CONUNDRUMS IN PULMONARY ARTERIAL HYPERTENSION

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POINTS FOR DISCUSSION

• What is the pathogenetic mechanism of PAH?
• Importance of RV function
• New therapies in the near future
• Monotherapy versus combination therapy
  • Role of Warfarin anticoagulation
  • Therapeutic targets in PAH
• Does PAH therapy reduce mortality?
• Management of the critically ill patient
• Role of ECLS and lung transplantation
• How do we make PAH treatment more widely available?
PATHOBIOLGY OF PAH

- BMPR2 MUTATION
SIMILARITY BETWEEN PAH AND CANCER

a) Hallmarks of cancer:
- Sustaining proliferative signalling
- Evading growth suppressors
- Activating invasion and metastasis
- Deregulating cellular energetics
- Resisting cell death
- Inducing angiogenesis
- Genome instability and mutation
- Enabling replicative immortality

b) Degree of similarity with cancer:

Pathogenic genes and genome instability:
- Enabling replicative immortality
- Genome instability and mutation

Intrinsic proliferative potential and cellular accumulation:
- Sustaining proliferative signalling
- Resisting cell death
- Evading growth suppressors
- Deregulating cellular energetics

Inflammation and dysimmunity:
- Tumour promoting inflammation
- Avoiding immune destruction
- Activating invasion and metastasis

Impaired angiogenesis and vasoreactivity:
- Inducing angiogenesis
- Impaired vasoreactivity

The diagram illustrates the similarities between PAH (Pulmonary Arterial Hypertension) and cancer by highlighting the common hallmarks and mechanisms involved in both conditions.
NEW POTENTIAL TARGETS FOR PAH THERAPY

Pathogenic mediators and pathways
- Vasoactive factors
- Ca²⁺ signalling
- Inflammatory mediators
- Growth factors
- BMPR2 mutations
- Metabolic dysfunction

Vasoconstriction
- Vascular tone
- Proliferation
- Vasoconstriction

Vascular remodelling
- Inflammatory cell recruitment
- Resistance to apoptosis
- Growth
- Proliferation

Vascular regeneration
- PDK PDH
- HDAC inhibitor
- NF-κB inhibitors
- Apelin blockers of BMP
- PDK inhibitor

Pathogenic outcome
- Vascular tone
- Proliferation
- Growth
- Prostaglandin
- NO
- Prostacyclin

Treatments
- Adrenomedullin
- eNOS couplers
- Thromboxane A2
- Serotonin
- Angiotensin II
- Fractalkine
- RANTES
- MCP-1
- IL-1β
- IL-6
- PDGF
- EGF
- FGF
- VEGF
- BMPR2
- Apelin
- Rho kinase inhibitors
- Elastase inhibitors
- HDAC1 inhibitors
- Kinase inhibitors
- NF-κB inhibitors
- Prostaglandin
- NO
- PDK inhibitors
- Metabolic dysfunction
- PDK PDH
- HDAC1 inhibitor
- Kinase inhibitors
- NF-κB inhibitors
- Elastase inhibitors
- PDK inhibitors
- Mesenchymal stem cells
- Progenitor stem cells

No.16a, gefitinib, erlotinib, lapatinib
- (chloroacetic acid)
- PPARα agonists
- (NO, FA, insulin)
- (NO, FA, insulin)
- (NO, FA, insulin)
- (NO, FA, insulin)
VASODILATOR IMBALANCE IN PAH
VASODILATOR IMBALANCE IN PAH

Bosentan
Macitentan
Ambrisentan
VASODILATOR IMBALANCE IN PAH

Bosentan
Macitentan
Ambrisentan

IV, inhaled or subcutaneous prostacyclin analogues
Selexipag (oral)
VASODILATOR IMBALANCE IN PAH

- Bosentan
- Macitentan
- Ambrisentan

Inhaled NO
- PDE5 inhibitors
  - Sildenafil
  - Vardenafil
  - Riociguat

IV, inhaled or subcutaneous prostacyclin analogues
- Selexipag (oral)
APPROACH TO TREATMENT IN PAH

- **Anticoagulate ± Diuretics ± Oxygen ± Digoxin**

  - **Positive**
    - **Acute Vasoreactivity Testing**

  - **Negative**
    - **DECISION TREE**
      - Oral CCB
        - **Sustained Response**
          - **Yes**
            - **Continue CCB**
          - **No**
            - **Anticoagulate ± Diuretics ± Oxygen ± Digoxin**

**DETERMINANTS OF RISK**

- **LOWER RISK**
  - No
  - Gradual
  - WHO class II, III
  - Longer (>400 m)
  - Peak VO₂ >10.4 mL/kg/min
  - Minimal RV dysfunction
  - RAP <10 mm Hg; CI >2.5 L/min/m²
  - Minimally elevated

- **HIGHER RISK**
  - Clinical evidence of RV failure
  - Progression of symptoms
  - WHO class IV
  - 6MWD
  - CPET
  - Echocardiography
  - Hemodynamics
  - BNP
  - Pericardial effusion, significant RV enlargement/dysfunction; RA enlargement
  - RAP >20 mm Hg; CI <2.0 L/min/m²
  - Significantly elevated

**WHO class**

- **Class I**
- **Class II**
- **Class III**
- **Class IV**

**6MWD**

- **Longer (>400 m)**
- **Shorter (<300 m)**

**Peak VO₂**

- **>10.4 mL/kg/min**
- **<10.4 mL/kg/min**

**RAP**

- **<10 mm Hg**
- **>20 mm Hg**

**CI**

- **>2.5 L/min/m²**
- **<2.0 L/min/m²**
ACC/AHA CONSENSUS PAH TREATMENT ALGORITHM

Anticoagulate ± Diuretics ± Oxygen ± Digoxin

Acute Vasoreactivity Testing

Positive

Oral CCB

Sustained Response

Lower Risk

ERAs or PDE-5 Is (oral)
Epoprostenol or Treprostinil (IV)
Iloprost (inhaled)
Treprostinil (SC, inhaled)

Reassess: consider combo-therapy

Investigational Protocols

No

Yes

Continue CCB

Negative

Higher Risk

Epoprostenol or Treprostinil (IV)
Iloprost (inhaled)
ERAs or PDE-5 Is (oral)
Treprostinil (SC)

Atrial septostomy
Lung transplant

Anticoagulate ± Diuretics ± Oxygen ± Digoxin ± Diuretics ± Oxygen ± Digoxin
• Combination therapy is the cornerstone of therapy of many other serious illnesses including cancer, HIV, hypertension and heart failure

• Combination therapy
  • Upfront?
  • Rapid sequential?
• 500 patients with PAH
• Randomised to Ambrisentan + Tadanafil vs monotherapy with Ambrisentan or Tadanafil
• Primary endpoint defined as a composite of death, hospitalisation for worsening PAH, disease progression or unsatisfactory long term clinical response
INITIAL USE OF AMBRISENTAN AND TADANAFIL IN PAH - AMBITION TRIAL
Galie et al; NEJM;2015:834-44
• Double blind placebo controlled trial
• 1156 patients randomised to Selexipag or placebo
• 3 year follow up
• Primary endpoint also clinical failure ie composite of death and hospital admission for worsening symptoms
• 47% on background monotherapy with either ERB or PDE5 inhibitor and 33% on dual therapy
SELEXIPAG FOR THE TREATMENT OF PAH-GRIPHON TRIAL
Sitbon et al, NEJM;2015;373:2522-33

HR 0.6
P < 0.001
• 742 patients with FC 2-3 symptoms randomised to Macitentan or placebo
• 66% on background therapy with PDE5 inhibitor
• Primary endpoint clinical failure
MACITENTAN AND MORBIDITY AND MORTALITY IN PAH SERAPHIN TRIAL
Pulido et al, NEJM 2013;369:889-18

HR 0.55
P<0.001
RECOMMENDATIONS

Management of pulmonary hypertension

M R Essop, N Galie, D B Badesch, U Laloo, A G Mahomed, D P Naidoo, M Ntsekhe, P G Williams

Consequently, the Committee unanimously resolved to: (i) increase awareness of PAH, promoting education and research and establishing databases and registries; (ii) provisionally adopt the European Guidelines for PAH\textsuperscript{[1]} as a working document for SA while making amendments pertinent to the practice of medicine in this country; (iii) engage with funders to provide essential therapies to patients with PAH; (iv) inform the Medicines Control Council of the need to expedite approval of essential therapies and encourage suppliers of such therapies to provide these at an optimal cost given SA’s financial constraints; and (v) serve as arbitrator when there are conflicting views on how a patient with PAH should be managed best.
The Joint SA Heart/SATS Working Group Committee concluded that local medical expertise should remain current and not lag behind other developing nations. While PAH remains an uncommon disease, it affects mainly younger people and has a prognosis worse than those of most malignancies, and therefore merits treatment. Although treatment is expensive, it is probably in proportion to that of other diseases with a poor prognosis. The prognosis of PAH is steadily improving as a result of advances in medical therapy, and SA patients should have access to these. In this regard, there is an urgent need for introduction and registration of at least one drug from each of the four major therapeutic classes.
Progression of PAH

Asymptomatic (I)

Moderate symptoms (II-III)

Severe symptoms (IV)

Cardiac output at peak exercise

Pulmonary pressure

Cardiac output at rest

Level

Time

Adapted from Rich S. Prog Cardiovasc Dis 1998; 31:205-38.
IMPAIRED HOMEOSTASIS CAUSED BY BMPRII MUTATION
Pathogenesis of PAH

RISK FACTORS AND ASSOCIATED CONDITIONS
- CTD
- CHD
- Portal hypertension
- HIV
- Drugs and toxins
- Pregnancy

SUSCEPTIBILITY
- BMPR2 mutation
- Other genetic factors

VASCULAR INJURY
- Endothelial dysfunction
- ↓ NO synthase
- ↓ PGI₂ production
- ↑ Thromboxane production
- ↑ ET-1 production

DISEASE PROGRESSION

Normal
Reversible disease
Irreversible disease

CHD = congenital heart disease; CTD = connective tissue disease; ET-1 = endothelin-1; HIV = human immunodeficiency disease; NO = nitric oxide; PAH = pulmonary arterial hypertension; PGI₂ = prostacyclin
Adapted from Gaine S. JAMA 2000;284:3160–8.
Pulmonary hypertension diagnostic approach

I. PH suspicion
- Symptoms & physical examination
- Screening procedures
- Incidental findings

II. PH detection
- ECG
- Chest radiography
- TT echocardiography

III. PH class identification
- Pulmonary function tests & ABG
- Ventilation / perfusion lung scan
- High resolution CT
- Spiral CT
- Pulmonary angiography

IV. PH evaluation: Type
- Blood tests & immunology
- HIV test
- Abdominal ultrasound scan

V. Severity Assessment
- 6-minute walk test, peak VO₂
- RHC + vasoreactivity, biomarkers

ESC and ACCP Guidelines
Suspected Pulmonary Hypertension

Echocardiogram

- Left heart disease
- Valvular/Congenital Heart Disease

Chest X-Ray

- Emphysema
- Fibrosis
- Thoracic abnl

PFT's

Autoantibody tests

- Scleroderma
- SLE
- RA
- Vasculitis

Ventilation-Perfusion scan, angiography

- HIV test

LFTs and clinical evidence of cirrhosis and portal htn

Sleep Study

- Sleep disorder

Chronic Thromboembolism

- Scleroderma
- SLE
- RA
- Vasculitis

HIV infection

Portopulmonary Hypertension

Diagnosis of Pulmonary Hypertension Required When Clinically Indicated
### Prevalence of PAH in Associated Conditions

**4th World Symposium on PH (2008)**

<table>
<thead>
<tr>
<th>Associated Condition</th>
<th>Prevalence of PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic sclerosis</td>
<td>7-12 %</td>
</tr>
<tr>
<td>HIV infection</td>
<td>0.46-0.5 %</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>2-6 %</td>
</tr>
<tr>
<td><strong>Congenital heart disease</strong></td>
<td>1.6-12.5 per million in those with congenital systemic-</td>
</tr>
<tr>
<td></td>
<td>to-pulmonary shunts → 25-50 % affected by Eisenmenger</td>
</tr>
<tr>
<td></td>
<td>syndrome</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>4.6 % in those with hepatosplenic disease</td>
</tr>
<tr>
<td>Chronic hemolytic anemia</td>
<td>Highly variable; currently being studied</td>
</tr>
</tbody>
</table>

FBK – 22 year old female

- Progressive fatigue and dyspnea
- Several episodes of syncope
- ITP on treatment several years – Platelets 20
- One pregnancy 2 years earlier - ? Uncomplicated
- Negative ANF and normal CTPA
- Severe PHT – PASP 9040/60mmHg
- PDE 5 inhibitor + steroids
2 months later...

Chest pain
+ D-Dimer
CTPA +
APLA ++
ENA ++

SLE + APAH

Improvement with Clexane +
Azothiaprine
UTILITY OF ECHOCARDIOGRAPHY FOR PULMONARY HYPERTENSION

• Quantification of pulmonary artery pressure
• Defining the etiology for PH
• Evaluation of impact on RV size and function
• Monitoring response to pharmacologic or interventional procedure
CAUSES FOR PULMONARY HYPERTENSION IDENTIFIED BY ECHOCARDIOGRAPHY

Conditions That Predispose to Pulmonary Hypertension

- Congenital or acquired valvular disease (MR, MS, AS, prosthetic valve dysfunction)
- Left ventricular systolic dysfunction
- Impaired left ventricular diastolic function (hypertensive heart disease, HCM, Fabry’s disease, infiltrative cardiomyopathies)
- Other obstructive lesions (coarctation, supravalvular AS, subaortic membrane, cor triatriatum)
- Congenital disease with shunt (ASD, VSD, coronary fistula, patent ductus arteriosus, anomalous pulmonary venous return)
- Pulmonary embolus (thrombus in IVC, right-sided cardiac chamber, or PA; tricuspid or pulmonic valve vegetation)
- Pulmonary vein thrombosis/stenosis

Findings That Suggest Specific Disease Entity

- Left-sided valve changes (SLE, anorexigen use)
- Intra-pulmonary shunts (hereditary hemorrhagic telangiectasia)
- Pericardial effusion (IPAH, SLE, systemic sclerosis)
CALCULATION OF PULMONARY ARTERY SYSTOLIC PRESSURE

\[ \Delta P_{RV-RA} = 4(\text{TR-jet})^2 \]

\[ \text{PAP} = \Delta P_{RV-RA} + \text{RAP} \]
DOPPLER ECHOCARDIOGRAPHY
## ESTIMATION OF RIGHT ATRIAL PRESSURE

<table>
<thead>
<tr>
<th>RAP (mmHg)</th>
<th>IVC DIAMETER (mm)</th>
<th>IVC COLLAPSE (%)</th>
<th>HEPATIC VEIN DILATATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>&lt; 10</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>5-10</td>
<td>10-15</td>
<td>&gt; 50</td>
<td>-</td>
</tr>
<tr>
<td>10-15</td>
<td>15-20</td>
<td>&lt; 50</td>
<td>-</td>
</tr>
<tr>
<td>15-20</td>
<td>&gt; 20</td>
<td>&lt; 50</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>&gt; 20</td>
<td>&lt; 50 (or sniff neg)</td>
<td>+</td>
</tr>
</tbody>
</table>
DOPPLER ECHOCARDIOGRAPHY
IMPACT OF PULMONARY HYPERTENSION ON RV
PRESSURE OVERLOAD OF THE RV
RIGHT VENTRICULAR DILATATION

- RV:LV area
- Normal  < 0.6
- Mild 0.6-1
- Severe  > 1
RIGHT VENTRICULAR HYPERTROPHY

• FREE WALL THICKNESS
  • Normal  < 2-5mm
  • RVH  > 5mm
SYSTOLIC APICAL MOTION OF THE TRICUSPID ANNULUS
RIGHT VENTRICULAR FUNCTION

• Systolic apical displacement of the tricuspid annulus
  • Normal RV function > 20mm
  • Mild RV dysfunction 10-20mm
  • Severe RV dysfunction < 10mm
OTHER WAYS TO ASSESS PULMONARY HYPERTENSION

• Time to peak PA velocity: <80msec = PH, > 110msec = normal PA pressure
• Mid-systolic closure of PV on M-Mode
• Mid-systolic notch in PA velocity
• In the presence of a VSD, PA systolic pressure can be estimated as: SBP – Doppler pressure gradient across VSD
Echocardiography in PAH

• Sensitivity and Specificity for PAH greatest when cut-off value for RVSP estimate used is >45 mm Hg
• Modest changes in RVSP may not accurately reflect true hemodynamic changes over time
• Survival does not correlate with PA pressure
• Other echo parameters correlate with survival

1 Arcasoy et al: AJRCCM 2003; 167: 735
2 McLaughlin et al: Circulation 2002;106:1477
3 Raymond et al: JACC 2002;39:1214
ECHO Predictors of Outcome

Right Atrial Size
- RA size < median
- RA size > median

Pericardial Effusion
- No effusion
- Effusion

LV-Eccentricity Index
- EI < median
- EI > median

Years
Survival (%)
- 0
- 20
- 40
- 60
- 80
- 100

Freedom from Composite Endpoint (%)
- 0
- 20
- 40
- 60
- 80
- 100

TAPSE and Mortality in the PAH Patient

A. Overall cohort

- TAPSE ≥ 1.8 cm
- TAPSE < 1.8 cm

Log rank $\chi^2$ 10.0

$P$-value = 0.002

B. PAH only

- TAPSE ≥ 1.8 cm
- TAPSE < 1.8 cm

Log rank $\chi^2$ 6.8

$P$-value = 0.009

Forfia et al. 2006.
Influence of 6 Minute Walk on Survival in PPH

Sitbon et al, JACC 2002: 40: 780-788
Right heart catheterization (RHC)

Definite confirmation of PAH diagnosis
Assessment of the severity of haemodynamic impairment
Testing of the vasoreactivity of the pulmonary circulation
Hemodynamics — NIH Registry

Mean Pulmonary Artery Pressure (mm Hg)

- Normal Range

Cardiac Index (L/Min/M²)

- Normal Range

Right Atrial Pressure (mm Hg)

- Normal Range

Pulmonary Vascular Resistance Index (L/Min/M²)

- Normal Range
Acute vasodilator testing
Definition of "true responder"

Reduction of mean PAP ≥ 10 mmHg
To reach mean PAP ≤ 40 mmHg
With an increased or unchanged cardiac output
DRUGS FOR VASO-REACTIVITY TESTING

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Half-life</th>
<th>Dose range$^a$</th>
<th>Increments$^b$</th>
<th>Duration$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol</td>
<td>Intravenous</td>
<td>3 min</td>
<td>2–12 ng/kg/min</td>
<td>2 ng/kg/min</td>
<td>10 min</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Intravenous</td>
<td>5–10 s</td>
<td>50–350 μg/kg/min</td>
<td>50 μg/kg/min</td>
<td>2 min</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Inhaled</td>
<td>15–30 s</td>
<td>10–20 p.p.m</td>
<td>–</td>
<td>5 min$^d$</td>
</tr>
</tbody>
</table>

$^a$Initial dose and maximal tolerated dose suggested (maximal dose limited by side effects such as hypotension, headache, flushing, etc.).

$^b$Increments of dose by each step.

$^c$Duration of administration on each step.

$^d$For NO, a single step within the dose range is suggested.
# PAH Determinants of Patient Risk

**ACC/AHA Expert Consensus**

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Determinants of Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Gradual</td>
<td>Disease progression</td>
<td>Rapid</td>
</tr>
<tr>
<td>II, III</td>
<td>WHO functional class</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt; 400 meters)</td>
<td>6-MWD</td>
<td>Shorter (&lt; 300 meters)</td>
</tr>
<tr>
<td>Peak VO₂ &gt; 10.4 mL/kg/min</td>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO₂ &lt; 10.4 mL/kg/min</td>
</tr>
<tr>
<td>Minimally elevated and stable</td>
<td>BNP/NT-proBNP</td>
<td>Significantly elevated</td>
</tr>
<tr>
<td>PaCO₂ &gt; 34 mm Hg</td>
<td>Blood gasses</td>
<td>PaCO₂ &lt; 32 mm Hg</td>
</tr>
<tr>
<td>Minimal RV dysfunction</td>
<td>ECHO findings</td>
<td>Pericardial effusion, RV dysfunction, RA enlargement</td>
</tr>
<tr>
<td>RAP &lt; 10 mm Hg; CI &gt; 2.5 L/min/m²</td>
<td>Hemodynamics</td>
<td>RAP &gt; 20 mm Hg; CI &lt; 2 L/min/m²</td>
</tr>
</tbody>
</table>

THE FUTURE

• Resign trials in PAH
• Identify molecular and genetic markers of PAH
• Identify patients earlier
• Refer patients to specialised centers
• Promote awareness
• Enhance access to proven therapies