Advances in Pulmonary Arterial Hypertension Associated with Congenital Heart Disease

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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 Engelfriet et al Heart 2007
- Eisenmenger patients extreme end of the spectrum (~ 2% of contemporary hospital cohorts) Duffels et al Int J Card 2007

- Other CHD candidates for PAH targeted therapies
  - Class II patients
  - Patients with increased PVR aiming towards symptomatic improvement and potential repair? Dimopoulos et al Int J Card 2008
  - 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
Adults with Eisenmenger Syndrome
Survival

Diller et al  EHJ 2006

Standardised mortality ratio 3.8; 95% CI 2.0 – 7.0; p<0.0001
Mortality in Eisenmenger Syndrome

Calculation for 40-years old patients

Kempny et al., manuscript in preparation
Exercise capacity in adults with CHD
MVO2 and underlying diagnosis

Aortic coarctation
Tetralogy of Fallot
VSD
Mustard-operation
Valvular disease
Ebstein's 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 ± 6.2
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
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)
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…

3 Months of Iron Replacement Therapy (Oral)

Tay et al. Int J Card July 2010
Eisenmenger syndrome

General management principles

- Avoid dehydration, extreme isometric exercise
- Avoid high altitude
- Air travel is safe \textit{Broberg et al. Heart 2006}
- Special anaesthetic management
- Special care around angiography and non-cardiac surgery
- Avoid pregnancy \textit{Bedard et al. Eur Heart J 2009} (≈ 30% maternal mortality)
- Contraception issues
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 (%)
- Serum neuropeptide level (pmol/l)
- Peak exercise O₂ consumption

- Right ventricle
- Left ventricle
- ANP
- BNP
- Peak VO₂

- No thrombus
- Thrombus

* p<0.05

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

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 ?

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

Baseline

16 Weeks

Bosentan
125 mg bid

Placebo
125 mg bid

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

Placebo (n=17) Bosentan (n=36)

T.E. = -472 dyn.sec.cm$^{-5}$  
$p=0.04$

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

**Graph:**
- **Y-axis:** 6MWD (m) Change from baseline
- **X-axis:** Placebo (n=17) Bosentan (n=37)
- **Legend:**
  - Placebo: light blue bar
  - Bosentan: yellow bar

**Statistics:**
- 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

BREATH-5

Bosentan/placebo

16 weeks

Bosentan 62.5 mg bid

4 weeks

Bosentan 125 mg bid

BREATHE-5 OLE

20 weeks

Baseline OLE

Bosentan increased exercise capacity

Baseline BREATHE-5

Baseline BREATHE-5 OLE

End BREATHE-5 OLE

Change 6MWD (m)

Ex-bosentan

Ex-placebo

mean (± SEM)

+33.2 m (23.9)

+61.3 m (8.0)

Baseline

BREATHE-5

BREATHE-5 OLE

End

BREATHE-5 OLE
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

BREATHE-5
Ex-placebo  (n = 11)

To end

BREATHE-5

To end

BREATHE-5 OLE

To end

BREATHE-5
Ex-bosentan  (n = 26)

To end

BREATHE-5 OLE

WHO functional class

Gatzoulis et al for Breathe-5,  Int J Card 2007
Changes with advanced therapy in PAH associated with CHD

The 6 Minute Walk Test and NYHA Class

O2 Sats at rest and exercise

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

Diller et al  Int J Card  2012
Eisenmenger syndrome: Prognostication

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

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)

Relative importance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Importance</th>
</tr>
</thead>
<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>
Echo Indices Predict Outcome in Eisenmenger Syndrome

Moceri et al, Circulation 2012
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>TAPS Velocity, per 10 cm/sec</td>
<td>0.73 (0.55-0.97)</td>
<td>0.029</td>
</tr>
<tr>
<td>RA area, per 10 cm²</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 10 mmHg</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 10 cm</td>
<td>0.89 (0.79-1.00)</td>
<td>0.044</td>
</tr>
<tr>
<td>t-IVT adjusted for HR, per 10 sec/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 10 m/sec</td>
<td>0.11 (0.02-0.70)</td>
<td>0.019</td>
</tr>
</tbody>
</table>
a) TAPSE
   - True Positive: 0.0 to 1.0
   - False Positive: 0.0 to 1.0
   - AUC = 0.67 ± 0.00

b) Echocardiographic Composite Score
   - True Positive: 0.0 to 1.0
   - False Positive: 0.0 to 1.0
   - AUC = 0.90 ± 0.01

c) Echocardiographic Composite Score with E'/A' and Em
   - True Positive: 0.0 to 1.0
   - False Positive: 0.0 to 1.0
   - AUC = 0.90 ± 0.02

d) Echocardiographic Composite Score with BNP and Saturations
   - True Positive: 0.0 to 1.0
   - False Positive: 0.0 to 1.0
   - AUC = 0.89 ± 0.01
6MWT and $O_2$ Sats Predict Survival in Eisenmenger

Kempny et al, Int J Cardiol 2013

*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 FC1b</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</td>
<td>Echocardiographic findings⁵</td>
<td>TAPSE &lt; 1.5 cm</td>
</tr>
<tr>
<td>RA area &lt; 25cm²</td>
<td></td>
<td>RA area ≥ 25cm²</td>
</tr>
<tr>
<td>RA/LA &lt; 1.5</td>
<td></td>
<td>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
Inclusion criteria:
- Eisenmenger syndrome
- Complete baseline and follow-up data on
  - Clinical status (functional class, \( \text{SO}_2 \))
  - ECG parameters
  - Mortality

Mortality in Eisenmenger (334 contemporary patients)
<table>
<thead>
<tr>
<th>Study population (n=334)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36.6 [27.4-44.9]</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>127 (38%)</td>
</tr>
<tr>
<td>Down syndrome (n)</td>
<td>121 (36%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Shunt location</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretricuspid, n (%)</td>
<td>30 (9%)</td>
</tr>
<tr>
<td>Posttricuspid, n (%)</td>
<td>190 (57%)</td>
</tr>
<tr>
<td>Complex, n (%)</td>
<td>114 (34%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA FC I/II/III/IV, %</td>
<td>2/39/56/3%</td>
</tr>
<tr>
<td>SO₂ at rest, %</td>
<td>85.0 [79.0-90.0]</td>
</tr>
<tr>
<td>6MWT distance, m</td>
<td>310 [240-370]</td>
</tr>
</tbody>
</table>

| Follow-up time, y        | 2.9 [1.6-4.4] |
| All cause mortality, n (%) | 78 (23%) |
| Patients on AT at baseline, n (%) | 98 (29%) |
| Patients on AT at any time , n (%) | 182 (54%) |

*Kempny et al., manuscript in preparation*
## Mode of death

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Kempny A et al (*) Years 2000-2013, n=78</th>
<th>Somerville J, IJC 1998 Years -1998, n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n/∑</td>
</tr>
<tr>
<td>Cardiac Chronic</td>
<td>29</td>
<td>37%</td>
</tr>
<tr>
<td>Sudden</td>
<td>12</td>
<td>15%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12</td>
<td>15%</td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
<td>12%</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>5</td>
<td>7%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5</td>
<td>6%</td>
</tr>
<tr>
<td>CVA/ABSCESS</td>
<td>3</td>
<td>4%</td>
</tr>
<tr>
<td>Transplantation</td>
<td>2</td>
<td>3%</td>
</tr>
<tr>
<td>Extracardiac operation</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>CVS operation</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Injury</td>
<td>1</td>
<td>1%</td>
</tr>
</tbody>
</table>

(*) Kempny et al., manuscript in preparation
Univariate Cox regression analysis

Kempny et al., manuscript in preparation
Multivariate Cox regression analysis

- AT therapy is a **time-dependent variable**, since many patients were started on AT during follow-up

![Predictors of outcome on multivariate analysis](image)

<table>
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<tr>
<th>Variables</th>
<th>HR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, 10y</td>
<td>1.43 (1.07–1.92)</td>
<td>0.014</td>
</tr>
<tr>
<td>SO₂, %</td>
<td>0.92 (0.87–0.97)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>3.19 (1.47–6.92)</td>
<td>0.003</td>
</tr>
<tr>
<td>Albumin, 10g/L</td>
<td>0.55 (0.31–0.96)</td>
<td>0.037</td>
</tr>
<tr>
<td>AT for PAH</td>
<td>0.46 (0.22–0.98)</td>
<td>0.043</td>
</tr>
</tbody>
</table>
Survival benefits with advanced therapy

No advanced therapies

Advanced therapies

Cumulative mortality (%)

Time (years)

$p = 0.01$

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

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>229</th>
<th>197</th>
<th>169</th>
<th>145</th>
<th>116</th>
<th>92</th>
<th>69</th>
<th>52</th>
</tr>
</thead>
</table>

Cumulative mortality (%)

All FC patients

FC I-II

FC III-IV

Dimopoulos et al Circulation 2010
Clinical update

Pulmonary hypertension related to congenital heart disease: a call for action

Konstantinos Dimopoulos, Stephen John Wort, and Michael A. Gatzoulis

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Received 15 July 2013; revised 7 September 2013; accepted 26 September 2013

Pulmonary arterial hypertension related to congenital heart disease (PAH-CHD) is a common type of pulmonary arterial hypertension (PAH). Despite this, little emphasis has been given to this group of patients until recently, when compared with idiopathic PAH. This is largely because of the complexity and the wide range of underlying cardiac anatomy and physiology, with a multitude of adaptive mechanisms not fully understood. Pulmonary arterial hypertension related to congenital heart disease is, therefore, best diagnosed and managed in centres specializing in both CHD and PAH, to avoid common pitfalls and old practices and to provide state-of-the-art care. We discuss the optimal management of PAH-CHD patients in a series of actions to be taken in order to optimize short- and long-term outcome, based on current knowledge of the condition and the advent of targeted advanced therapies.

Keywords
Eisenmenger syndrome • Congenital heart disease • Pulmonary hypertension • Advanced therapies • Targeted therapies • Treat and repair • Pulmonary vascular disease
PAH-CHD subgroups

A. Eisenmenger S.

B. PAH & L to R shunts

C. Small defects & PAH

D. Operated CHD & PAH

Gatzoulis et al, Int J Card 2014