Pulmonary vascular remodelling: causes, mechanisms and consequences

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Definition Remodeling

outward (positive) remodeling

inward (negative) remodeling

Structural changes of the vascular wall characterized by intimal, medial and adventitial thickening in response to hypoxia, inflammation, hemodynamic changes or vascular diseases
Remodeling affects all vascular layers

Endothelium

Media (smooth muscle cells)

Adventitia (connective tissue)
Pulmonary vascular diseases

Latent PH:
- COPD
- Fibrosis
- Left heart failure
- Aging

Manifest PH
- CTD

Severe PH
Clinical Classification of Pulmonary Hypertension (Dana Point)

1. PAH
   - Idiopathic PAH
   - Heritable
   - Drug- and toxin-induced
   - Persistent PH of newborn
   - Associated with:
     - CTD
     - HIV infection
     - portal hypertension
     - CHD
     - schistosomiasis
     - chronic hemolytic anemia

1’. PVOD and/or PCH

2. PH Owing to Left Heart Disease
   - Systolic dysfunction
   - Diastolic dysfunction
   - Valvular disease

3. PH Owing to Lung Diseases and/or Hypoxia
   - COPD
   - ILD
   - Other pulmonary diseases with mixed restrictive and obstructive pattern
   - Sleep-disordered breathing
   - Alveolar hypoventilation disorders
   - Chronic exposure to high altitude
   - Developmental abnormalities

4. CTEPH

5. PH With Unclear Multifactorial Mechanisms
   - Hematologic disorders
   - Systemic disorders
   - Metabolic disorders
   - Others

Causes of pulmonary vascular remodeling

Schermuly et al; Nat Rev Cardiol 2011
**Changes in Paradigm**

Vasoconstriction $\rightarrow$ *Hyperproliferative Disease*

“Fixed Pulmonary Hypertension“$\rightarrow$ *Reverse Remodeling*

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- Healthy Resistance Vessel
- Chronic “Remodeling“
  - Loss of Patency
- Reverse Remodeling
Remodeling: (pseudo)malignant disease?

- Proliferation
- Apoptosis
- Metabolism
- Inflammation
Effects of Imatinib on proliferation and apoptosis

PCNA-staining

in situ TUNEL assay

Schermuly et al., J Clin Invest, 2005
Pulmonary Vascular Remodeling: consequences

I  Preclinical / No symptoms
II  Symptomatic / Stable
III  Progression / declining

Adaptive hypertrophy  maladaptive hypertrophy

Pulm pressure  Cardiac output  RV function

Therapeutic window

Years  Months

Time

Level
Outcome studies of right ventricular function in cardiovascular diseases

Heart Failure

PE

PAH

Fig. 1 Selected outcomes studies of right ventricular function in cardiovascular disease. a Results of a recent study [4–•] demonstrating the predictive value of right ventricular function in a modern series of patients with chronic heart failure; b predictive value of right ventricular dysfunction in the ICO/PER study of acute pulmonary embolism [6]; c and d predictive of hemodynamic and echocardiographic indices of RV dysfunction in patients with pulmonary arterial hypertension [5••, 7]. RVEF—right ventricular ejection fraction; TAPSE—tricuspid annular plane excursion. (Data from Meyer et al. [4–•], Forfia et al. [5••], Goldhaber et al. [6], and D’Alonzo et al. [7].)
Hypothetical molecular and cellular mechanisms involved in the development of right-heart failure in pulmonary hypertension

Bogaard et al., CHEST 2009
Model of RV Hypertrophy: Pulmonary Artery Banding (PAB)
Pulmonary Artery Banding (PAB)

Material: titanium

Ø ~ 0.4 mm
MRI-Imaging
Short-axis view of a healthy mouse heart and its 3D reconstruction
Mouse Heart: Before and 5 Weeks after PAB

Before surgery

5 weeks after PAB
Summary

- Pulmonary vascular remodeling involves intima, media, and adventitia.
- Causes: PAH (unknown, genetics, drugs, collagen vascular disease, HIV, schistosomiasis), left heart failure, hypoxia, pulmonary thrombosis, ....
- Mechanisms: Vasoconstriction, proliferation/apoptosis, migration, metabolism, and inflammation.
- Consequences: Right heart failure.
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