Pulmonary Hypertension causes and medical management in children and young people with Down syndrome

Professor Robert Tulloh DM FRCPCH
Consultant Congenital Cardiologist
University Hospitals Bristol NHS Foundation Trust
and
Bristol Heart Institute, University of Bristol
## Background – What is PH?

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Hypertension</td>
<td>Mean PAP &gt;25mmHg</td>
<td>All</td>
</tr>
<tr>
<td>Pre-capillary PAH</td>
<td>mPAP&gt;25mmHg mLA&lt;15mmHg Normal/Low CO</td>
<td>PAH</td>
</tr>
<tr>
<td>Post capillary PH</td>
<td>mPAP&gt;25mmHg mLA&gt;15mmHg Normal/Low CO</td>
<td>PVH</td>
</tr>
</tbody>
</table>

- Not practical for screening so we use
  - **Pulmonary Systolic pressure is > half the Systemic Systolic pressure in infants**
  - **TR jet>2.8m/s with evidence of Increased PVR**
  - **Pressure = Flow x Resistance (V = I x R)**
What is Pulmonary Hypertension?

- Much confusion!

- All people with a large VSD or large AVSD will have high pulmonary artery PRESSURES, until operated.
Circulation - VSD

RA → RV → PA → SVR

LA → LV → Ao

PVR
Remember

- \( V = I \times R \)
- \( \text{Pressure} = \text{Flow} \times \text{resistance} \)
- \( \text{Resistance} = \frac{\text{Pressure}}{\text{Flow}} \)
- \( \text{PVR} = \frac{\text{mPAp} - \text{mLAp}}{\text{Qp}} \)
- Indexed in children = \( \text{WUnits} \times M^2 \)
What sort of heart defects?

- AVSD
  - Often have no symptoms
  - May be blue at birth and breathless later
  - Routinely have heart surgery at 3 months
Evolution of Pulmonary Vascular Disease

- Increased pulmonary blood flow = shear stress
- Endothelial proliferation
- Smooth muscle cell proliferation
- Increased Elastin production
- Distal extension of EC + SMC
- Fibrinoid necrosis
- Vessel Occlusion
  - HENCE increased Pulmonary vascular resistance
Eisenmenger pathophysiology

- Left-to-right shunt
  - Increased pulmonary blood flow (shear stress)
    - Endothelial dysfunction
      - Increase in pulmonary vascular resistance
        - Inverted shunt: right-to-left
          - Cyanosis (Eisenmenger’s)

Proliferation of smooth muscle cells
Increase in extracellular matrix
Intravascular thrombosis
Classification of Pulmonary Hypertension (Dana Point 2008)

1. Pulmonary arterial hypertension
2. Pulmonary venous hypertension due to left heart disease
3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia
4. Pulmonary hypertension caused by chronic thrombotic and/or embolic disease
5. Pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature

http://content.onlinejacc.org/cgi/content/full/54/1_Suppl_S/S43
1. Pulmonary arterial hypertension

1.1 Idiopathic

1.2 Heritable
   - BMPR2
   - ALK1
   - Unknown

1.3 Drugs and Toxins

1.4 Associated with
   - 1. Connective tissue disease
   - 2. HIV
   - 3. Portal hypertension
   - 4. Congenital Heart Disease
   - 5. Schistosomiasis
   - 6. Chronic Haemolytic anaemia

1.5 Persistent pulmonary hypertension of the newborn
Group 1.1/1.2 PAH

- Idiopathic/Primary/Hereditary
  - Rare (1-2/ 1000000 )
  - Evidence for genetic cause 2q31-32, BMPR2, Alk-1
  - Genes in 60% familial, 25% sporadic

- pPA often >60mmHg
- F>M (Barst et al, 1987)
- Usually in young women
- Poor prognosis (median survival after diagnosis 2-3 years)
3. PH associated with disorders of the respiratory system

3.1 Chronic obstructive pulmonary disease
- Upper Airway Obstruction
  - Tonsils, OSA, webs
  - Soft tissue, palato-pharyngeal incoordination, Down synd (30%)
  - Laryngo-Tracheo-broncho malacia or Bronchial abnormality
  - Vascular ring / sling
  - Left atrial or left pulmonary artery compression

3.2 Interstitial lung disease
- Alveolar filling defects, granuloma
- Cystic Fibrosis, BPD, Bronchiectasis, Ciliary dyskinesia

3.3 Sleep disordered breathing

3.4 Alveolar hypoventilation disorders
- Scoliosis, Neuromuscular, inflammatory

3.5 Chronic exposure to high altitude

3.6 Neonatal lung disease

3.7 Alveolar-capillary dysplasia

3.8 Other
What are the risk factors for PH in Down syndrome?

- DS caused by trisomy at 21q22.3
- Many genes involved – cysteine rich epidermal growth factor like domain
  - CRELD1 (important in AVSD formation)
  - GATA4
  - MNB/DYRK1A (Alzheimer)

Starts before birth in the lungs

- Hypoplastic lungs – is there any evidence?
  

- Emphysema, reduced elastic fibres in alveolar wall

- Failure to develop properly
  
  - Arrested alveolar maturation

- Alveolar capillary dysplasia

- Pulmonary oedema at sea level

- Pulmonary embolism with abnormal myelopoiesis

- Lymphangiectasis
Issues immediately at birth

- Failure of Pulmonary vascular resistance to fall
- SSRI in mother?
- Rate of PPHN is high up to 5% in DS
- Why?
  - Those with large holes (VSD / AVSD), the pressures in the pulmonary (lung) artery are high from birth
  - DS have smaller upper airways and hence keep up the resistance to lung blood flow
  - These children may not show the classical signs of heart failure early on
Congenital Heart Disease in DS

- 40% have CHD
  - 40% VSD, 40% AVSD, 10% Fallot
- DS with AVSD have disproportionately high rate of PAH for their age.
- PAH is more frequent and develops earlier in these patients.

Freedom RM in The Natural and Modified History of Congenital Heart Disease. 2004; 44–5527, 28,29, 30
Congenital Heart Disease

In addition to VSD and AVSD:

- **Persistent Arterial Duct**
  - Closed in cardiac catheter laboratory with coil or device
  - Careful of R->L

- **Atrial Septal defect**
  - Usually closed in cardiac catheter lab – fenestrate?
Problems before cardiac surgery

- Acquired virus infections especially RSV
  - **Protect with Palivizumab**
- Gastro-oesophageal reflux
- Structural lung abnormalities
  - Diaphragmatic hernia
  - Hernia of Morgagni or Bochdalek
  - Bronchus suis

Molecular differences in DS

- Blood levels of arginine and NO are lower
- Response to NO less
- Endothelin-1 higher
- Reduced Prostacyclin (PGI2) but increased Thromboxane2.
- Small peripheral capillaries

Upper airway obstruction

- Snoring, Sleepiness, Poor concentration
- Adenoids, macroglossia, glossoptosis, laryngomalacia, midfacial hypoplasia, reduced muscle tone, hypoventilation, aspiration pneumonia
- Abnormal aryepiglottic folds, oesophagobronchial fistulae
Surely you won’t have Pulmonary hypertension if you have this?

- Tetralogy of Fallot
  - Residual VSD
  - Collateral arteries (MAPCAs)
  - Unilateral branch PA stenosis
- Single ventricle
  - pulmonary artery band too loose
  - restrictive septums
  - Abnormal physiology
Cardiac issues that can arise – after cardiac surgery

- No cardiac operation is “corrective”
- May be due to back pressure from a leaky mitral (left AV) valve after AVSD repair
- May be due to poor left heart function
- Mitral valve prolapse in 30-50% teenagers with DS
Causes of Pulmonary hypertension

- Risk for Pulmonary hypertension
  - Older age at surgery, partially corrected
  - Upper airway obstruction
  - Previous RSV infection
  - Concomitant disease – Mitral, Aortic
  - Diabetic, vascular disease
  - LV dysfunction, increasing LA pressure
3. PH associated with disorders of the respiratory system

3.1 Chronic obstructive pulmonary disease
- Upper Airway Obstruction
  - Tonsils, OSA, webs
  - Soft tissue, palato-pharyngeal incoordination, Down’s (30%)
  - Laryngo-Tracheo-broncho malacia or Bronchial abnormality
  - Vascular ring / sling
  - Left atrial or left pulmonary artery compression

3.2 Interstitial lung disease
- Alveolar filling defects, granuloma
- Cystic Fibrosis, BPD, Bronchiectasis, Cilial dyskinesia

3.3 Sleep disordered breathing

3.4 Alveolar hypoventilation disorders
- Scoliosis, Neuromuscular, inflammatory

3.5 Chronic exposure to high altitude

3.6 Neonatal lung disease

3.7 Alveolar-capillary dysplasia

3.8 Other
1. Pulmonary arterial hypertension
1’. Pulmonary hypertension due to PVOD/PCH
2. Pulmonary venous hypertension due to left heart disease
3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia
4. Pulmonary hypertension caused by chronic thrombotic and/or embolic disease
5. Pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature
Bristol Pulmonary Hypertension Clinic

- Largest shared care in UK
- 80% are adult congenital heart disease, 50% are DS
- Link with HHT (adults) GOS (children)
  - PH Nurses
  - Academic Clinical lecturer, 2 AFP
  - 3 research registrars
  - Psychologist
  - Imaging – CT, MRI
  - Technicians (Echo / Respiratory)
40 PCTs with at least one historical patient
Growing numbers of patients

- Children
- Adults
Clinical assessment

◆ Symptoms
  □ Lack of symptoms!
  □ Reduction in exercise tolerance
  □ Syncope, Nose bleeds, oedema

◆ Signs
  □ Loud P2
  □ RVH
  □ Cyanosed!
  □ Murmur – PSM or EDM
  □ JVP, Liver, Oedema
## Clinical assessment

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking on Flat</td>
<td>Breathless at rest.</td>
<td>Breathless on minimal exertion</td>
<td>30-50 yds slowly all right.</td>
<td>100-400 yards slowly all right</td>
<td>2 miles slowly all right.</td>
</tr>
<tr>
<td>Stairs</td>
<td>Never tries</td>
<td>Difficulty with 1 flight</td>
<td>Difficulty with two flights (1 alright)</td>
<td>2 flights all right at average speed.</td>
<td>Normal</td>
</tr>
<tr>
<td>Running</td>
<td>Never</td>
<td>Few paces only</td>
<td>20 yards gently all right</td>
<td>100 yards jogging all right</td>
<td>Normal speed 100 yards</td>
</tr>
<tr>
<td>Tiredness</td>
<td>Always</td>
<td>Very quickly tired after each day at school</td>
<td>Frequently tired</td>
<td>Sometimes after a long day</td>
<td>Normal</td>
</tr>
<tr>
<td>Appetite</td>
<td>Eats small amount rarely</td>
<td>Often leaves food</td>
<td>Needs encouragement to eat meal</td>
<td>Sometimes does not feel like eating</td>
<td>Eats three normal meals a day</td>
</tr>
</tbody>
</table>

Parental Questionnaire (Bowyer et al, 1986)
**Clinical features**

Clubbing, from PH in tricuspid atresia, VSD

Differential cyanosis
Large PDA, which has developed Eisenmenger syndrome
Pulmonary Hypertension Diagnosis - Radiography

- Pre-capillary Pulmonary Hypertension
  - Central arterial enlargement
  - Sharply pruned peripheral vasculature
  - Right ventricle hypertrophy and dilatation (on lateral radiograph)

- Post-capillary Pulmonary Hypertension
  - Prominent septal lines
  - Small pleural effusions
  - Air space opacities
Pulmonary Hypertension Diagnosis - Echocardiography

- Anatomy
- RV dilation, function
- Pericardial effusion
- TR jet (accurate for RV systolic pressure, if present)
- LV Eccentricity index
- PR jet (accurate for PA diastolic pressure, if present)
- AT
- Tissue Doppler, Strain, 3D
Pulmonary Hypertension Diagnosis - Echocardiography

- Arterial Ducts
  - Useful to help assess PA pressure
  - Are they instrumental in worsening PAH?
Pulmonary Hypertension Diagnosis – Blood tests

- **Haematology**
  - FBC, LFT
  - Sickle
  - Clotting, procoagulation

- **Biochemistry**
  - U+ E and Glucose
  - LFT including Cholesterol, TG, CRP
  - A1 AT,
    - **BNP**

- **Immunology**
  - C3c, C4, Rh F
  - IgG, IgA, IgM, IgE
  - anti-DsDNA, c/pANCA
  - Mitochondrial, anti cardiolipin Ab

- **Genetics**
  - 2q31-32 gene
  - BMPR2 receptor

- **Virology**
  - CMV, EBV, Hep BCDE, HIV
  - TORCH
ECG in Children

- RVH
- May have superior axis in AVSD
- T waves!
Six minute walk test – 6MWT

- For measuring the response to medication for patients with mod-severe cardiopulmonary disease
  - Measures distance walked in 6 min
  - Oxygen Saturations each minute
  - Index of breathlessness (Borg)
- Can be variable between patients, but very repeatable in same patient
- Normal is around 600m
- Eisenmenger happily exist with 100m
- Not useful in Down syndrome?
Correlation of 6MWD with TAPSE

WHO Functional Class 2
WHO Functional Class 3
32 were in the normal platelet group. Of this group;

- The most common diagnosis was VSD
- Mean oxygen saturation of 91% at rest and 81% on exercise
- Mean 6mwd was 348.4 metres

34 patients in the low platelet group. Of these;

- The most common diagnosis was AVSD
- Mean oxygen saturation of 82% at rest and 72% on exercise
- Mean 6mwd was 282.7 metres

*Shortland et al Cardiol Young 2015 AEPC suppl*
Pulmonary Hypertension
Diagnosis – CT scan

- High resolution CT
  - Interstitial disease
  - Structural lung disease
    - Emphysema
  - Thrombo-embolic
  - Pleural
  - Lung volume?
- CTPA
  - Thrombus
Magnetic Resonance Imaging

- Dilated PA
- Anatomic defects
- Peripheral Thrombus
- RV function
- RV/PA coupling
CMR in Pulmonary Hypertension

- Review anatomy
  - Pulmonary venous or mitral valve obstruction

- Accurate pulmonary blood flow measurement

- Possible assessment of PVR using CMR

CMR Cardiac Catheterisation

- Pulmonary hypertension studies in MR
  - Avoids Radiation
  - Much faster data acquisition
  - Often without anaesthetic in DS
  - Determine effects of new medications
Segmental compliance

- Measure of MPA compliance
- Area curves and pressure curve
- Difficult with current techniques
- New SSFP techniques improve analysis
- Dynamic compliance
Wave reflection

- May be important PH
- -ve wave reflection in PA
- Query positive in PVD
- Significant effect on afterload

Simulations by J.-F. Gerbeau, F. Nobile and Prof. Alfio Quarteroni. Institute of Analysis and Scientific Computing of EPFL, Lausanne (Switzerland)
How do we decide about timing of surgery?

- Assessment of the right time for surgery is difficult: requires assessment of resistance to lung blood flow (Pulmonary resistance)

- How?
  - Clinically – Breathless, large heart
  - Chest X-ray - Large heart, wet lungs
  - Echocardiogram - Large left sided chambers
  - Cardiac Catheter - Pulmonary hypertension study
How do we decide about timing of surgery?

- Pulmonary hypertension study
  - Anaesthetic
  - Cardiac catheter
  - Measure pressures, flows in lungs
  - Measures effects of oxygen and other medicines to increase lung blood flow
- If resistance is not high, and can reverse with medicines, then suitable for surgery
Current Therapies for PH

- Treatment strategies vary
- Congenital Heart Disease
  - Screening for CHD (may need to repeat it later)
  - Early cardiac surgery (3-6 months)
  - Careful of residual defects
  - Ask for cardiac catheterisation if needed, to assess pulmonary resistance + Bronchoscopy
  - Make sure the pressures fall after surgery (by 1 year)
Current Therapies

- Upper airway obstruction
  - NME
  - Sleep studies help decide
  - Tonsils and adenoids removal
  - Night time Oxygen
  - Positive airway pressure (CPAP)
  - Surgery to larynx (aryo-epiglotti- plasty)
Current Therapies

- Structural lung disease
  - Check for lung structure (CT scan of lungs)
  - Repair Diaphragmatic hernia
  - Reduce infection risk
    - Palivizumab for RSVirus
    - Influenza vaccination

- Idiopathic
  - Medicines
Standard Therapies for PH

- Treatment strategies not yet standardised
  - Palliation, generally bad idea
  - Early surgery, ask questions later!
- Anticoagulants, not usually
  - Aspirin, Warfarin
- Oxygen
  - Night time?
  - No change in PA pressure or survival benefit in adults after 2 years of nocturnal O2 therapy (Sandoval et al Am J Resp Crit Care Med 2001)
- Calcium channel blockers
  - Amlodipine
In patients with ASD increases pulmonary blood flow, and decreases pPA \((Swan \ HJC \ et \ al, \ 1959)\).

Pilot study showed that long term treatment with 100% oxygen is well tolerated and improved survival of children with PVD over 5 year period \((Bowyer \ 1986)\).

Improves exercise tolerance in COPD adults \((Dean \ NC \ et \ al, \ 1992)\)

The longer the duration the greater the benefit (min 15 hours a day recommended) \((Salvaterra \ CG \ et \ al \ 1993)\)
**PICU**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pO₂</strong></td>
<td>15-20kPa</td>
</tr>
<tr>
<td><strong>pCO₂</strong></td>
<td>3.5-4.5kPa</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.35-7.45</td>
</tr>
</tbody>
</table>

- Sedate and Paralyse
  - Atracurium (200-600mcg/kg/hr)
- Give analgesia
  - Fentanyl (1-3mcg/kg/hr)
- Inotrope/ vasodilation
  - Milrinone (0.1-0.5mg/kg/min)
  - SNP (1-5mcg/kg/min)
  - Dobutamine (5-20mcg/kg/min)
- “Dry out” lungs
  - Furosemide (1mg/kg/8hr)
Nitric Oxide pathway

ENDOTHELIAL CELL

L-Arginine + Oxygen → NADPH + Mg++ → L-Citrulline + Ca++

NOS

GTP → cGMP → GC → cGMP

SMOOTH MUSCLE CELL

ACh → Ca++

NO → SR → cGMP

RELAXATION
Nitric Oxide pathway

ENDOTHELIAL CELL

Add L-Arg
Add Mg
Add O2

L-Arginine
Oxygen

NOS
PK
G

ACh
Ca++

Add NO

L-Arginine

NADPH

Mg++

L-Citrulline

NO

GTP

cGMP

GC

SR

SMOOTH MUSCLE CELL

RELAXATION

Stimulate GC

SR

Ca++

Add PDEi

GTP

cGMP

SR

S

ve

Nitric Oxide pathway

Add O2
Add L-Arg
Add Mg
Maximal reactivity seen with O$_2$ and NO

PGI only further reduced SVR and SBP
In cardiac catheter lab, Sildenafil more effective than NO at reducing PVRI
- Assists in weaning from NO
  - *Trachte ATS 2005;79:194*

Little evidence yet that Sildenafil reduces PVRI longterm
- *Stocker C Intens Care Med 2003;29:1996*

Increased cGMP activates a kinase resulting in reduced Ca2+ entry But also thought to inhibit Inositol Triphosphate IP3
Riociguat

- New type of DMT
- sGC stimulator
- Only licensed for CTEPH currently
Endothelin is increased in patients with PAH associated with CHD

Bosentan - BREATHE - 5 reduces pulmonary vascular resistance

PVRi (dyn·sec·cm$^{-5}$)
Change from baseline

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

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

- **Ambrisentan**
  - Once a day
  - ETα relative selective
  - Fewer liver side effects
  - Reduced drug-drug interactions

- **Macitentan**
  - Just been released
  - Dual receptor antagonist
  - Evidence of effect on negative feedback loops
Prostanoids

- Prostacyclin – Epoprostenol
  - First reported to reduce PAP in 1980
  - Inhibits platelet aggregation and smooth muscle proliferation
  - Other modalities – treprostinil, inhaled
- Oral prostanoids
  - Selexipag
Fontan circuit

- Single ventricle physiology
- Raised PA resistance, but not pulmonary hypertensive
- Poor PA compliance?
Fontan

- Factors leading to increased PVR
  - Timing and nature of initial palliation
  - Failing ventricle
    - decreased pre-load, increased afterload
  - Lack of pulsatile flow
  - Micro-embolism
  - Arrhythmias
  - Plastic bronchitis
  - Increased ETa + reduced NOS
- Sildenafil and Bonsentan effective in Fontan
Bosentan increases exercise capacity

Eisenmenger Syndrome

- Transplantation
  - HLT superior to LT (Waddell et al J Heart & Lung Transpl 2001) 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 (Stoica et al, Ann Thorac Surg 2001) 51 pts with Eisenmenger HLT
- Similar long-term survival with non-Eisenmenger
- Selection criteria and timing in Down syndrome?
The Future

- Further research into pathophysiology needed
  - Why do some get worse symptoms
  - Role of RV/PA coupling
  - Effects of Airway stiffness
  - Effects on exercise
  - Effects of psychological intervention
- Role of CPET?
- Role of biomarkers BNP/NT proBNP
- QoL, TTCW
The future

- Role of prevention
  - Enhancers of Apoptosis, anti-angiogenesis
  - PDEi vs ERA (ETA+B or ETA?)
- Newer pharmacological strategies
  - Rho Kinase inhibitors, Tyrosine Kinase inhibitors
  - Pyruvate dehydrogenase kinase inhibitors
  - Immunosuppressants, Survivin inhibitors
  - DHEA
  - Vasodilator peptides VIP
  - Statins
  - Prostacyclin analogues
  - Cell cycle inhibitors – rapamycin
  - Imatinib
Thank you