therapies. Examination of the degree of pulmonary microvascular perfusion in PAH has offered additional insights. During the acute vasodilator challenge, VR-PAH patients demonstrate true vasodilation with recruitment and increased perfusion of the capillary bed, while VN-PAH patients are unable to recruit vasculature. In the very few reports of lung histology, VR-PAH has more medial thickening in the precapillary arterioles, while VN-PAH has the classic histology of PAH, including intimal thickening. VR-PAH is a disorder with a phenotype distinct from VN-PAH and other types of PAH, and should be considered separately in the classification of PAH.

Pulmonary Circulation 2017; 7(3) 1–10

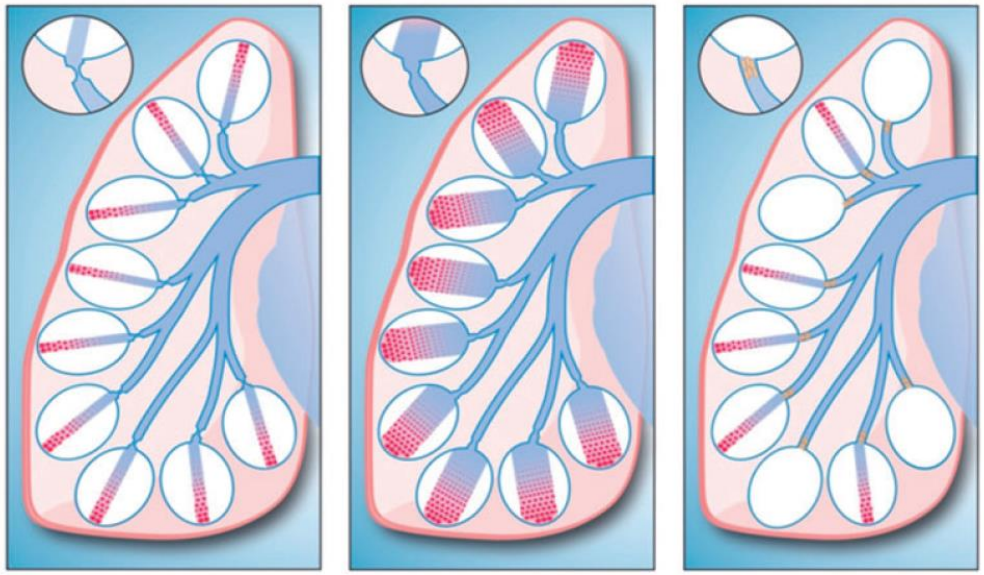

Fig. 8. Schematic (not anatomic, nor positional) illustrations of pulmonary capillary perfusion in VR-PAH and VN-PAH. The ovals represent only a potential amount of capillary perfusion and do not represent acini. The blue vessels represent pulmonary arteries feeding into the capillaries. Pulmonary venous drainage is not shown. Left: VR-PAH, prior to vasodilation. Precapillary constriction increases PVR and reduces capillary perfusion diffusely; center: VR-PAH, during successful vasodilation. A marked increase in capillary perfusion occurs; right: VN-PAH. The pre-capillary arterioles have intraluminal cellular obstruction that greatly reduces or eliminates capillary perfusion. Any increased pulmonary blood flow during the acute vasodilator challenge is accommodated via distention of perfused capillaries, and not via recruitment.

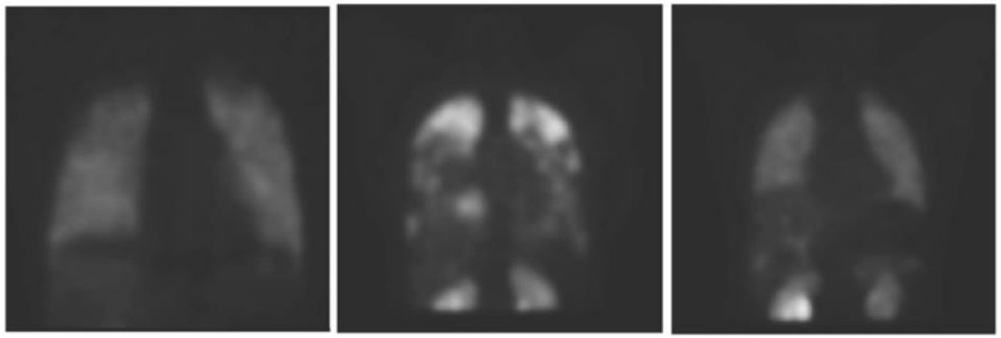

Fig. 9. Radionuclide lung scans, using a molecule that binds to the endothelial adrenomedullin receptor, 99mTc-PulmoBind. Left: normal human; center: NR-PAH; right: VR-PAH on high dose calcium blocker therapy. Note the normal pattern of perfusion in VR-PAH as opposed to NR-PAH. Reproduced with permission from Harel et al.[77]

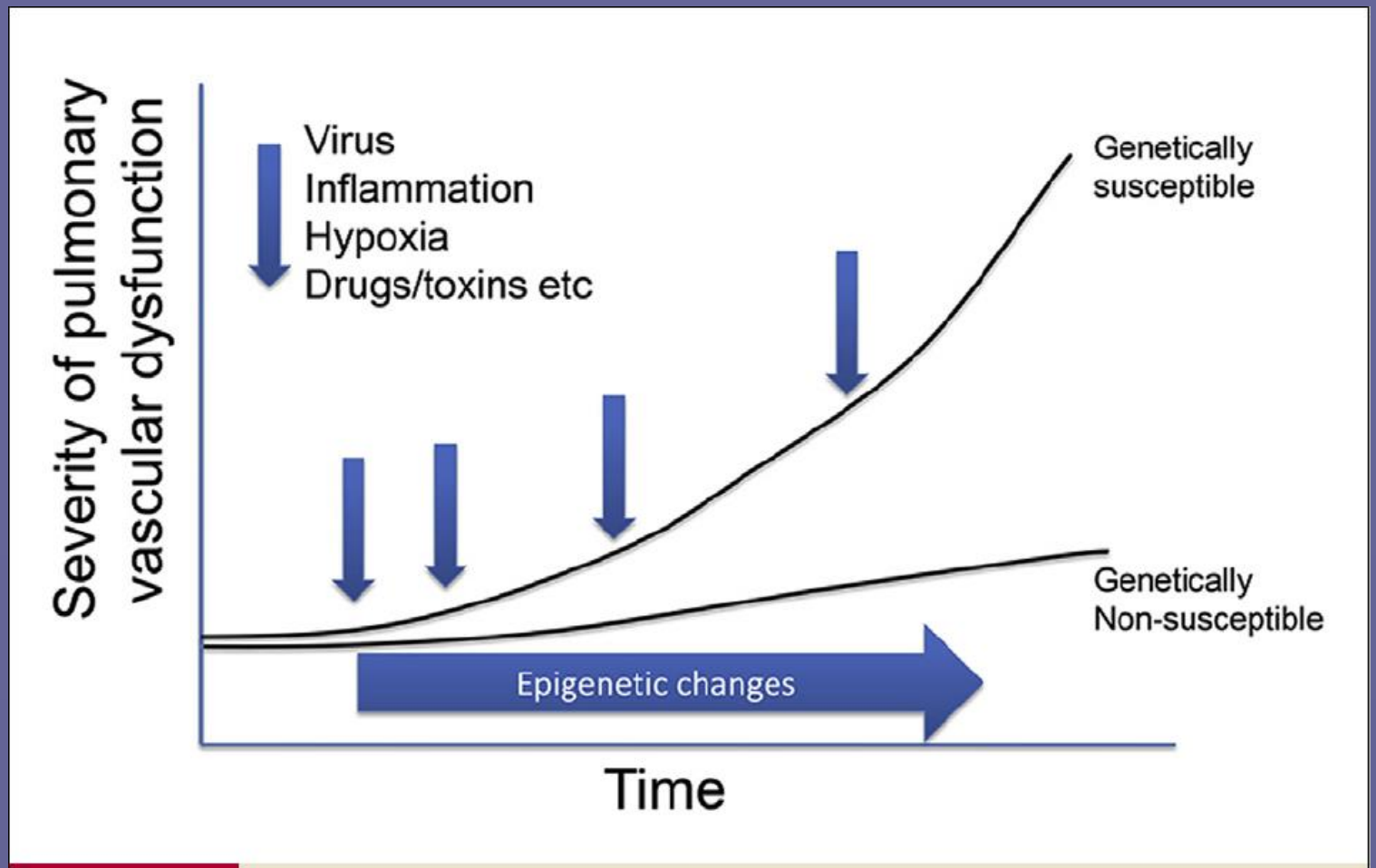

Figure 1 **Proposed Multifactorial Factors Influencing Progression of Pulmonary Hypertension**

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WHY IS THIS PLANT STILL BEING WATERED?

IT'S EASY TO JUST FOLLOW THE INSTRUCTIONS, BUT TREATING TOO LONG WITHOUT RECOGNIZING FAILURE IS DANGEROUS

- **IRREPLACEABLE TIME IS LOST BEFORE SWITCHING THERAPIES**
- **NEED EXPERIENCED FOLLOWUP**
- ***…και Καλή Συνεργασία με Εξειδικευμένα Κέντρα !!!***

- ***Ευχαριστώ για την υπομονή σας***