Chronic Thromboembolic Disease

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Improving People's Lives Through Innovations in Personalized Health Care
Disclosure

Research: Actelion, Bayer, Gilead, UT, IKARIA

Consultant: Gilead, Bayer, UT
Pulmonary Circulation

- Originates from the RV
- Low Pressure, low resistance circuit
- Thin-walled vessels
- High compliance
- Receives entire CO from RV
- Accommodates wide range of CO without increase in PVR
Pulmonary vasculature

- Normal pressures mean 15mmHg (25/8)

- Pulmonary hypertension Mean > 25mmHg
Pulmonary Hypertension
Diagnostic classification
5th World Symposium on PAH – Nice, 2013

<table>
<thead>
<tr>
<th>1. Pulmonary arterial hypertension</th>
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<tbody>
<tr>
<td>• Idiopathic PAH</td>
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<td>• Familial PAH</td>
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<tr>
<td>• Related to:</td>
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<tr>
<td>- Connective tissue diseases</td>
</tr>
<tr>
<td>- HIV</td>
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<tr>
<td>- Portal hypertension</td>
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<tr>
<td>- Anorexigens</td>
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<td>• PPHN</td>
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<td>• PAH with venule/cap inv (PVOD)</td>
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<tr>
<th>2. PH with left heart disease</th>
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<tr>
<td>2.1. Left Ventricular Systolic Dysfunction</td>
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<tr>
<td>2.2 Left Ventricular Diastolic Dysfunction</td>
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<tr>
<td>2.3 Valvular Disease</td>
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<td>2.4 Congenital/Aquired Left Heart inflow tract obstruction and congenital cardiomyopathies</td>
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<th>3. PH with Lung Diseases/Hypoxemia</th>
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<tr>
<td>• COPD</td>
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<tr>
<td>• Interstitial lung diseases</td>
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<tr>
<td>• Sleep-disordered breathing</td>
</tr>
<tr>
<td>• Developmental abnormalities</td>
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<th>4. PH due to chronic thrombotic and/or embolic disease</th>
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<tr>
<td>• TE obstruction of proximal PA</td>
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<td>• TE obstruction of distal PA</td>
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<tr>
<td>• Non thrombotic Pulm embolism</td>
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<th>5. Miscellaneous</th>
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Pulmonary hypertension

mean pulmonary artery pressure

> 25 mm Hg

Right Heart Dysfunction

Symptom Threshold

CO

PAP

PVR

Time
Case

- 24-year-old lady referred for evaluation PH
- Healthy until pregnant with her 3rd child
- Mild systemic hypertension during pregnancy
- Admitted respiratory failure, pneumonia
Case

- Severely enlarged right ventricle
- Septal deviation
- Normal LV function
- RVSP 55mmHg
- No pericardial effusion
Case

- Past medical None
- Social
  - Non smoker
- Treated with diuretics and antibiotics
- Referred here
Exam

- BP 112/70, HR 90/min/R-18 Sats 99%,
- HEENT unremarkable
- Cardiac:
  - Mildly Prominent P2
- Respiratory: CTA
- ABD: Benign
- Ext: no edema
Pulmonary Function Tests

- FVC - 80%
- FeV1 – 86%
- Fev1/FVC- 93%
- TLC – 82%
- DLCO- 62%
- 6 minute walk 457 meters
Case
Echocardiogram

- Normal left ventricular size and systolic function
  - EF 65%.
- Mildly dilated RV with normal right ventricular function.
- Moderate pulmonary hypertension; RVSP calculated at 55 mm Hg
Pulmonary Angiogram
Cardiac Catheterization

- mRA- 5mmHg
- RV 60/8
- PA 53/23 mean 31
- Pwedge 9
- CO 4.47L
- CI 2.65L
- PA sat 70%
Acute PE: Outcomes

Acute PE → Full Recovery

Shock, Death → Asymptomatic

Asymptomatic → Recurrent PE

Recurrent PE → CTEPH
Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Vascular disorder characterized by the obstruction of pulmonary arteries by organized thrombus /fibrotic material and vascular remodeling

Characterized by

- Elevated pulmonary artery pressures
  - At least one perfusion defect detected by lung scanning, CT angiography or Pulmonary angiography
  - After 3 months of adequate anticoagulation
Chronic Thromboembolic Pulmonary Hypertension (CTPH)

- Under-recognized
- Estimated incidence –0.5 to 4% patients with PE
- 250,000 hospitalizations per year
  - Incidence 3,000- 24,000 - new cases
- All patients with CTPH do not have history of PE/DVT
Registry

- Centers from Europe and Canada
- < 6 month of diagnosis
- 2007-2009

Pepke-Zaba et al Circulation 2011
Patient disposition.

Recruited
n = 679

→ 5 patients with no operability data (non-operated)

Operable
n = 427

Non-operable
n = 247

Non-operated
n = 54
7 died
37 refused surgery
10 waiting for surgery

Operated
n = 373

Operated*
n = 13

Non-operated
n = 234

Operated
n = 386 (56.8%)

Table 1. Patients’ Characteristics at Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=679)</th>
<th>Operable Patients* (n=427)</th>
<th>Nonoperable Patients* (n=247)</th>
<th>P (Exploratory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, % male</td>
<td>50.1</td>
<td>53.4</td>
<td>44.5</td>
<td>0.0308</td>
</tr>
<tr>
<td>Ethnicity, % white</td>
<td>95.9</td>
<td>95.3</td>
<td>96.7</td>
<td>0.4277</td>
</tr>
<tr>
<td>Age, y, median [Q1;Q3]</td>
<td>63 [51; 72]</td>
<td>61 [48; 70]</td>
<td>67 [57; 74]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, kg, median [Q1;Q3]</td>
<td>75 [65; 87]</td>
<td>76 [66; 88]</td>
<td>73 [63; 82]</td>
<td>0.0161</td>
</tr>
<tr>
<td>NYHA class, % I/II/III/IV</td>
<td>0.7/17.8/68.6/12.8</td>
<td>0.5/19.2/67.7/12.6</td>
<td>1.2/15.8/70.4/12.6</td>
<td>0.4922</td>
</tr>
<tr>
<td>6MWD, m, median [Q1; Q3] (n)</td>
<td>329 [245; 427] (589)</td>
<td>340 [250; 435] (373)</td>
<td>315 [223; 400] (214)</td>
<td>0.0219</td>
</tr>
<tr>
<td>Blood group non-0, % (n)</td>
<td>76.0 (366)</td>
<td>79.5 (249)</td>
<td>68.4 (117)</td>
<td>0.0255</td>
</tr>
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Pepke-Zaba
Risk Factors

- Which patients with PE will develop CTEPH?
Risk Factors

- Acute and recurrent PE
- Non provoked PE
- Large perfusion defects
- PA systolic > 50 mmHg
- Older patients

Pengo et al. NEJM 2004
Arch Bronchopulm 2010
Becattini Chest 2006
Ribeiro et al. Circulation 1999
Hematological Factors

- No association with
  - protein C or S deficiency
  - G20210 A mutation
  - Hyperhomocysteinemia

- Elevated level of Factor VIII
- Von Willibrant factor
- Antiphospholipid antibodies
- Expression of type 1 plasminogen activator inhibitor
Hematological Risk factors

- Abnormal Fibrinogen structure
  - Resistant to Fibrinolysis
  - Heterozygous fibrinogen Thr312A1a

- non-O blood group
  - 77% with CTEPH vs 58% PAH

- Elevated levels of lipoprotein
  - CTEPH vs PAH
Associated Medical Conditions

- Chronic Inflammatory Disease
  - 10% of patients with CTEPH
- Previous Cancer
- Splenectomy
  - 5.5% - 9% patients with CTEPH
- Abnormal erythrocytes
- Reactive Thrombocytosis
- Atrial-Venous Shunt
  - Clots on the catheter
  - Infection
  - brain thromboplastin in the cerebrospinal fluid (CSF)
  - increased levels of VEGF in the CSF
Chronic Thromboembolic Disease

- Infection and inflammation
- Immunity
- Genetics

VTE → Acute PE

Incomplete resolution and organisation of thrombus

Lack of thrombus angiogenesis

Development of fibrotic stenoses/occlusions

Adaptive vascular remodelling of resistance vessels

In situ thrombosis

Lang: Eur Resp Journal 2013
Diagnostic Evaluation

- No all PE leads to CTPEH
- Not all PH is related to clot
Diagnostic Approach

Echocardiogram

PFTs

Sleep study

Emphysema
ILD
Thoracic abnl

Sleep disorder

Autoantibody tests

Scleroderma
SLE
RA
Vasculitis

Ventilation-perfusion scan, Contrast CT, Angiography

HIV test

HIV

RVE, RAE, ↑RVSP
Left heart disease
VHD
CHD

LFTs and clinical evidence of cirrhosis and portal htn

Portopulmonary hypertension

Exam
CXR
ECG

PFTs

• Functional test
  • BNP
  • RH cath
  • Vasodilator test

Chronic thromboembolism

Pulmonary Angiogram
Right Heart Catheterization

- Invasive measurement of:
  - Right atrial Pressure
  - Right ventricular Pressures
  - PA Pressure
  - Pulmonary capillary wedge pressure
  - Mixed venous oxygen saturation
  - Cardiac output
  - Vasodilator challenge
Diagnosis of CTEPH

- Pulmonary hypertension
  - mPA pressure > 25
  - Pwedge < 15mmHg
- Evidence of Clot by
  - Abnormal V/Q scan
  - Pulmonary angiogram
  - CT angiogram
- At least 3 months of adequate anticoagulation
**Pulmonary Thromboendarterectomy**

- **Type 1** (30% cases)
  - Fresh thrombus in main or lobar pulm aa.
- **Type 2** (60% cases)
  - Intimal thickening and fibrosis +/- thrombus
  - Proximal to segmental arteries
- **Type 3** (10% cases)
  - Fibrosis, webbing and thickening +/- thrombus
  - Distal segmental and subsegmental arteries
- **Type 4** (inoperable)
  - Microscopic distal arteriolar vasculopathy without visible thromboembolic disease
  - Not classic CTPH


Chronic Thromboembolic Pulmonary Hypertension (CTPH)

- 5 year survival
  - 30% if mean PAP > 40 mm Hg
  - 10% if mean PAP > 50 mm Hg

- Mean survival 6.8 yrs in a japanese study of 48 patients
Pulmonary Thromboendarterectomy

**Indications**
- 1. Symptomatic patients
- 2. Hemodynamic or ventilatory impairment at rest or exercise
- 3. Location and extent most critical
  - For acceptable hemodynamic outcome

**Contraindications**
- 1. Only ABSOLUTE contraindication is severe underlying lung disease
- 2. advanced age, collateral disease
Thromboendarterectomy

- Potential to cure
- Specialized anesthesia with establishment of extracorporeal circulation with hypothermia
- Endarterectomy carried out with periods of circulatory arrests
Thromboendarterectomy

- Contraindications
  - Inaccessible thrombus
  - Co morbidities
    - Renal failure
    - Immunosuppression
    - LV dysfunction
    - Severe Lung disease
  - Very high PVR > 1500 dynes sec cm$^3$
Outcomes

- In house mortality 4-1.7%

Complications
- Atelectasis
- Pleural effusions
- Pericardial effusions
- Bleeding
- Reperfusion injury
- Residual PH
Outcome

- In hospital mortality related to number of cases done per year
  - Upto 7.4% when less than 10 cases
  - 3.4 % > 50 cases

UCSD:
Decreasing trend since 1990 to a 2.2 % event

10 % patients may have residual PAH
Mechanisms of Action of PAH-specific Therapies

1. Nitric oxide pathway
   - Preproendothelin → Proendothelin
   - Endothelial cells
   - Nitric oxide
   - L-arginine
   - Endothelin-1
   - vasoconstriction and antiproliferation
   - Endothelin-receptor A
   - Endothelin-receptor B

2. Endothelin pathway
   - Endothelin-receptor antagonists

3. Prostacyclin pathway
   - Arachidonic acid → Prostaglandin I₂
   - Prostacyclin derivates
   - cAMP
   - Vasodilation and antiproliferation

4. Phosphodiesterase type 5 inhibitor
5. Soluble guanylate cyclase stimulator
6. Phosphodiesterase type 5 inhibitor

Riociguat in CTEPH

Riociguat in CTEPH

Medical therapy

- BENEFiT: (Bosantan) No improvement in 6 minute walk
- Prostacyclins
- PDE5 inhibitors
Case : History

- 71y/o old man
- Admitted to the ICU with acute respiratory failure
- History of an ER visit 6 months prior 2 months after a long road trip
- Dx with PE
- Started on Coumadin
- Improved was back to work
- Now presented with acute dyspnea
Case

- PMH: Hypertension
- Prostate Cancer
- SH: 60 pack yr history tobacco Quit 1982, no alcohol or drugs.
- FH: Non –significant
Echocardiogram

- Left ventricular EF 45%
- The right ventricular chamber severely dilated and systolic function is severely reduced.
- Systolic flattening of interventricular septum consistent with pressure overload.
- A mobile elongated mass attached to the tricuspid valve leaflet possibly a thrombus, flailing in the RV
- Moderate TR
Pulmonary Function Tests

- FVC: 4.27 (106%)
- FEV1: 2.98 (103%)
- FEV1/FVC: 70%
- TLC: 8.04 (117%)
- RV: 3.56 (140%)
- DLCO: 18.54 (59%)
Cardiac Cath

Mean PA: 43
- Mean RA: 5
- Wedge: 12
- PA sat: 44
- PVR: 637
- CO (thermal) 4.27
- Positive Vasodilator challenge with Adenosine
- PVR 600dynes
Examination

- BP 97/78, HR 100/min oxygen Sat 94% on 15L
- HEENT unremarkable
- Cardiac:
  - Distended JVD
  - RRR
- Respiratory: CTA
- ABD: Benign
- Ext : minimal edema
CT Chest
Pulmonary hypertension

- Multifactorial
  - Advanced lung Disease
  - Possible LV dysfunction
  - Chronic clot

- Treatment of RVF
  - Supplemental oxygen
  - Optimize COPD
  - Anticoagulation
F/U

- Improved RV failure

- 6 minute walk 521m on RA

- Improved biventricular function on echo
- severe dilatation of RV
Case : History

- 46y/o old man
- Hx of recurrent PE
- Dyspnea of 3 yrs duration
- Has difficulty doing his job
- Episodes of presyncope
Case 1

- PMH: Hypertension
  - PE/DVT
  - Hereditary sperocytosis
- SH: 15 pack yr history tobacco alcohol or drugs.
- FH: Non–significant
Echocardiogram

- Left ventricular EF 65%
- The right ventricular chamber severely dilated and RV wall is thickened
- Systolic flattening of interventricular septum consistent with pressure overload.
- Moderate TR RVSP 75mmHg
Pulmonary Function Tests

- FVC: 4.84 (94%)
- FEV1: 3.81 (95%)
- FEV1/FVC: 79%
- TLC: 7.84 (113%)
- RV: 2.86 (145%)
- DLCO: 21.9 (70%)

- 6 minute walk 411m
Cardiac Cath

- mRA : 7mm Hg
- PA : 95/35/55
- Pwedge: 10
- CO/ CI 4.15 /2.0
- PVR: 11 woods unit / 880 dynes
Examination

- BP 138/96, HR 82/min oxygen Sat 95% on RA
- HEENT unremarkable
- Cardiac:
  - Distended JVD
  - RRR
- Respiratory: CTA
- ABD: Benign
- Ext : minimal edema
Pulmonary hypertension

- Chronic thromboembolism

- Treatment of RVF
- Supplemental oxygen
- Initiated on Riociguat

- 6 minute walk 545 meters
- Echo: NI LV function
- Severely dilated RV
Conclusion

- Management of CTEPH
- Systematic evaluation
- Pulmonary thromboendartectomy can be curative
- Multidisciplinary approach to assess operability
- Specialized post op management
- Close follow up to ensure resolution of RV dysfunction and PAH
- Medical therapy for those who have inoperable disease