Νεότερα Δεδομένα στη Διάγνωση της Πνευμονικής Αρτηριακής Υπέρτασης

Ι. Μητρούσκα
Δ. Πατριανάκος
Δ. Γεωργόπουλος

Διακλινικό Ιατρείο Πνευμονικής Υπέρτασης
Πανεπιστημιακό Νοσοκομείο Κρήτης (ΠΑΓΝΗ)
Disclosure

- Actelion
- Bayer
- MSD
- GSK
- Elpen
- Menarini
- Boehringer
- Astra-Zeneca
Current
State-of-the-art Diagnostic algorithm

1. Outside the PH expert center
   - Assess probability of PH
   - Identify high-risk patients
   - Diagnose common causes of PH

2. Focusing on the diagnosis of PH
   - Diagnose rare causes of PH

Proceedings of 6TH World Symposium for Pulmonary hypertension
Frost A; ERJ 2019
Clinical suspicion of PH

Symptoms
Symptoms of PH are non-specific: exertional dyspnoea, fatigue, weakness, chest pain, light-headedness/syncope and, less frequently, cough. Progressive right-sided heart failure (oedema, ascites, abdominal distension) occurs in later or more accelerated disease. Rarely, haemoptysis, Ortner’s syndrome/hoarseness (unilateral vocal chord paralysis) and arrhythmias may characterise PH.

Physical findings
Physical findings include augmented second heart sound (P2 component), right ventricular lift, jugular venous distension, hepatojugular reflux, ascites, hepatomegaly and/or splenomegaly, oedema, tricuspid regurgitant or pulmonary regurgitant murmurs, and S3 gallop.

Diseases associated with PH can be suggested by history and physical exam.
Symptoms (IPAH)

Διερεύνηση δύσπνοιας

Lung parenchyma
Time from symptoms to definitive diagnosis of idiopathic pulmonary arterial hypertension: The delay study.

WHO Functional Class at symptom onset and at definitive diagnosis.

At symptom onset:
WHO FC II = 95% of pts
WHO FC III = 5%

At diagnosis:
FC II = 0%
FC III = 94%
FC IV = 6%

UK/Ireland registry
PAH
85% FC=III and IV
Ling Y AJRCCM 2012

French Registry
75% SSc pts
FN III-IV at diagnosis
Launay d 2013

Dyspnoea

Chest X-ray

ECG

Spirometry

Sources of error

Parameters of lung function:

- FVC: Forced Vital Capacity (sensfon)
- FEV1: Forced Expiratory Volume in 1 second (sensfon)
- VC: Vital Capacity (sensfon)
- FEV1/VC: The part of the vital capacity (%) that is expired during the first second of the expiration

Flow-Volume curve

Normal, Man, 26 years, 187cm

Asthma, Man, 27 years, 196cm

Do we know enough for diagnosis and management?
Established diagnostic tools
Electrocardiography

Blood tests and immunology

Pulmonary function tests and arterial blood gases

Cardiopulmonary exercise testing

Transthoracic echocardiography

Ventilation/perfusion lung scanning

Chest computed tomography

Practice recommendations (including high-risk population screening recommendations)
Patients with congenital heart disease (CHD), CTD, HIV and portopulmonary hypertension (POPH) are at increased risk for PH. As little or no progress has been made in earlier diagnosis, this Task Force recommends more aggressive assessment and screening of some of these high-risk populations.
Διαγνωστική προσέγγιση
ΗΚΓ πνευμονικής αρτηριακής υπέρτασης

- RAD,
- -T, V₁-V₄
- R/S > 1 V₁
- rSR V₁
- qR V₁
- P > 2.5mm II III aVF

Ευαισθησία: 55% Ειδικότητα: 70%

Athearn G. Chest 2002; 122: 524

Όταν υπάρχουν
Κακή πρόγνωση
Εργαστηριακός έλεγχος αιματολογικός: Μη διαγνωστικός

• Ανοσολογικός
  – Antinuclear, anti-DNA (ΣΕΛ)
  – Anti-Scl-70, antinuclear (σκληρόδερμα)
  – Anticentromere (CREST syndrome)
  – RF (ρευματοειδής αρθρίτις)
  – Anti-Ro, anti-La (Sjogren’s synd)
  – Anti-Jo-1 (δερματομυοσίτις/πολυμυοσίτις)
  – Anti-U1 RNP (συνδετικού ιστού)

• Νατριουρετικό πεπτίδιο (BNP – NT-proBNP)
  – Σχετίζεται με δυσλειτουργία Δεξιάς κοιλίας (PVR = overload)
Established diagnostic tools
Electrocardiography

Blood tests and immunology

Pulmonary function tests and arterial blood gases

Cardiopulmonary exercise testing

Transthoracic echocardiography

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Practice recommendations (including high-risk population screening recommendations)
Patients with congenital heart disease (CHD), CTD, HIV and portopulmonary hypertension (POPH) are at increased risk for PH. As little or no progress has been made in earlier diagnosis, this Task Force recommends more aggressive assessment and screening of some of these high-risk populations.
<table>
<thead>
<tr>
<th>Table</th>
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Time: 10:36:48
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Date: 19/10/16
Time: 09:52:00

Patient data
Identification:
First Name:
Last Name:
Date of Birth:

FAV in

Act
Pred
TLC ITGV RV

5 10 15 20 25 30 35 40 45 50
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<th>Act1</th>
<th>%R1/P</th>
<th>Act2</th>
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<td>RV/TL-C-He [%]</td>
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<td>TICO/HO [mmol/min/kPa/L]</td>
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<td>84.8</td>
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<tr>
<td>FE He [%]</td>
<td></td>
<td>9.30</td>
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<tr>
<td>ER He [%]</td>
<td></td>
<td>4.96</td>
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<td>ER CO [%]</td>
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<td>0.27</td>
<td></td>
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<td>ER CO [%]</td>
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<td>Tr [%]</td>
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<td>ERV [L]</td>
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<td>EBC+TLC-He [%]</td>
<td>54.70</td>
<td>46.64</td>
<td>85.3</td>
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<td>Hb [g/100ml]</td>
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<td>13.90</td>
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<td>TICOc SB [mmol/min/kPa]</td>
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<td>2.30</td>
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<td>TICOc/VA [mmol/min/kPa/L]</td>
<td>1.61</td>
<td>0.90</td>
<td>56.1</td>
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</table>

VA/TL-C >90%
Vin/Vmax >93%
PFTs in PAH

Cardiopulmonary exercise testing

Useful for determining the nature of exercise limitation in patient with unexplained dyspnoea

Screening tool for asymptomatic subjects at risk for developing PAH

- Peak Oxygen uptake (VO2 max) (lower)
- VE/Vco2 (higher)
- PETco2
At diagnosis Abnormal in 90% of IPAH pts No correlation with the degree of PH

Chest radiograph in PAH

Normal

PAH with evidence of cardiomegaly and enlarged pulmonary arteries

NB. A normal chest x-ray does not exclude PAH
CT SCAN

Enlarged main PA on CT

Standard view

Coronal view
For the detection of PH
Sensitivity = 70%
Specificity = 92%
Vascular changes

Highest PA/Ao in

1. PAH-CHD – Eisenmenger
2. IPAH

PAH  The pulmonary artery (PA) aorta ratio was obtained by measuring the widest transverse diameter of the PA (blue) and the corresponding transverse diameter of aorta (red).
PAH

PE
‘mosaic’
lung attenuation
CTPA

CT Chest (PA/A Diameter). CT of chest shows underlying ILD and enlarged pulmonary artery (PA) with PA:aorta ratio>1 (aorta: blue line, PA: red line).

Pulmonary Hypertension in Diffuse Parenchymal Lung Diseases
Oksana A. Shlobin MD1, A. Whitney Brown MD1, Steven D. Nathan MD1

- High-resolution CT (HRCT) scanning of the chest has a role in the evaluation of pulmonary HTN in patients with suspected diffuse lung disease, eg (COPD, interstitial lung disease).

- Axial contrast-enhanced CT image obtained with lung window settings shows severe emphysema with loss of lung parenchyma, contributors to pulmonary hypertension.
Enlarged pulmonary artery

Lobular nodular opacities with ground-glass halos

Mildly enlarged lymph node
Pulmonary veno-occlusive disease


Eur Resp J 2009
Algorithm for the diagnosis of Pulmonary hypertension And its causes (triage of urgent cases and diagnosis of common conditions)

Assess probability of PH

Identify high-risk patients

Diagnose common causes of PH

Diagnose rare causes of PH
Algorithm for the diagnosis of Pulmonary hypertension And its causes (triage of urgent cases and diagnosis of common conditions)

1. History, symptoms, signs and/or laboratory tests suggestive of PH
2. Echocardiographic probability of PH
   - Low
   - High or intermediate
     - Consider V/Q scan to screen for CTEPH
6. Consider left heart disease (assess pre-test probability) and lung disease
   - No clinically significant left heart disease or lung disease
   - Refer to PH expert centre
Echocardiographic signs suggesting pulmonary hypertension

<table>
<thead>
<tr>
<th>A: The ventricles</th>
<th>B: Pulmonary artery</th>
<th>C: Inferior vena cava and right atrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle/left ventricle basal diameter ratio &gt; 1.0</td>
<td>Right ventricular outflow Doppler acceleration time &lt; 105 ms and/or mid-systolic notching</td>
<td>Inferior cava diameter &gt; 21 mm with decreased inspiratory collapse (&lt;50% with a sniff or &lt;20% with quiet inspiration)</td>
</tr>
<tr>
<td>Flattening of the interventricular septum (left ventricular eccentricity index &gt; 1.1 in systole and/or diastole)</td>
<td>Early diastolic pulmonary regurgitation velocity &gt; 2.2 m·s⁻¹</td>
<td>Right atrial area (end-systole) &gt; 18 cm²</td>
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</tbody>
</table>

Pulmonary artery diameter > 25 mm
**Echocardiographic probability of pulmonary hypertension (PH) in symptomatic patients with a suspicion of PH**

<table>
<thead>
<tr>
<th>Peak tricuspid regurgitation velocity m·s⁻¹</th>
<th>Presence of other echocardiographic &quot;PH signs&quot;#</th>
<th>Echocardiographic probability of PH</th>
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<tr>
<td>≤2.8 or not measurable</td>
<td>No</td>
<td>Low</td>
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<tr>
<td>≤2.8 or not measurable 2.9-3.4</td>
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<td>Intermediate</td>
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<td>2.9-3.4</td>
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<td>2.9-3.4</td>
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<td>&gt;3.4</td>
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Diagnosis of pulmonary hypertension

More than 70% presented in WHO functional class III or IV

No abnormal shadow in chest roentgenogram or out-of-proportion PH compared with abnormalities in pulmonary function test and/or chest roentgenogram

Ventilation/perfusion scan

- Ventilation
- Perfusion
- Ventilation
- Perfusion
- Ventilation
- Perfusion

Normal or Mottled pattern
- PAH

At least one segmental perfusion defects inconsistent with ventilation scan findings
- CTEPH or other pulmonary vascular diseases

Perfusion defects consistent with ventilation defects
- PH due to lung diseases and/or hypoxemia
Diagnosis of pulmonary hypertension

CTEPH diagnostic algorithm

Any mismatched perfusion defect

Review or perform V/Q scan

Normal perfusion

Multimodality diagnostic assessment

RHC for PH diagnosis and haemodynamic characterisation

PH confirmed

Review by multidisciplinary PH team

PH classified

Appropriate treatment

Monitor and reassess

PH classification not certain

Consider trial of treatment

CTEPH not confirmed

Consider other causes

PH not confirmed

CTEPH confirmed

Management at PH expert centre
Fall in mPAP > 10 mmHg
+ mPAP < 40 mmHg
+ Normal CO

Close monitoring of long-term clinical and hemodynamic effects

ACCP Guidelines. Chest 2004;126:1S-92S.
## Recommendations for Vasoreactivity testing

**ERS/ESC 2015**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
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<td>Vasoreactivity testing is indicated only in expert centres</td>
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<td>Vasoreactivity testing is recommended in patients with IPAH, HPAH and PAH associated with drugs use to detect patients who can be treated with high doses of a CCB</td>
<td>I</td>
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<tr>
<td>A positive response to vasoreactivity testing is defined as a reduction of mean PAP ( \geq 10 ) mmHg to reach an absolute value of mean PAP ( \leq 40 ) mmHg with an increased or unchanged cardiac output</td>
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<tr>
<td>Nitric oxide is recommended for performing vasoreactivity testing</td>
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<tr>
<td>Intravenous epoprostenol is recommended for performing vasoreactivity testing as an alternative</td>
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<tr>
<td>Adenosine should be considered for performing vasoreactivity testing as an alternative</td>
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<tr>
<td>Inhaled iloprost may be considered for performing vasoreactivity testing as an alternative</td>
<td>IIb</td>
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<tr>
<td>The use of oral or intravenous CCBs in acute vasoreactivity testing is not recommended</td>
<td>III</td>
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<tr>
<td>Vasoreactivity testing to detect patients who can be safely treated with high doses of a CCB is not recommended in patients with PAH other than IPAH, HPAH and PAH associated with drugs use and is not recommended in PH groups 2, 3, 4 and 5</td>
<td>III</td>
</tr>
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</table>
Updated clinical classification Of Pulmonary Hypertension

1 PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH (table 3)
1.4 PAH associated with:
   1.4.1 Connective tissue disease
   1.4.2 HIV infection
   1.4.3 Portal hypertension
   1.4.4 Congenital heart disease
   1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers (table 4)
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
1.7 Persistent PH of the newborn syndrome

Acute pulmonary vasoreactivity for patients with idiopathic, hereditable or drug-induced PAH

Reduction of mPAP ≥10 mmHg to reach an absolute value of mPAP ≤40 mmHg
Increased or unchanged cardiac output

Long-term response to CCBs

New York Heart Association Functional Class I/II
With sustained haemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only
Updated clinical classification of Pulmonary Hypertension

1 PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH (table 3)
1.4 PAH associated with:
   1.4.1 Connective tissue disease
   1.4.2 HIV infection
   1.4.3 Portal hypertension
   1.4.4 Congenital heart disease
   1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers (table 4)
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
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

4 PH due to pulmonary artery obstructions (table 6)
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms (table 7)
5.1 Haematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease
Pulmonary arterial hypertension: baseline characteristics (*REVEAL Registry*)

Practice recommendations (including high-risk population screening recommendations)

Patients with congenital heart disease (CHD), CTD, HIV and portopulmonary hypertension (POPH) are at increased risk for PH. As little or no progress has been made in earlier diagnosis, this Task Force recommends more aggressive assessment and screening of some of these high-risk populations.
### Significant predictors of mortality at time of diagnosis with pulmonary arterial hypertension

<table>
<thead>
<tr>
<th>PAH Subgroup</th>
<th>5-y Survival (%)</th>
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</thead>
<tbody>
<tr>
<td>APAH–congenital heart disease</td>
<td>74.4</td>
</tr>
<tr>
<td>APAH–drugs and toxins</td>
<td>73.5</td>
</tr>
<tr>
<td>IPAH</td>
<td>64.3</td>
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<tr>
<td>APAH–HIV</td>
<td>63.8</td>
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<tr>
<td>HPAH</td>
<td>60.1</td>
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<tr>
<td>APAH–connective tissue disease</td>
<td>43.7</td>
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<tr>
<td>APAH–portal hypertension</td>
<td>39.4</td>
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</table>

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Hazard Ratio for Death</th>
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</thead>
<tbody>
<tr>
<td>Group 1 PAH subgroup</td>
<td></td>
</tr>
<tr>
<td>APAH–portal hypertension</td>
<td>3.60</td>
</tr>
<tr>
<td>HPAH</td>
<td>2.17</td>
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<tr>
<td>APAH–connective tissue disease</td>
<td>1.59</td>
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<tr>
<td>Demographics and comorbidities</td>
<td></td>
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<tr>
<td>Men &gt;60 y in age</td>
<td>2.18</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1.90</td>
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<tr>
<td>WHO functional class</td>
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</tr>
<tr>
<td>IV</td>
<td>3.13</td>
</tr>
<tr>
<td>III</td>
<td>1.41</td>
</tr>
<tr>
<td>I</td>
<td>0.42</td>
</tr>
</tbody>
</table>

| Vitals                            |                        |
| Systolic blood pressure <110 mm Hg| 1.67                   |
| Heart rate > 92 beats/min         | 1.39                   |
| 6-min walk distance               |                        |
| <165 m                            | 1.68                   |
| >440 m                            | 0.58                   |
| Brain natriuretic peptide level   |                        |
| >180 pg/mL                        | 1.97                   |
| <50 pg/mL                         | 0.50                   |
| Echocardiographic findings        |                        |
| Pericardial effusion              | 1.35                   |
| DLCO                              |                        |
| % predicted DLCO ≤32              | 1.46                   |
| % predicted DLCO >80              | 0.59                   |
| Hemodynamics                      |                        |
| PVR >32 Wood units                | 4.08                   |
| Right atrial pressure >20 mm Hg   | 1.79                   |
Heritable PAH

mutations 16.9% in sporadic and 89% in familial

• Genetic counseling of all idiopathic, anorexiant and familial PAH pts and first-generations asymptomatic family members of patients with known genetic mutations

• Subsequent evaluations for PAH should be offered (e.g. CPET and TTE) in mutation positive individuals
  – Annual echocardiography

• National databases for genotyping all PAH patients should be advocated by the WSPH
Scleroderma (systemic sclerosis) and scleroderma spectrum

- Patients with SSc and SSC spectrum
  - Uncorrected DLCO > 80%

- Patients with SSc and SSC spectrum
  - Uncorrected DLCO < 80%
  - Screening tools
    - DETECT
      - Step 1 (telangiectasia, EKG, Anti-centrome, Nt-proBNP, urate ets)
      - Step 2 (TRV, RA area)
    - ESC/ERS recommend for TTE or FVC/DlCO ratio > 1.6 (no interstitial disease) and >2fold upper limit of normal NT-proBNP
PAH in HIV patients

- Higher-risk features
  - Female sex
  - IV drug use/cocaine use
  - Hepatitis C virus infection
  - Origin from high-prevalence country
  - Known Nef (negative regulatory factor) or Tat HIV proteins and
  - US African-American patients independent of symptoms

Screen for PAH in HIV pts with symptoms
Or
> one risk factor for HIV-PAH
Νεότερες διαγνωστικές δυνατότητες

- V/Q single photon emission (CT SPECT)
- Dual-energy CT pulmonary perfusion (DECT)
- Three-dimensional dynamic contrast-enhanced magnetic resonance lung perfusion
- Functional magnetic resonance imaging ventilation
- Subclinical right ventricular dysfunction
  - Parametric mapping
- Right ventricle strain
- Pulmonary artery four-dimensional flow imaging
- Intravascular ultrasound and optical coherence tomography in PAH
- Future Biomarkers
  - Dimethylarginine/cystatin C
  - Exhaled gases (NO, derivatives)
CLUES TO THE DIAGNOSIS
- PA diameter
- PA/Ao diameter ratio
- RV size
- Interventricular septal flattening

ETIOLOGY
- Parenchymal lung disease
- Congenital heart disease
- PE

PATHOPHYSIOLOGY
- 4D PA flow characteristics
- PA wall shear stress
- PA stiffness measures

CONSEQUENCES
- Abnormal RV mechanics
- RV failure: contrast reflux into IVC
- RV fibrosis
Relationship between PH on exercise and resting PAH