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What’s special in Eisenmenger syndrome?

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What’s special in Eisenmenger syndrome... as compared to other PAH patients...

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Shunts...for the better and for the worse...
Shunts…for the better and for the worse…

For the better

For the worse

Benza et al, Chest 2012
Background

1897: V. Eisenmenger described man with cyanosis and VSD.

50ies: Cyanosis resulted from bidirectionnal shunt or reversed shunt caused by pulmonary hypertension.

1950: P. Wood: position of the shunt was of little relevance when it comes to physiology.
Egalisation of pulmonary and systemic pressures

Fig. 8.—Identical systolic pressures in the brachial artery, pulmonary artery, and right ventricle in a case of Eisenmenger’s complex. Note the normal right atrial pressure pulse.

Wood P, BMJ 1958
Evolution to Eisenmenger

- Left-to-right shunt
- Increased pulmonary blood flow (shear stress/circumferential stretch)
- Endothelial dysfunction and vascular remodeling
  - Smooth muscle cell proliferation, increase in extracellular matrix, intravascular thrombosis
  - Increase in PVR
- Inverted shunt: right-to-left
- Cyanosis (Eisenmenger syndrome)

Figure 1: Key Stages in the Development of Eisenmenger Syndrome

Reproduced, with permission, from Vongpatanasin et al. (5). PVR = pulmonary vascular resistance.

Beghetti, Galié, JACC 2009
Prevalence

Concor registry: 5970 adult patients with CHD, 86 centers

Eisenmenger: 1.1% of the GUCH population

### Baseline characteristics of patients with a septal defect and PAH

<table>
<thead>
<tr>
<th>Underlying diagnosis (%)</th>
<th>Eisenmenger syndrome (n=65)</th>
<th>Non-Eisenmenger</th>
<th>Total (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not closed (n=17)</td>
<td>Closed defect (n=30)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40%</td>
<td>41%</td>
<td>57 (23–80)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>36 (18–70)</td>
<td>57 (23–80)</td>
<td>37 (21–81)</td>
</tr>
</tbody>
</table>

**VSD**: 31 (48)

**ASD II**: 8 (12)

**ASD I**: 3 (5)

**AVSD**: 23 (35)

**Mean PAP, mm Hg (±SD)**

<table>
<thead>
<tr>
<th>NYHA classification (%)</th>
<th>Eisenmenger syndrome (n=65)</th>
<th>Non-Eisenmenger</th>
<th>Total (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6 (12)</td>
<td>4 (29)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>II</td>
<td>15 (29)</td>
<td>8 (57)</td>
<td>8 (30)</td>
</tr>
<tr>
<td>III</td>
<td>28 (54)</td>
<td>0 (0)</td>
<td>6 (22)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (6)</td>
<td>2 (14)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Duffels MG et al, Int J Cardiol 2007
Functional capacity

Diller et al, Circulation 2005

Worse functional capacity of all CHD

Survival

Diller GP et al. Eur Heart J 2006

Diller et all, Heart 2014
Shunts...for the better...

Benza et al, Chest 2012

...And for the worse...

Cyanosis

Erythrocytosis

Multisystemic disease

Complications:

hyperviscosity symptoms; bleeding and thrombosis; cerebrovascular accident; infectious complications;...
Secondary erythrocytosis

- Physiological adaptation
- Essential for tissue oxygenation
- Chronic cyanosis $\rightarrow$ *appropriate* renal production of EPO $\rightarrow$ erythropoiesis and secondary erythrocytosis $= isolated$ increase in red blood cell mass
Not only number…but morphology of RBC

Iron deficient RBC:
- less flexible, less deformable
- More susceptible to lysis
- Tend to aggregate
- ? increased blood viscosity debated

Oechslin E, Int. J. Cardiol 2004
Iron: a vital ion

In iron replete patients, inversed relation between resting saturation and hemoglobin.
Avoid anemia

Essential measurement
Hemoglobin
Hematocrit
MCV
Serum ferritin

Iron replacement therapy
Ferritin < 20mg/l or
Ferritin < 50mg/l AND transferrin saturation < 20%

Oechslin E, Int. J. Cardiol. 2004
Iron replacement therapy

- 25 iron deficient cyanotic patients
- Oral iron replacement therapy x 3 months
- 6MWT, QoL score and Vo2 max at baseline and after 3 months
- Significant increase in 6MWT and QoL, no change in Vo2 max.

Tay et al, Int. J. Cardiol 2011
No phlebotomy…except

- moderate to severe hyperviscosity symptoms
- In absence of iron deficiency
- In absence of dehydration

Fig. 1. Management of hyperviscosity symptoms.

Oechslin E, Int. J. Cardiol. 2004
Hyperviscosity symptoms

- Headache
- Faintness, dizziness, lightheadness
- Slow mentation, irritability
- Visual disturbance
- Paresthesia
- Tinnitus
- Fatigue, lethargy
- Myalgias
- Restless legs

Oeschlin 2004; Perloff 1988
Bleeding and thrombosis...

...The BIG dilemma
Hemostatic Abnormalities

Platelets:
• Decreased production and reduced platelets survival → thrombocytopenia
• Decreased function → thrombasthenia

Coagulation parameters
• Vit K dependent clotting factor and factor V reduced
• Increased fibrinolytic activity
• Depletion of vWF

Vascular factors
• Endothelial dysfunction

INCREASED BLEEDING RISK. NO PROTECTION AGAINST THROMBOSIS

Oechslin et al, Current Cardiol Rev. 2010
Bleeding

Minor bleeding:
dental bleeding, epistaxis, easy bruising, menorrhagia

Hemoptysis:
Most common major bleeding event
Incidence: 11-100% (!) increasing with age
Alarming symptom for the patient (…and the doctor)
Uncommon mode of death \(^1\); \(^2\)
Not predictive of mortality \(^1\)

\(^1\) Cantor W et al, Am J Cardiol 1999  \(^2\) Oechslin et al Cur. Cardiol. Rev. 2010
Bleeding: no change in survival

188 Eisenmenger patients
31 years of follow-up
20.2% : at least 1 episode of hemoptysis
Risk factor for hemoptysis
➢ Venesection

Thrombosis: cerebrovascular accident

23153 CHD patients from 5 centers
458 (2%) patients with CVA
Eisenmenger 2% of the population but 5.1% of CVA

Hoffmann A et al, Heart 2010

<p>| Table 1: Patients with CVA and total ACHD population in various diagnostic categories |
|----------------------------------|------------------------|------------------------------------------------|</p>
<table>
<thead>
<tr>
<th><strong>Number</strong></th>
<th><strong>Total population</strong></th>
<th><strong>CVA cases</strong></th>
<th><strong>p Value (χ² test between cases and total population)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age at follow-up (range)</strong></td>
<td>36.4 (16–91)</td>
<td>45.4 (14–86)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mean age at first CVA (range)</strong></td>
<td>–</td>
<td>37.0 (0.5–85)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>11,433 (49.4 % of ACHD population)</td>
<td>228 (49.8 % of CVA cases)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Closed ASD/VSD</strong></td>
<td>4035</td>
<td>57 (1.4)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td><strong>Open ASD</strong></td>
<td>2351</td>
<td>93 (4.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Fallot’s tetralogy</strong></td>
<td>2196</td>
<td>52 (2.4)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>TGA atrial switch</strong></td>
<td>690</td>
<td>22 (3.2)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td><strong>Coarctation</strong></td>
<td>2027</td>
<td>41 (2.0)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Fontan</strong></td>
<td>484</td>
<td>20 (4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Eisenmenger</strong></td>
<td>467</td>
<td>24 (5.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Cyanotic (non-Eisenmenger)</strong></td>
<td>215</td>
<td>50 (23.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Mechanical valve prostheses</strong></td>
<td>882</td>
<td>29 (3.3)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>10,688</td>
<td>70 (0.7)</td>
<td>-----------</td>
</tr>
</tbody>
</table>

Results are shown as the percentage of the total population (if not stated otherwise). ACHD, adults with congenital heart disease; ASD, atrial septal defect; CVA, cerebrovascular accident; TGA, transposition of the great arteries; VSD ventricular septal defect.
Thrombosis: cerebrovascular accident

CVA more prevalent in Eisenmenger

Highest risk in cyanotic patients attributed to the right to left shunt and systemic emboli

→ Filters on IV lines

Hoffmann A et al, Heart 2010
Thrombosis: risk of stroke

- 112 cyanotic patients
- Strict selection and exclusion criteria
- Patients with added risk factors (AF,…) excluded
- 2 groups: compensated/decompensated erythrocytosis with phlebotomy
- No CVA
- *Phlebotomy does not protect*

- 162 cyanotic patients
- 13.6% with CVA
- No differences between 2 groups in Hb/Hct
- *Iron deficiency and phlebotomy strongly associated with CVA*

Perloff, Marelli et al, Circulation 1993
Ammash and Warnes JACC 1996
Infectious complications: cerebral abscess

Right to left shunt $\rightarrow$ blood is not «filtered» in the lungs

Increased viscosity $\rightarrow$ focal area of ischemia = nidus for bacteria

Lumbiganon et al, 2013
Infectious complications: cerebral abscess

More frequent in children
Symptoms might be very progressive and/or atypical
Cyanotic CHD: major predisposing factor
Mortality decreased with cerebral imaging and ttt

Infectious complications: infectious endocarditis

Increased prevalence in unrepaired cyanotic CHD: 8.2/1000pts-years\(^1\) (N= 1.5-6/100000pt/y)

Predictors of IE in children

- 34279 children with CHD
- 2196 with cyanotic defect
- 136 cases of endocarditis
- Cyanotic CHD: major risk factor

Rushani et al, Circulation 2013
Other complications

- *Gout*, related to increased RBC/Hb turnover and decreased renal clearance
- *Cholelithiasis* due to increased turnover of heme, leading to increased unconjugated bilirubin
- *Hypertrophic osteopathy*: local cell proliferation, periostitis. Etiology unknown
## Risk reduction strategies

<table>
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<th>Table 4</th>
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<td>Risk reduction strategies</td>
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</table>

- Avoidance of inappropriate (prophylactic) phlebotomies
- Avoidance and treatment of anemia (caveat: cyanotic patients require a higher hemoglobin level than healthy adults!)
- Avoidance of iron deficiency
- Avoidance of dehydration
- Avoidance of anti-inflammatory drugs/routine oral anticoagulation
- Avoidance of smoking
- Avoidance of air embolism (paradoxical air embolism) by the use of an air filter in case of an intravenous line
- Avoidance of infectious diseases (annual flu shot, pneumovax vaccination)
Take home message

- Better survival than other PH
- Multisystemic disorder
- Iron: a vital ion
- Bleeding-thrombosis dilemma
- Hematocrit not related to CVA
- Phlebotomy per se not indicated, only in symptomatic patient in absence of dehydratation or iron deficiency
Thank you for your attention