Cyanotic Heart Disease and Eisenmenger’s Syndrome

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Cardiology Resident’s Core Curriculum
Congenital Heart Disease

1. Introduction to congenital heart disease
2. Bicuspid aortic valve disease
3. ASD/PFO
4. VSD
5. AVSD
6. ToF
7. CoA
8. TGA
9. CCTGA and the systemic right ventricle
10. Single ventricles and the Fontan operation
11. Cyanotic heart disease and Eisenmenger syndrome
12. Marfan’s syndrome
13. Lesions of the right heart: pulmonary stenosis and pulmonary atresia, Ebstein’s anomaly
14. Congenital mitral valve disease
15. Arterial anomalies (PDA, aortic arch abnormalities, truncus arteriosus, AP window)

Outline

- Cyanotic Congenital Heart Disease: Approach
- Eisenmenger Syndrome
  - Definition
  - Pathophysiology/Pathology
  - Clinical Presentation
  - Outcome
  - Treatment
    - Surgery
    - Medical
- Management of cyanosis
Cyanosis

- **Def.** bluish color skin/extremities
- Usually apparent once SaO2 < 85%
- Mean capillary concentration of deoxyHgb > 50g/L
  - Anemic patients: may not appear blue despite low SaO2
  - Polycythemic patients: appear blue with higher SaO2
- Also occurs when nonfunctional Hgb present
  - Methemoglobin
  - Sulphhemoglobin

Cyanosis

- **Peripheral**
  - Slowing of blood flow results in increased oxygen extraction
  - Results from vasoconstriction: cold, shock, CHF, PVD
- **Central**
  - Increased deoxyHgb: marked reduction in arterial oxygen saturation
  - Decreased inhaled oxygen: altitude
  - Impaired pulmonary function
    - Shunting
    - Intracardiac
    - Great vessel
    - Intrapulmonary: AVM, liver disease
  - Increased abnormal Hgb pigments

SaO2
Cyanotic Heart Disease

- Right to left shunting at some level
- Either due to
  - Too much pulmonary blood flow: Eisenmengers
  - Too little pulmonary blood flow:
    - Pulmonary stenosis/atria/pulmonary artery hypoplasia
    - tricuspid atresia
      - Usually associated with a septal defect

Cyanotic Heart Disease: Treatment

- General approach: increase pulmonary blood flow via a surgically created shunt
  - As palliation prior to complete repair
  - Sometimes is only long-term option
  - Blalock-Taussig: subclavian → PA
  - Classic – direct turn-down of subclavian
  - Modified – with connecting vortex tube
  - Waterston’s: Ascending aorta to RPA
  - Port’s: Descending aorta to LPA
  - Central: Ascending aorta to PA with connecting vortex tube
  - Glenn: SVC → PA

Cyanotic Heart Disease: Inadequate Pulmonary Blood Flow

- Tetralogy of Fallot: most common cyanotic CHD
- TGA: most common cause of neonatal cyanosis
- Conditions with obstructed pulmonary blood flow and septal defects
  - CCTGA
  - Double outlet right ventricle
  - Single ventricle forms: DILV, TA,
    - Pulmonary stenosis + VSD, ASD, PFO
  - Pulmonary atresia +/- VSD

- SVC → P
Eisenmenger’s Syndrome

- Reference
  - Diagnosis and Management of Adult Congenital Heart Disease, Eisenmenger’s syndrome chapter.
  - Canadian Guidelines of Management of CHD, 2009

Victor Eisenmenger

- 1864–1932
- Viennese laryngologist
- Personal physician to Archduke Francis Ferdinand
- Described a 32 y.o. cyanotic patient dying of hemoptysis.
  - Autopsy showed a VSD and no pulmonary stenosis
  - RV dilatation and hypertrophy
  - Pulmonary atherosclerosis PE and pulmonary infarction

1. Define Eisenmenger Syndrome.
Eisenmenger Syndrome

- Pulmonary hypertension due to high pulmonary vascular resistance with a reversed or bidirectional shunt

  - Eisenmenger Complex: Refers to the above due to a ventricular septal defect (as originally described by Eisenmenger)

  - Eisenmenger Syndrome/Physiology: Pulmonary vascular disease and from any large communication between the systemic and pulmonary circulations

2. List 3 defects other than a VSD that can lead to Eisenmenger's physiology

Defects that may cause Eisenmenger Physiology

- VSD > 1.5 cm
  - 3% of pts. with VSD < 1.5 cm
  - 50% of pts. with VSD > 1.5 cm
- ASD > 3 cm
  - 10% of large ASD
- AVSD, most if untreated (unless small primum ASD)
- PDA
  - 10% of moderate or large PDA
- Truncus arteriosus: most patients
- Aortopulmonary window > 0.7 cm
- MAPCAS (multiple, large)
- Complex congenital heart disease (usu. Assoc. with a large VSD)
- Transposition of the great arteries
- Univentricular hearts
- Surgically created anastomoses
- Potts
- Waterston
Eisenmenger’s Syndrome: Epidemiology

- <5% of patients in adult congenital clinics
- Incidence/prevalence decreasing due to earlier diagnosis and treatment of CHD
- Recent Canadian data:
  - 250 Eisenmenger patients in Canada
  - Up to 40% of Down’s patient with CHD have Eisenmenger’s syndrome

Pathophysiology of PHT in Congenital Heart Disease

Pathology of PHT: Heath–Edwards Classification

<table>
<thead>
<tr>
<th>TABLE 67.5: HEALTH-EDWARDS CLASSIFICATION OF PULMONARY VASCULAR OBSTRUCTIVE DISEASE</th>
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<tbody>
<tr>
<td>Grade</td>
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<tr>
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<tr>
<td>1</td>
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<td>2</td>
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<td>3</td>
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</table>
Pulmonary HTN: NO/Endothelin

- Strong correlation between ET-1 expression and PVR in Eisenmenger syndrome
- NO stimulates P shear, increases flow
- ET-1↓
- NO synthesis decreases ET-1 expression
- NO regulates ET-1 secretion
- ET-1↓ → ↓ ET-1 expression
- NO degradation increases ET-1 expression

Phosphodiesterases
- Degrade cGMP

Pulmonary HTN: Prostacyclin

- Synthesized from cyclooxygenase in vascular endothelium
  - Production impaired in PHTN
- Potent pulmonary vasodilator and anti-platelet aggregating properties
- Improves balance between ET1 release and clearance, increases VEGF levels, restores normal hemostasis

Pulmonary HTN: Hypercoagulabilty

- Endothelial dysfunction results in a pro-thrombotic state
  - Relative deficiency of antithrombotic molecules: prostacyclin, NO
  - Slowing of blood flow secondary to luminal narrowing enhances thrombogenicity
3. Patients with Eisenmenger's syndrome due to the following defects present as infants, children or adults. Why?
   A. ASD
   B. PDA
   C. VSD

Eisenmengers Syndrome:
Presentation
- ASD: 90% present during adulthood
- PDA and VSD: 80% present during infancy / first 2 years of life
- The pulmonary blood flow in VSD and PDA is occurring at near systemic pressures
- The pulmonary blood in ASD is by the lower pressure right ventricle

Eisenmenger's Syndrome:
Clinical Course
- The shunt produces congestive heart failure in infancy due to left to right shunting (substantial pulmonary blood flow)
- Eventually symptoms of pulmonary congestion abate (pulmonary vascular resistance increases)
  - Patient may symptomatically improve from less congestion
  - Mild exertional dyspnea and fatigues in childhood
- As pulmonary vascular resistance further increases, shunt reverses and becomes right to left leading to cyanosis
Eisenmenger: Presentation

- Symptoms
  - Breathlessness
  - Average VO2 12 mL/kg/min
  - >90% are NYHA > II
  - Chest pain
  - Syncope
- Signs

List 5 physical findings in Eisenmenger's syndrome.

Eisenmenger's Syndrome: Physical Examination

- Central cyanosis and clubbing of the nail bed
- PDA → lower limb cyanosis
- Pulses: diminished or normal aortic pulse
- Precordium: right parasternal heave, palpable pulmonary valve closure
- Auscultation:
  - Pulmonary ejection click from dilated main PA
  - Loud pulmonic component of S2, S4
  - S2 may be single (VSD) or widely split (ASD)
  - Graham-Steel murmur (high-pitched decrescendo murmur of MR)
  - Holosystolic murmur of TR, MR
  - Murmur related to VSD or PDA usually not present
- Abdominal tenderness, hepatic congestion
- Peripheral edema
Eisenmenger's Syndrome: ECG

Large muscular VSD

Eisenmenger's Syndrome: CXR

VSD

AVSD

Eisenmenger's Syndrome: VSD

Eisenmenger's Syndrome: CXR

- Prominent dilated central PA
  - Pruning of peripheral vascular markings not common or occurs late
- Calcification of PA may be present
- VSD usually have normal or minimally increased cardiothoracic ratio
  - Enlarged RV can occur late
- ASD usually have cardiomegaly due to dilatation of RV and RA
- PDA usually have enlarged aorta
  - Ductal calcification may be present

Eisenmenger's Syndrome: Echo
Eisenmenger's Syndrome: Long term Prognosis

- Prognosis for Eisenmenger’s syndrome is substantially better than prognosis of PPH

Survival rate:
- ES: 77% at 3 years
- PPH: 35% at 3 years

Median age at death
- ES: 53 years
- ~20 years less than expected

Am J Cardio 1999;84:677-681
Eur Heart J 2006;27:1731-42
Eisenmenger's Syndrome: Factors Affecting Prognosis
- Age
- Poor NYHA class
- Syncope
- Complex CHD
- Arrhythmias
- Low oxygen saturation
- High SCR, uric acid levels
- RV dysfunction
- ECG: RVH, QRS duration
- Down's syndrome

7. When is Surgery an option for Eisenmenger's syndrome?

Treatment of Eisenmenger's Syndrome: Surgery
- If the underlying defect is discovered before irreversible pulmonary vascular disease is established, surgical correction can be performed
  - Usually < 2 years of age for AVSD, VSD, PDA, AP window
  - Potentially older ages for larger ASD's
  - Demonstrable pulmonary artery reactivity and/or L→R shunt > 1.5:1
  - Surgical options:
    - PA banding
    - Primary intracardiac repair
- After irreversible pulmonary vascular disease occurs, closure of the defect will result in right heart failure and high operative mortality/death
  - Heart/lung transplant becomes the only surgical option
Eisenmenger's Syndrome: Medical Therapy

- Main principle of therapy is supportive care: avoidance of complications, medications and procedures that are potentially harmful and destabilize the physiology
  - Avoidance of dehydration
  - Avoidance of vasodilatation
  - Noncardiac surgery/anaesthesia are major risks
  - Strenuous exercise
  - Pregnancy
  - Avoidance of air embolism: air filters for IV's

- Management of pulmonary hypertension

Eisenmenger's Syndrome: Management of Noncardiac Surgery

- Risks:
  - Vasodilatation from anaesthetic: RV → LV shunt
  - Vasoconstriction: depressed ventricular function
  - Fluid shifts: volume depletion
  - Increased thrombosis: PE
  - Increased bleeding
  - Arrhythmias
  - Mortality of surgery:
    - Old studies: 50%
    - Recent: 7% for noncardiac surgery

- Management:
  - Experienced cardiac anaesthetist
  - Careful monitoring
  - Local anaesthetic when possible, otherwise GA
  - Consider preop phlebotomy if Hct > 45%?
  - Post-op hemodynamic instability may respond to inhaled NO + sildenafil

Eisenmenger's Syndrome: Pregnancy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients, n</td>
<td>70</td>
</tr>
<tr>
<td>Pregnancies, n</td>
<td>98</td>
</tr>
<tr>
<td>Overall mortality rate, n (%)</td>
<td>9/70 (14)</td>
</tr>
<tr>
<td>Mortality rate by cardiac defect, n (%)</td>
<td>6/16 (38)</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>6/16 (38)</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>16/40 (40)</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>0/19 (0)</td>
</tr>
<tr>
<td>Mortality rate by mode of delivery, n (%)</td>
<td>20/90 (33)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>20/90 (33)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>7/15 (47)</td>
</tr>
</tbody>
</table>

* Data obtained from references 75–84.

Pregnancy is contraindicated due to high risk of maternal and fetal complications.

What specific medical therapy is available for the pulmonary hypertension associated with Eisenmenger’s syndrome?

Eisenmenger’s Syndrome: Disease Targeting Therapy

- Prostacyclins
  - Benefits:
    - Improve functional capacity, oxygen sats and PAP
  - Risks:
    - IV administration often results in systemic vasodilation
    - Risk of air embolism
    - Oral (beroprost) or SC (treprostinil) potentially preferable

Eisenmenger’s Syndrome: Disease Targeting Therapy

- Pulmonary vasodilators
  - Phosphodiesterase Inhibitors
  - Endothelin Antagonists
    - Bosentan:
      - Safe, improve exercise capacity in PAH
      - Increasing evidence of altered disease course and improved prognosis
      - No RCT proof of reduced mortality
List 5 complications of cyanosis?

Complications of Cyanosis

- Hemodynamic abnormalities
- Cholelithiasis
- Eisenmenger syndrome
- Cyanotic CHD
- Hypertrophic osteoarthropathy
- Hyperviscosity
- Cerebrovascular accidents
- Hemoptysis
- Renal dysfunction
- Infections

Complications of Cyanosis: Hyperviscosity

- The strongest determinant of viscosity is Hct
  - Increased in cyanosis due to secondary erythrocytosis
- Hyperviscosity symptoms: fatigue, headache, faintness, dizziness, lightheadedness, altered mentation, blurred or double vision, paresthesias of fingers/lips/toes, tinnitus, myalgias, restless legs
  - Usually not present until Hct > 65%
Complications of Cyanosis: Thrombosis

- Mechanisms:
  - Hypercoagulable/prothrombotic state in pulmonary vascular bed
  - Hyperviscosity
  - Stasis of blood from low cardiac output, abnormal pulmonary vascular architecture
  - Atrial fibrillation/flutter: anticoagulation justified

- Manifestations:
  - Pulmonary arterial in-situ thrombosis
    - Prevalence: 21% of Eisenmenger’s syndrome
    - Anticoagulation controversial: probably not justified
  - Other emboli
    - Cerebrovascular events

Cerebrovascular Events

- Incidence:
  - 1.4%
  - 1/100 patient years

- Risk factors for CVA:
  - Hypertension
  - Atrial Fibrillation
  - Phlebotomy
  - Microangiopathy/iron deficiency

- Prevention of CV events:
  - Avoid transvenous pacemaker
  - Avoid air bubbles
    - IV lines: air filter
  - May lead to brain abscess

Complications of Cyanosis: Iron Deficiency

- Prevalence: >1/3 of Eisenmenger’s syndrome

- Etiology:
  - Excessive erythropoiesis
  - Inappropriate phlebotomy

- Consequence: increased stroke risk
  - Less deformable, more rigid RBC’s
  - Reduced cerebral oxygenation

- Iron replacement
  - Oral: ferrous sulfate 300 mg daily.
  - IV: for patients intolerant of PO
Complications of Cyanosis: Bleeding

- Mechanisms:
  - Thrombocytopenia due to peripheral consumption or destruction
  - Thrombocytopenia
  - Abnormalities of clotting factors
  - Vascular dilatation

- Manifestations:
  - Usually minor hemorrhage: dental epistaxis, menorrhagia
  - Traumatic bleeding
  - Major hemorrhage: GI bleeding, cerebral hemorrhage
    (uncommon), severe hemoptysis

Complications of Cyanosis: Rheumatologic

- Hyperuricemia and gout
- Hypertrophic pulmonary osteoarthropathy

Complications of Cyanosis: Renal and GI Dysfunction

- Renal
  - Hyperuricemia and urate nephropathy
  - Proteinuria
  - Nephrotic syndrome
  - Renal failure

- GI
  - Excess heme breakdown \(\rightarrow\) increased unconjugated bilirubin (insoluble)
  - Gallstones containing calcium bilirubinate
  - Cholecystitis
  - Hepatic congestion
Complications of Cyanosis: Infection
- Endocarditis risk is elevated
  - Lifetime risk may be 13%
- May be complicated by cerebral abscess
- Vigilence
- Endocarditis prophylaxis

Cyanotic heart disease: Assessment
- History: symptoms, hyperviscosity
- Physical exam including SaO₂
- ECG
- Echo
- Assess functional capacity: 6 minute walk
- Bloodwork: CBC and smear, serum ferritin, transferrin saturation, uric acid, lytes, Cr, (INR, aPTT), LFT’s
  - Laboratory must adjust amount of citrate for Hct in blue top tube for accurate coagulation parameters
- Imaging of pulmonary vascular bed, RV
  - CT or MRI

What are the indications for phlebotomy in Eisenmenger’s syndrome/Cyanotic heart disease?
Cyanotic Heart Disease: Phlebotomy

- Often over-utilized, resulting in iron deficiency
- Indications
  - Not based on Hct levels
  - Levels >70% may be well tolerated
  - Moderate to severe hyperviscosity symptoms
  - Symptom should improve within 24 hours
  - If not, consider iron deficiency
  - Preoperative to improve hemostasis
  - May correct thrombocytopenia, platelet dysfunction, and other coagulation abnormalities
- Method: withdraw 250–500 mL blood
  - No more than 4x/year
  - Replace 750–1000 mL NS

Phlebotomy? Y/N

- Dehydration?
  - Yes → Rehydration
  - No → Continue
- Undergoing noncardiac surgery?
  - Yes → Controversial
  - No → No phlebotomy
- Hyperviscosity symptoms?
  - Yes → Normocytic
    - Yes → Isovolumic phlebotomy
    - No → No phlebotomy
  - No → Microcytic
    - Yes → Isovolumic phlebotomy
      - (500 mL)
    - No → No phlebotomy

Aside from the cyanotic complications, list other cardiac complications of Eisenmenger’s syndrome/cyanotic heart disease

Cardiac Complications

- Pulmonary artery complications: aneurysms, thrombi, rupture
- Arrhythmias:
  - Aflutter, fib: 35%
  - Rarely VT
  - Bradyarrhythmias: use epicardial pacing system
- Progressive valvular disease
- CHF: RVH and LVH
- Sudden death: accounts for 50% of deaths
- No experience with AICD's
- Coronary arteries: dilated and tortuous
- Seldom atherosclerotic

Hemoptysis

<table>
<thead>
<tr>
<th>Cause</th>
<th>Therapy</th>
</tr>
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<tbody>
<tr>
<td>Bronchitis</td>
<td>Antimicrobial therapy; cough suppression</td>
</tr>
<tr>
<td>Pulmonary embolization</td>
<td>Anticoagulation, inferior vena cava filter</td>
</tr>
<tr>
<td>Bleeding diathesis</td>
<td>Platelet or fresh frozen plasma infusion;</td>
</tr>
<tr>
<td></td>
<td>desmopresin infusion</td>
</tr>
<tr>
<td>Rupture of aortopulmonary</td>
<td>Percutaneous catheter embolization</td>
</tr>
<tr>
<td>collaterals</td>
<td></td>
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<tr>
<td>Pulmonary artery or</td>
<td>Balloon tamponade; surgical repair;</td>
</tr>
<tr>
<td>arteriole rupture</td>
<td>pulmonary artery ligation;</td>
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<tr>
<td></td>
<td>embolization of arteriole with</td>
</tr>
<tr>
<td></td>
<td>percutaneous catheter</td>
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Hemoptysis

- Incidence increases with age: 11-100%
- Management:
  - Admit to hospital for bed rest
  - Cough suppression
  - Bronchoscopy is seldom useful; CXR and CT chest are important investigations
  - D/C ASA, NSAIDs, anticoagulants
  - If platelets < 100, consider plt transfusion
  - Volume and iron replacement
  - Most episodes are self limiting; uncommon cause of death; not predictive of mortality
Summary

- Cyanosis can be either from too little or too much pulmonary blood flow, leading to Eisenmenger’s syndrome
- Cyanosis has multisystem consequences
- ES: Pulmonary hypertension at a systemic level due to high pulmonary vascular resistance with a reversed or bidirectional shunt
  - Rare, decreasing in incidence and prevalence
- Main principle of therapy is supportive care: avoidance of events that destabilize the physiology
- New pulmonary hypertension directed therapies hold some promise, but so far have just been shown to improve functional capacity, not prognosis.