Eisenmenger Syndrome: A Call for Action
Pulmonary hypertension and congenital heart disease

- CHD is common (~ 1% of newborns)
- PAH is common amongst adults with CHD (~ 5-10%)
- Affects quality of life and outcome  
  - Eisenmenger patients extreme end of the spectrum (~ 2% of contemporary hospital cohorts)  
    
  

- Other CHD candidates for PAH targeted therapies
  - Class II patients
  - Patients with increased PVR aiming towards symptomatic improvement and potential repair
  - Patients without a subpulmonary ventricle (Fontan)
Eisenmenger syndrome

Severe Pulmonary Arterial Hypertension associated with Congenital Heart Disease and a large intra- or extra-cardiac shunt.

The shunt with time leads to right to left shunting (shunt reversal), chronic cyanosis and multi-organ involvement.

Brickner ME, NEJM 2005; 342(5):340
Eisenmenger syndrome
Multi-organ disease

- Heamatology (secondary erythrocytosis/thrombocytopenia)
- Haemoptysis/thrombosis
- Menorrhagia
- Renal dysfunction
- Increased uric acid (less commonly gout)
- Cholelithiasis
- Scoliosis
- Arthropathy (osteochondrosis)
- Acne
- Systemic infection
  - Brain abscess (focal neurology not to be confused for hyperviscosity symptoms)
- Arrhythmias (atrial & ventricular)
- Syncope/Sudden cardiac death
- Right heart failure (late, often ominous sign)
Adults with Eisenmenger Syndrome
Survival

Standardised mortality ratio 3.8; 95% CI 2.0 – 7.0; p<0.0001
Exercise capacity in adults with CHD

MVO2 and underlying diagnosis

Aortic coarctation
Tetralogy of fallot
VSD
Mustard-operation
Valvular disease
Ebsteins anomaly
Pulmonary atresia
Fontan-operation
ASD (late closure)
ccTGA
Complex anatomy
Eisenmenger

Mean ± SD

28.7 ± 10.4
25.5 ± 9.1
23.4 ± 8.9
23.3 ± 7.4
22.7 ± 7.6
20.8 ± 4.2
20.1 ± 6.5
19.8 ± 5.8
19.2 ± 6.2
18.6 ± 6.9
14.6 ± 4.7
11.5 ± 3.6

ANOVA p<0.0001

Diller et al  Circulation 2005
Peak VO$_2$ Predicts Combined End-Point of Hospitalization or Death

Diller et al, Circulation 2005
Eisenmenger syndrome

Therapy

– Not standardised until recently
– Targeted towards avoiding complications
Eisenmenger syndrome

General management principles

- Avoid dehydration, extreme isometric exercise
- Avoid high altitude
- Air travel is safe *Broberg et al. Heart 2006*
- Special anaesthetic management
- Special care around angiography and non-cardiac surgery
- Avoid pregnancy *Bedard et al. Eur Heart J 2009* (≈ 30% maternal mortality)
- Contraception issues
Pregnancy and PAH in association with CHD

Maternal mortality (%)

<table>
<thead>
<tr>
<th>Year Range</th>
<th>IPAH</th>
<th>PAH-CHD</th>
<th>Other PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997 - 2007</td>
<td>17</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>1978 - 1996</td>
<td>30</td>
<td>36</td>
<td>56</td>
</tr>
</tbody>
</table>

\[ p = 0.047 \]

...... the cyanotic CHD patient and the myth of “hyperviscosity” syndrome, therapeutic venesection and the risk of stroke.
Cyanosis and 2° erythrocytosis

Routine venesections:
- Compromise $O_2$ carrying capacity
- Increase risk of stroke
- Reduce exercise capacity
- Induce/augment pre-existing iron deficiency*

*So-called symptoms of “hyperviscosity” syndrome mimic symptoms of iron deficiency...

Optimal Hb* and its Relation with O₂Sats and Exercise

*With adequate erythropoiesis, i.e. without iron/folate/B12 deficiency, raised erythropoietin/reticulocytosis, or right-shifted oxygen-Hb curve

Broberg et al Am J Card 2011
3 Months of Iron Replacement Therapy (Oral)

Change in Hb vs Baseline Hb

Change in total Camphor score

Change in 6MWT distance

High CAMPHOR scores reflect worse QoL.

Tay et al. Int J Card July 2010
Assess annually
- Anaemia history
- Symptoms of hyperviscosity
- Measure oxygen saturation
- Laboratory measures
  - Haemoglobin; PCV, red-cell indices, serum ferritin, transferrin saturation

Serum ferritin ≤15 µg/l
  - Transferrin saturation ≤15%

Patient Fe-deficient
- Fe supplementation
- Address other causes of Fe-deficiency as identified from history

Reassess symptoms
- Repeat laboratory tests
- Consider cessation of Fe suppl. when Fe-replete (serum ferritin ≥ 15 µg/l and transferrin saturation ≥15%)
- Some patients will require chronic Fe suppl. for steady-state erythrocytosis
- Regularly reassess symptoms and lab tests

Patient Fe-replete
- No symptoms of hyperviscosity

Resolution of symptoms
- Patient remains iron-replete

Persistent moderate-severe hyperviscosity symptoms
- Packed cell volume >65%

Reassess every 6-12 months

Patient Fe-replete
- Symptoms of hyperviscosity

Assess for other causes of symptoms and treat accordingly: e.g. hypovolaemia, gout, brain abscess, hypothyroidism, depression

Trial of phlebotomy with fluid replacement

Eisenmenger syndrome

Therapy

– Not standardised until recently
– Targeted towards avoiding complications

• Anticoagulation
• Nocturnal oxygen
• Chronic prostacyclin therapy
• Nitric oxide
• Transplantation
• PDE-5 inhibitors
• Endothelin antagonists
Eisenmenger Syndrome: *Thrombosis*

Broberg, *et al.* Heart 2004
Silversides *et al.*, JACC 2003
Effect of pulmonary arterial thrombus formation in Eisenmenger syndrome

- Ventricular ejection fraction (%)
  - Right ventricle
  - Left ventricle

- Serum neuropeptide level (pmol/l)
  - ANP
  - BNP

- Peak exercise \(O_2\) consumption

- No thrombus
- Thrombus

* \(p<0.05\)

Eisenmenger syndrome

Therapy

– Not standardised until recently
– Targeted towards avoiding complications
  • Anticoagulation
  • Nocturnal oxygen
  • Chronic prostacyclin therapy
  • Nitric oxide
  • Transplantation
  • PDE-5 inhibitors
  • Endothelin antagonists
Eisenmenger syndrome

• Nocturnal oxygen
  – Survival benefits in children with PHT\(^1\)
    • 9/9 on O\(_2\) alive vs 1/6 alive in controls (over 5 yrs)
  
  – No change in PA pressure or survival benefit in 23 adults with Eisenmenger complex after 2 years of nocturnal O\(_2\) therapy\(^2\)
  
  – Data limited, inconclusive
  
  – Use on empiric basis

Eisenmenger syndrome

- **Chronic prostacyclin therapy**
  - 20 pts on IV prostacyclin\(^1\) at 12 months
    - PA pressure ↓ 20% (no acute response)
    - 6 minute walk test ↑ (408 to 460 m)
    - Toxicity
    - Problems with IV lines
  - 15 children on aerosolized iloprost\(^2\) at 12 months
    - Improved right sided haemodynamics
    - Improved 6 minute walk test
    - Short half life (inhalation every 3-4 hrs)
    - Similar side effects with IV (flushing and jaw pain)
    - May have a role in pregnancy

Eisenmenger syndrome

NO
- Selective pulmonary vasodilator
- No systemic disturbance

23 pts with Eisenmenger
- 30% responders (80ppm)
- All with L-to-R shunts
- Responders had improved survival

• Administration challenges

Establishing the Diagnosis of Eisenmenger Syndrome

Oechslin E. “Chapter on Eisenmenger Syndrome”
Gatzoulis, Webb and Daubenay. 2nd Edition Elsevier 2011
Eisenmenger syndrome

• Transplantation
  – H/LT superior to LT\(^1\)
  – 435/605 Tx in CHD pts period 1988-98 from the International Registry
    • 1 year survival 81% and 70% respectively
    • 5-year survival approximately 50%
  – Increased peri-operative risk\(^2\)
  – 51 pts with Eisenmenger HLT
  – Similar long-term survival with non-Eisenmenger pts
• Selection criteria and timing ?

Eisenmenger syndrome

- Phosphodiesterase inhibitors
  - Short-term randomized data at present in adult patients
  - Sildenafil (high dose, 100mg tds) \(^1\)
    - 10 patients (age 15, 4-35 years), RC cross over study, 6 weeks
    - Non-invasive
    - 6MWT improved on sildenafil (269+/-99 to 358.9+/-96.5 m)
  - Tadalafil (40mg od) \(^2\)
    - 28 patients (>30Kg in weight), RC cross over study, 6 weeks
    - 6MWT improved on tadalafil (358+/-73 to 404+/-70)
    - PVR fell (-7.32+/-1.58, P<0.001)

\(^1\)Singh et al. Amer Heart J 2006
\(^2\)Mukhopadyay et al. Cong Heart Dis 2011
Eisenmenger syndrome
Sildenafil

Change in 6MWD (m)

CAMPHOR score

p < 0.001

Tay et al  Int J Card  2010
Endothelin Pathway
BREATHE-5: Study design

Screening

2:1 Randomization

Bosentan 62.5 mg bid

Placebo 62.5 mg bid

2 weeks 4 weeks 12 weeks 16 Weeks

Baseline

Bosentan 125 mg bid

Placebo 125 mg bid

Galie et al for Breathe-5, Circulation 2006
Bosentan reduces pulmonary vascular resistance indexed

Galie et al for Breathe-5, Circulation 2006
Bosentan increases exercise capacity

6MWD (m)
Change from baseline

Placebo (n=17) Bosentan (n=37)

T.E. = 53.1 m
p=0.008

Galie et al for Breathe-5, Circulation 2006
BREATHE-5 open label extension (OLE) study

Study design

Bosentan 125 mg bid

16 weeks

Baseline OLE

Bosentan/placebo

BREATHE-5

Bosentan 62.5 mg bid

4 weeks

BREATHE-5 OLE

Gatzoulis et al for Breathe-5, Int J Card 2007
Bosentan increased exercise capacity

**Change 6MWD (m)**

- **Ex-bosentan**
  - Baseline BREATHE-5: 0 m
  - Baseline BREATHE-5 OLE: 33.2 m (23.9) mean (± SEM)
  - End BREATHE-5 OLE: 61.3 m (8.0) mean (± SEM)

- **Ex-placebo**
  - Baseline BREATHE-5: 0 m
  - Baseline BREATHE-5 OLE: 0 m
  - End BREATHE-5 OLE: 0 m

**n** values:
- Ex-bosentan: n = 26
- Ex-placebo: n = 9
WHO functional class

Change in WHO functional class
(all patients in WHO FC III at baseline of BREATHE-5)

Patients (%)

100
90
80
70
60
50
40
30
20
10
0

Class II
Class III

To end
To end
To end
To end

BREATHE-5
BREATHE-5 OLE
BREATHE-5
BREATHE-5 OLE

Ex-placebo (n = 11)
Ex-bosentan (n = 26)

18%
64%
35%
65%

82%
36%
65%
35%

Gatzoulis et al for Breathe-5, Int J Card 2007
Bosentan and Eisenmenger Syndrome
Longer-term 6 minute walk test

P = 0.0009*  P = 0.005*  P = 0.03*

* Comparison to baseline
Wilcoxon paired rank test

<table>
<thead>
<tr>
<th>Time</th>
<th>Distance (m)</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>284±144 m</td>
<td></td>
</tr>
<tr>
<td>0-6 mths</td>
<td>363±124 m</td>
<td></td>
</tr>
<tr>
<td>6-12 mths</td>
<td>380±91 m</td>
<td></td>
</tr>
<tr>
<td>1-2 years</td>
<td>408±114</td>
<td></td>
</tr>
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</table>

Diller et al Heart 2007
Changes with advanced therapy in PAH associated with CHD

The 6 Minute Walk Test and NYHA Class

- 79 adults with Eisenmenger syndrome
- Mean age 34+/−10 years
- Follow-up of 3.3 years (on advanced therapy)
- 2 patients died

O2 Sats at rest and exercise

- Mean change in 6-minute walk test distance
- Mean change in NYHA class

Diller et al  Int J Card  2012
Hazard ratios for all cause mortality for changes in BNP within 1 year
181 pts with Eisenmenger S. (31% with Down S.)
Mean age 37 yrs, median FU 3.3 yrs, retrospective study

Figure 5.
Change in BNP within 1 year: Conventional vs Targeting PAH Therapy
181 pts with Eisenmenger S. (31% with Down S.)
Mean age 37 yrs, median FU 3.3 yrs, retrospective study
Change in BNP from baseline: Conventional vs Targeting PAH Therapy

181 pts with Eisenmenger S. (31% with Down S.)
Mean age 37 yrs, median FU 3.3 yrs, retrospective study

B)

Patients not treated with disease targeting therapies

Patients on disease targeting therapies

Change in BNP (pmol/L) vs Change in BNP (pg/mL)

Deaths

No deaths

Diller et al  Heart 2012
Random survival forest analysis
181 pts with Eisenmenger S. (31% with Down S.)
Mean age 37 yrs, median FU 3.3 yrs, retrospective study

A)

Variable importance

Relative importance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Importance</th>
</tr>
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<tbody>
<tr>
<td>BNP</td>
<td>100%</td>
</tr>
<tr>
<td>6-minute walk test distance</td>
<td>37%</td>
</tr>
<tr>
<td>Creatinine</td>
<td>16%</td>
</tr>
<tr>
<td>Down Syndrome</td>
<td>13%</td>
</tr>
<tr>
<td>Age</td>
<td>0%</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>0%</td>
</tr>
</tbody>
</table>

Diller et al  Heart 2012
Moceri et al. Circulation 2012

Logrank p=0.0004

Cumulative mortality (%)

TAPSE<15
TAPSE>=15

time (years)

0 0.5 1 1.5 2 2.5 3

0 10 20 30 40 50 60

30.8

5.4
### Predictors of death in model including ATs

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAPSE, per 10mm</td>
<td>0.17 (0.07-0.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAPSVelocity, per 10cm/sec</td>
<td>0.73 (0.55-0.97)</td>
<td>0.029</td>
</tr>
<tr>
<td>RA area, per 10cm²</td>
<td>5.91 (2.97-11.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RA/LA area</td>
<td>8.91 (2.90-27.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RA pressure, per 10mmHg</td>
<td>4.68 (1.89-11.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tricuspid E′/A′</td>
<td>2.26 (1.38-3.71)</td>
<td>0.001</td>
</tr>
<tr>
<td>RVOT VTI, per 10cm</td>
<td>0.89 (0.79-1.00)</td>
<td>0.044</td>
</tr>
<tr>
<td>t-IVT adjusted for HR, per 10sec/min</td>
<td>1.86 (0.98-3.53)</td>
<td>0.056</td>
</tr>
<tr>
<td>S:D ratio</td>
<td>1.84 (1.09-3.11)</td>
<td>0.023</td>
</tr>
<tr>
<td>E′m, per 10m/sec</td>
<td>0.11 (0.02-0.70)</td>
<td>0.019</td>
</tr>
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</table>
Evolving markers for assessing prognosis, disease severity, disease progression and response to therapy in PAH-CHD @

<table>
<thead>
<tr>
<th>Better Prognosis</th>
<th>Determinants of Prognosis</th>
<th>Worse Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable</td>
<td>RV failure: of limited value for early prognostication in ES*</td>
<td>Yes, guarded prognosis</td>
</tr>
<tr>
<td>Slow</td>
<td>Rate of progression of symptoms</td>
<td>Rapid</td>
</tr>
<tr>
<td>No</td>
<td>Syncope††¹a</td>
<td>Uncertain</td>
</tr>
<tr>
<td>I, II</td>
<td>WHO FC†¹b</td>
<td>II, IV</td>
</tr>
<tr>
<td>Longer (&gt; 400 m)</td>
<td>6MWD²</td>
<td>Shorter (&lt; 300 m)</td>
</tr>
<tr>
<td>Percentage predicted peak O₂ consumption &gt; 46%</td>
<td>Cardio-pulmonary exercise testing³</td>
<td>Percentage predicted peak O₂ consumption &lt; 31%</td>
</tr>
<tr>
<td>Normal (&lt;13.9 pmol/L) or near normal</td>
<td>BNP plasma levels⁴</td>
<td>&gt; 30 pmol/L</td>
</tr>
<tr>
<td>TAPSE ≥ 1.5 cm RA area &lt; 25 cm² RA/LA &lt; 1.5</td>
<td>Echocardiographic findings⁵</td>
<td>TAPSE &lt; 1.5 cm RA area ≥ 25 cm² RA/LA ≥ 1.5</td>
</tr>
<tr>
<td>RAP &lt; 8 mmHg and CI ≥2.5 L/min/m²</td>
<td>Haemodynamics‡ Not routinely examined</td>
<td>RAP &gt; 15 mmHg and CI ≤ 2.0 L/min/m²</td>
</tr>
</tbody>
</table>

@ (adapted from Galiè N et al. *Eur Heart J* 2009; 30:2493–537).
*RV failure in ES patients is an ominous sign and of limited value for early prognostication;
†Syncope in patients with ES and chronic cyanosis may also be vasovagal, due to autonomic nervous dysfunction; ¹a syncope does not predict death; Diller et al EHJ 2006
‡Baseline haemodynamics may be necessary in some ES patients. Repeat haemodynamics are not routinely recommended in ES
Survival benefits with advanced therapy

Dimopoulos et al, Circulation 2010
Contemporary survival in Eisenmenger syndrome: Relation to functional class

Patients at risk
229 197 169 145 116 92 69 52

Cumulative mortality (%)

Time (years)

All FC patients

FC I-II

FC III-IV

Dimopoulos et al  Circulation 2010
PAH-CHD Groups and Therapy

a. Eisenmenger syndrome
b. Operated shunt (VSD)
c. PAH with a small shunt
d. PAH with L→R shunt
e. Fontan circulation
DISEASES
OF THE
HEART
AND
CIRCULATION

Second, revised and enlarged edition
Third impression

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