Eisenmenger’s syndrome

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Disclosures

- Consultant
  Actelion, Bayer Schering, Novartis, GSK,
  Pfizer/encysive, Mondobiotech, iNOtherapeutics
- Speakers Bureau
  Actelion, Schering, iNO therapeutics, Encysive
- Grant Support
  Schering, Actelion

Venice 2003: Clinical classification of PH

Pulmonary arterial hypertension
- Idiopathic PAH
- Familial PAH
- Associated with:
  Connective tissue disease
  Congenital systemic-to-pulmonary shunt
  Portal hypertension
  HIV infection
  Drugs and toxins
  Other

PH with left heart disease
- Atrial or ventricular
- Valvular

PH with lung diseases/hypoxaemia
- COPD
- Interstitial lung disease
- Sleep-disordered breathing
- Developmental abnormalities

PH due to chronic thrombotic and/or embolic disease
- PE obstruction of proximal PA
- TE obstruction of distal PA
- Non-thrombotic PE

Miscellaneous
- Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)


Prevalence of PAH-CHD increases with age


Silde courtesy of Barbara Mulder.

n = 795 open ASD + VSD, p < 0.01

n = 274, p = 0.05

PAH-CHD (%)

Age (years)

0 5 10 15 20 25

VSD (n = 521, p < 0.01)

ASD II (n = 274, p = 0.05)


Slide courtesy of Barbara Mulder.
The demographic profile of CHD is changing

- Adults with CHD
- Children with CHD (90% of live births with CHD)
- 18 y.o. with CHD (80% of children with CHD)
- Live births with CHD (0.8% of live births)

2005: ca. 120,000 adults with CHD (in Germany); 2020: more adults than children

Left-to-right shunt: Evolution

- ASD, VSD or complex defect, ↑ Qp and/or PAP, with left-to-right shunting
- Over time, PVR ↑ resulting in bi-directional flow
- Resistance ↑ further with reversal of shunt: right-to-left → Eisenmenger syndrome → patient becomes ↑ cyanotic

Shear stress and circumferential stretch

- These hemodynamic forces are translated into biochemical signals
- Hemodynamic forces → reaction in vessels → messengers → cellular response

PAH emergence depends on type of CHD

<table>
<thead>
<tr>
<th>Defect</th>
<th>Developed Eisenmenger’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults w. CHD</td>
<td>8%</td>
</tr>
<tr>
<td>Adults w. LR shunt</td>
<td>11%</td>
</tr>
<tr>
<td>Large Tr.arterios.</td>
<td>~100%</td>
</tr>
<tr>
<td>Small VSD</td>
<td>3% (adults)</td>
</tr>
<tr>
<td>Large VSD</td>
<td>50%</td>
</tr>
<tr>
<td>Large PDA</td>
<td>50%</td>
</tr>
<tr>
<td>Large ASD</td>
<td>10% → Onset during adulthood 90%</td>
</tr>
</tbody>
</table>

Defect | PAP increased |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus venosus</td>
<td>26% → Onset at a younger age</td>
</tr>
<tr>
<td>Secundum ASD</td>
<td>9%</td>
</tr>
</tbody>
</table>

Genetic susceptibility?

<table>
<thead>
<tr>
<th>Normal</th>
<th>Permissive Genotype</th>
<th>PPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>Serotonin</td>
<td></td>
</tr>
<tr>
<td>NO+PGI2</td>
<td>ET-1+TXA2</td>
<td></td>
</tr>
<tr>
<td>Elastin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collagen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adventitia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMC Proliferation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elastase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMPs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Pulmonary hypertension

- Combination of three main factors:
  - Vasoconstriction
  - Vascular remodeling
  - Thrombosis

which explain the increase in PVR

BMPR2 in CHD:
6% (40 adults and 66 children)¹

<table>
<thead>
<tr>
<th>ADULTS</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Repaired</td>
<td>BMPR2</td>
</tr>
<tr>
<td>PDA</td>
<td>2 0</td>
</tr>
<tr>
<td>ASD</td>
<td>17 7</td>
</tr>
<tr>
<td>ASD/PAPVR</td>
<td>3 0</td>
</tr>
<tr>
<td>VSD</td>
<td>8  1</td>
</tr>
<tr>
<td>PAPVR</td>
<td>1  0</td>
</tr>
<tr>
<td>TGA</td>
<td>3  3</td>
</tr>
<tr>
<td>AVSD</td>
<td>4  1</td>
</tr>
<tr>
<td>RARE</td>
<td>2  0</td>
</tr>
<tr>
<td>Total</td>
<td>40 12</td>
</tr>
</tbody>
</table>

| Total Repaired| BMPR2          |
| PDA           | 6  3           |
| ASD           | 21 5           |
| ASD/PAPVR     | 0  1           |
| VSD           | 15 8           |
| PAPVR         | 3  2           |
| TGA           | 7  3           |
| AVSD          | 6  3           |
| RARE          | 8  5           |
| Total         | 66 29          |

• 8% fenfluramine²
• 26% IPAH
• 50% familial PAH


Therapeutic approach

- L-to-R shunt with high pulmonary blood flow and low PVR
  - SURGERY as lesion are thought reversible
- Bidirectional shunt with normal or slightly increased pulmonary blood flow and moderate increase in PVR
  - No surgery as high risk of no reversibility
- R-to-L shunt with decreased pulmonary blood flow and high PVR
  - No surgery as lesions thought irreversible
Eisenmenger syndrome: Management

- Not standardised
  - Targeted towards avoiding complications
    - Anticoagulation
    - Diuretics
    - Digoxin
    - Oxygen
    - Phlebotomy
    - Iron

- Calcium channel blockers (CCB)
- Other vasodilators
- “New therapies”
- Heart/lung-lung transplantation

Management

- PRIMUM NON NOCERE
  - Regular follow-up in experienced centers
  - Avoid unnecessary non-cardiac surgery or in expert center with trained anesthetist and cardiac staff
  - Contraception and avoid pregnancy
  - Avoid strenuous exercise
  - Maintain fluid balance, avoid dehydration
  - Annual immunization (influenza, pneumococcus)

- Keep the physiological balance
- Prevent complications
  - Endocarditis prophylaxis

Digoxin/ACE/CCB

- No study showing benefits of digoxin, role in arrhythmias?
- Calcium channel blockers (CCBs) are considered as potentially dangerous (systemic vasodilation) and empiric therapy should be avoided
- No study showing benefit of ACEi but may be considered for trials, CAVE vasodilation

Oxygen

- Controversial
- No real report of efficacy
  - Positive in children with CHD and PVD
    - (Bower et al BHJ 1986)
  - No effect of long-term nocturnal O₂ on natural history or physical capacity in Eisenmenger
    - (Sandoval ARJCCM 2001)
- Lung disease, desaturation
- Use indicated in specific cases
- 23% of 171 cases on O₂ for specific reasons
  - (Diller et al EHJ 2006)
- Tailored O₂ therapy
Anticoagulation

- Endothelial dysfunction, may improve with therapy
- Decreased fibrinolytic activity and release of procoagulant factors in PAH
- Substantial risk of thrombosis
  - Women and low O₂ sat at higher risk
  - Silversides et al. JACC 2003;42:1982
- Correlation with pulmonary blood flow velocity
  - Broberg et al. JACC 2007;634-42
- But hemoptysis
- How to anticoagulate
  - Antiplatelet, coumadin, other …
  - Ideal INR ??? May be 1.5 to 2

Phlebotomy

- Only in patients with symptoms of hyperviscosity
  - Headaches, fatigue, vision problems, dyspnea, paresthesia, hemoptysis, …
- Performed slowly with simultaneous volume replacement (air filters)
  - 250-500 ml in 45 min
- Microcytosis and iron deficiency should be treated immediately

New Therapies

PAH – CHD: Haemodynamic effects of acute and chronic iv epoprostenol

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Acute PG12</th>
<th>Chronic PG12 (1 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPm (mmHg)</td>
<td>77 ± 20</td>
<td>77 ± 20</td>
<td>61 ± 15</td>
</tr>
<tr>
<td>CI (l / min / m²)</td>
<td>3.5 ± 1.6</td>
<td>4.6 ± 2.4*</td>
<td>5.9 ± 2.7</td>
</tr>
<tr>
<td>PVRi (U · m²)</td>
<td>25 ± 13</td>
<td>21 ± 14</td>
<td>12 ± 7</td>
</tr>
<tr>
<td>MVsat (%)</td>
<td>64 ± 7</td>
<td>67 ± 9</td>
<td>70 ± 8</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>6 ± 5</td>
<td>6 ± 4</td>
<td>8 ± 4</td>
</tr>
</tbody>
</table>

*p < 0.01 chronic vs. baseline & chronic vs acute testing
†p < 0.01 chronic vs. baseline & p < 0.05 chronic vs acute testing
‡p < 0.01 chronic vs. baseline
n=16
mean ± SD

**Efficacy of bosentan in PAH-CHD patients**

<table>
<thead>
<tr>
<th>PAH sub-group</th>
<th>Parameters</th>
<th>Impact of bosentan</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH-CHD</td>
<td>6-MWD, NYHA class, haemodynamics</td>
<td>✓</td>
</tr>
<tr>
<td>Eisenmenger’s physiology (incl. BREATHE-5)</td>
<td>6-MWD, NYHA class, haemodynamics, Borg dyspnoea index</td>
<td>✓</td>
</tr>
<tr>
<td>Children (IPAH or PAH-CHD) (incl. BREATHE-3)</td>
<td>Long-term outcome, haemodynamics, NYHA class</td>
<td>✓</td>
</tr>
</tbody>
</table>

- No adverse effect on systemic O$_2$ saturation in EP patients
- Well tolerated

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**BREATHE-5: Reduced PVR and increased 6-MWD**

![Graph showing the reduction in PVR and increase in 6-MWD](image)

- T.E. = -472 dyn·s·cm$^{-5}$, $p<0.038$
- T.E. = 53.1 m, $p<0.008$

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**BREATHE-5 OLE: Bosentan increased exercise capacity**

![Graph showing increased exercise capacity](image)

- Mean (± SEM)
  - Ex-bosentan: $n=26$, $+33.2$ m (23.9)
  - Ex-placebo: $n=9$, $+61.3$ m (8.1)

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- Major interest for other therapies
  - Bosentan
  - ETA specific blockers
  - Sildenafil
  - Prostanoids (inhaled, subcutaneous)

---

- Thrombosis: emboli
- Infection: endocarditis
- System
- Rebound??

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- Major interest for other therapies
  - Bosentan
  - ETA specific blockers
  - Sildenafil
  - Prostanoids (inhaled, subcutaneous)

---

**Long term Brompton experience**

Kaplan–Meier curves for primary endpoint (death from any cause)
Log rank test
\[ p = 0.51 \]


**Other therapies: No dedicated controlled trials in PAH-CHD**

- **Sildenafil (PDE-5 inhibitor)**
  - In CHD seems similar to IPAH
  - Singh et al, Am Heart J 2006
  - Okay et al, Cardiol Rev 2005
  - Agapito et al, Rev Port Cardiol 2005
  - Rosenthal, Circulation 2004
  - Lim et al, Int J Cardiol 2006 3 ASD, PVR from 7.58 to 3.8
  - Chau et al Int J Cardiol 2006 6 months improvement in sat and haemodynamics
  - Paediatric RCT involving some CHD patients in progress
  - Numerous uncontrolled series coming (abstract or manuscripts)
- **Sitaxentan**
  - Barst et al, abstract AHA 2007 uncontrolled study
  - Randomised trial ??
  - Combination therapies coming

**Predictors/risk factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline NYHA</td>
<td>3.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>NYHA changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasoreactivity testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Post et al EHJ 2004;25:1651</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>12.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Phlebotomy, iron</td>
<td>0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BNP</td>
<td>1.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Others …</td>
<td>0.1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Kaplan–Meier curves for minor secondary endpoint (death or effective transplant)
Log rank test
\[ p = 0.0011 \]


**Predictors of deterioration or death!**


**Transplant**

- Heart/lungs or lung transplant and heart surgery
- Optimal timing ???
- 10 year survival for heart/lung is around 30-40% compared to Eisenmenger survival!!!
- New therapies
- Predictors of deterioration or death!
**Heart failure**

Impact of left ventricular function on survival in Eisenmenger patients

![Graph showing survival vs age and LVEF](image)

Predictors of mortality in Eisenmenger Patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA 3.0</td>
<td>0.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Signs of heart failure</td>
<td>10.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of documented arrhythmia</td>
<td>12.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Low albumin</td>
<td>0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>High gGt</td>
<td>1.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Low potassium</td>
<td>0.1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Conventional approach**

- PRIMUM NON NOCERE
- Regular follow-up in experienced centers
- Patient education
- Keep the physiological balance
- Prevent complications
- Endocarditis prophylaxis
- Avoid unnecessary non-cardiac surgery or if mandatory perform it in expert center with trained anesthetist and cardiac staff
- Contraception and avoid pregnancy
- Avoid strenuous but allow mild to moderate exercise
- Maintain fluid balance, avoid dehydration
- Annual immunization (influenza, pneumococcus)
- Oxygen: tailored approach
- Anticoagulation: tailored approach

**Eisenmenger syndrome: UK Management algorithm**

Diagnosis: referral to PAH/CHD centre

- History & examination, CXR & ECG
- Non-invasive tests-ECHO, cardiac MRI, cardiac CT
- Cardiac catheterisation for selected patients only

Functional class/other investigations

- 6-MWT
- Quality of life questionnaire
- Biochemistry, iron studies (transferrin saturation)

Education

- Endocarditis prophylaxis, advice on exercise and other lifestyle issues
- Effective contraception-risk of pregnancy very high

**Therapy -general**

- Correct iron deficiency
- Consider thromboprophylaxis
- Is there a role for reparative surgery/catheter based intervention?

**Therapy -advanced**

- Bosentan therapy for class III patients
- Consider other advanced therapies if evidence base widens
- Prostanoids as a bridge to transplantation (or as destination therapy?)
- Inhaled NO or iloprost may have a role for the pregnant patient with PAH

**Therapy -other**

- Lung or heart/lung transplantation for selected patients failing medical therapy
- Bosentan therapy for class III patients
- Consider other advanced therapies if evidence base widens
- Prostanoids as a bridge to transplantation (or as destination therapy?)

Conventional approach

- PRIMUM NON NOCERE
- Regular follow-up in experienced centers
- Patient education
- Keep the physiological balance
- Prevent complications
- Endocarditis prophylaxis
- Avoid unnecessary non-cardiac surgery or if mandatory perform it in expert center with trained anesthetist and cardiac staff
- Contraception and avoid pregnancy
- Avoid strenuous but allow mild to moderate exercise
- Maintain fluid balance, avoid dehydration
- Annual immunization (influenza, pneumococcus)
- Oxygen: tailored approach
- Anticoagulation: tailored approach
Conclusions

- Expert center of CHD associated with PAH experience
- Familiar with updated approach
- Even if survival has been considered better Eisenmenger patients deserve modern therapies

Summary

- Profile of CHD is changing
- Improved understanding of natural history and pathophysiology:
  - Proposals for revised classification
  - Targeted therapies and dedicated trials
- Early intervention may further improve prognosis in the PAH-CHD/EP population
  - Well-designed studies