Survival and Predictors of Death in Eisenmenger Syndrome


Cardiology, Second University of Naples - Monaldi Hospital, Naples, Italy
Clinical classification of congenital systemic-to-pulmonary shunts associated with PAH

- **Eisenmenger syndrome**: Large defects and reversed (pulmonary-to-systemic) or bidirectional shunts (eritrocytosis, cyanosis: O2 sat <90%).

- **PAH associated to systemic-to-pulmonary shunts**: Moderate to large systemic-to-pulmonary shunts (largely prevalent) (O2 sat >90%).

- **PAH con small defects**: similar to idiopathic PAH.

- Pulmonary arterial hypertension **after corrective cardiac surgery**.
Epidemiology

Euro Heart Survey registry: 1897 GUCH patients, **28%** PAH, **7.1%** Eisenmenger syndrome (ES)\(^1\).

Dutch registry on CHD: 1824 GUCH patients, **6.1%** PAH, **3.5%** (ES)\(^2\).

PAH and CHD prevalence in western countries: **1.6 - 12.5 / 1 milion of adults** (25-50% ES)\(^3\).

1 - Engelfriet et al, Heart 2007;93:682-7
2 - Duffels et al, Int J Cradiol 2007;120:198-204
3 - Galiè et al, Drugs 2008;68:1049-66
Survival in PAH

Percent Survival

Years

CHD
CVD
HIV
IPAH
Portopulm

Mc Laughlin VV, CHEST 2004; 126:78S–92S
Why the survival is better in Eisenmenger Patients than IPAH Patients?

“The hearts of patients with Eisenmenger syndrome are more like normal fetal hearts than normal adult hearts”

FIGURE 1. Nonrestrictive hemodynamics. (A) Schematic diagram depicting hemodynamics in the normal fetal heart. Note the equal right and left ventricular systolic pressure secondary to the nonrestrictive ductus arteriosus (from Rudolph, with permission*). (B) Pressure tracings from the aorta and pulmonary artery of a 20-year-old woman with a nonrestrictive patent ductus arteriosus and Eisenmenger syndrome. (C) Right and left ventricular pressure tracings from a 40-year-old man with a nonrestrictive perimembranous ventricular septal defect and Eisenmenger syndrome. (D) Right ventricular and aortic pressure tracings from a 25-year-old woman with truncus arteriosus and Eisenmenger syndrome.

FIGURE 4. Wall thickness and age. Right and left ventricular wall thickness is depicted in fetuses with normal hearts, infants with nonrestrictive ventricular septal defects and left-to-right shunt (pre-Eisenmenger phase), and adolescents and adults of various ages with nonrestrictive post-tricuspid defects and Eisenmenger syndrome. The bars and error bars represent mean values and 1 SD, respectively.

Severe Pulmonary Hypertension Without Right Ventricular Failure: The Unique Hearts of Patients With Eisenmenger Syndrome

William E. Hopkins, MD, and Alan D. Waggoner, MD, FACC

[Am J Cardiol 2002;89:34–38]
Right Ventricle in Eisenmenger Syndrome

(C and D). The right ventricle in the patient with idiopathic pulmonary hypertension is dilated at end-diastole, and the septum curves leftwards at early diastole. In the Eisenmenger patient, the interventricular septum maintains its rightward curvature throughout diastole and systole.

Diller et al, Eur Heart J 2007; Supplement H:H54–H60
Survival in pz with Eisenmenger Syndrome

Model of chronic adaptation: right ventricular function in Eisenmenger syndrome

Gerhard-Paul Diller¹,², Konstantinos Dimopoulos¹,², Henryk Kafka³, Siew Yen Ho⁴, and Michael A. Gatzoulis¹,²*

Eur Heart J 2007; Supplement H:H54–H60

“... cohort of 171 Eisenmenger patients followed up at our tertiary centre with a 5 year survival rate of 88%, in clear contrast to patients with idiopathic PAH who have a devastating short-term prognosis and a reported median survival of 2.8 years”.

When compared with healthy individuals, median survival was reduced by 20 years in Eisenmenger patients and was worst in those with complex lesions.
Objective

To assess, in a large centre for adult with congenital heart disease, Eisenmenger patients survival and identify predictors of death in this population.
Methods

All Eisenmenger patients under follow-up at our centre since 2000 (n. 51, mean age 37±16 years) were included. Data including symptoms of heart failure (HF), functional class (NYHA), medication, laboratory, six minutes walking test (6MWT) and haemodynamic parameters were considered.
Survival in Eisenmenger Syndrome

Pts tot. 51

Survival at 68±18 months: 84%

Causes of death
- 4 sudden death
- 4 refractory heart failure

Mean age at death: 28±12 yrs
Avoid pregnancy (I-C)
Influenza and pneumococcal immunization (I-C)
Supervised rehabilitation (IIa-B)
Psycho-social support (IIa-C)
Avoid excessive physical activity (III-C)

General measures and supportive therapy
Expert Referral (I-C)

Acute vasoreactivity test
(I-C for IPAH)
(IIb-C for APAH)

VASOREACTIVE

NON VASOREACTIVE

WHO-FC I-III
CCB (I-C)

Sustained response (WHO-FC I-II)

YES

Continued CCB

NO

Initial Therapy

<table>
<thead>
<tr>
<th>Recommendation-Evidence</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-A</td>
<td>Ambrisentan, Bosentan, Sildenafil</td>
<td>Ambrisentan, Bosentan, Sitaxentan, Sildenafil</td>
<td>Epoprostenol i.v.</td>
</tr>
<tr>
<td>I-B</td>
<td>Tadalafil†</td>
<td>Tadalafil†</td>
<td>Treprostinil s.c., inhaled†</td>
</tr>
<tr>
<td>IIa-C</td>
<td>Sitaxentan</td>
<td>Iloprost i.v., Treprostinil i.v.</td>
<td>Ambrisentan, Bosentan, Sitaxentan, Sildenafil, Tadalafil†, Iloprost inhaled, and i.v. Treprostinil s.c., i.v., inhaled† Initial Combination Therapy</td>
</tr>
<tr>
<td>IIb-B</td>
<td>Beraprost</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inadequate clinical response

Sequential combination therapy (IIa-B) §

ERA
Prostanoids + PDE-5 I
Parameters for assessing disease severity, stability and prognosis in PAH

<table>
<thead>
<tr>
<th>Better prognosis</th>
<th>Determinants of prognosis</th>
<th>Worse prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Slow</td>
<td>Rate of progression of symptoms</td>
<td>Rapid</td>
</tr>
<tr>
<td>No</td>
<td>Syncope</td>
<td>Yes</td>
</tr>
<tr>
<td>I, II</td>
<td>WHO-FC</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt;500 m)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6MWT</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Peak O&lt;sub&gt;2&lt;/sub&gt; consumption &gt;15 mL/min/kg</td>
<td>Cardio-pulmonary exercise testing</td>
<td>Peak O&lt;sub&gt;2&lt;/sub&gt; consumption &lt;12 mL/min/kg</td>
</tr>
<tr>
<td>Normal or near-normal</td>
<td>BNP/NT-proBNP plasma levels</td>
<td>Very elevated and rising</td>
</tr>
<tr>
<td>No pericardial effusion TAPSE&lt;sup&gt;b&lt;/sup&gt; &gt;2.0 cm</td>
<td>Echocardiographic findings&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pericardial effusion TAPSE&lt;sup&gt;b&lt;/sup&gt; &lt;1.5 cm</td>
</tr>
<tr>
<td>RAP &lt;8 mmHg and CI &gt;2.5 L/min/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Haemodynamics</td>
<td>RAP &gt;15 mmHg or CI &lt;2.0 L/min/m&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ESC/ERS Guidelines 2009

Stable and Satisfactory

Unstable and deteriorating

Stable and not Satisfactory
Results at univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
<th>Died</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>38±17</td>
<td>28±12</td>
<td>ns</td>
</tr>
<tr>
<td><strong>NYHA</strong></td>
<td>2,9±0,4</td>
<td>3,4±0,5</td>
<td>p&lt;0.005</td>
</tr>
<tr>
<td><strong>HF signs</strong></td>
<td>14 (27,4%)</td>
<td>7 (87,5%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Clin. Worsen.</strong></td>
<td>5 (9,8%)</td>
<td>4 (50%)</td>
<td>p&lt;0.005</td>
</tr>
<tr>
<td><strong>Arrhytm</strong></td>
<td>4 (7,8%)</td>
<td>2 (25%)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Prostanoids</strong></td>
<td>3 (5,9%)</td>
<td>3 (37,5%)</td>
<td>p&lt;0.005</td>
</tr>
</tbody>
</table>
### Results at univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
<th>Died</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT mt.</td>
<td>326±92</td>
<td>273±80</td>
<td>ns</td>
</tr>
<tr>
<td>6MWT %</td>
<td>74±24</td>
<td>52±15</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Borg</td>
<td>4,3±2,2</td>
<td>4,3±1,7</td>
<td>ns</td>
</tr>
<tr>
<td>Δ Sat O2</td>
<td>11,2±8,3</td>
<td>18,3±5,1</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>PAPm</td>
<td>67,3±22,8</td>
<td>73,3±22,7</td>
<td>ns</td>
</tr>
<tr>
<td>RAP</td>
<td>11,3±5,1</td>
<td>9,6±4,5</td>
<td>ns</td>
</tr>
<tr>
<td>QP/QS</td>
<td>1,1±0,6</td>
<td>0,9±0,6</td>
<td>ns</td>
</tr>
<tr>
<td>ΔPVR %</td>
<td>52±14</td>
<td>29±21</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>
On logistic regression analysis only presence of HF signs (OR=3.2, 95% CI 1.12-10.3, p=0.042), deteriorating NYHA functional class (OR=5.1, 95% CI 1.12-23.1, p=0.032), need for prostanoids (OR=6.3, 95% CI 1.13-37.2, p=0.039) and ΔPVR (OR=2.4, 95% CI: 1.9-8.9; p=0.034) were found to be predictive of death.

In contrast, a history of clinical arrhythmia, ECG features (QRS duration and QTc interval), previous history of pulmonary or systemic emboli, laboratory, near-syncope or syncope, were not significantly different between the two outcome groups.
Sudden Death in ES

“Death in ES is difficult to predict.

The following factors suggest it may be imminent (within next 1-2 y):

1. Pregnancy
2. Cerebral vascular accident
3. Increasing hypoxia at rest with decreasing effort tolerance
4. RV failure
5. Fresh haemoptysis at least 100 ml
6. Syncope on effort
7. Atrial arrhythmias
8. Ventricular runs (>3 ectopics)
9. Operation requiring general anesthesia
10. Need for pacing
11. Dangerous lifestyle habits (alcohol, disco, hot bats, sauna, drug abuse)”.

Fig. 5. Basic event leading to death in patients with the Eisenmenger reaction. CVA = cerebral vascular accident; CVS = cardiovascular system; No. = number; Op. = operation; R. = right; Vent. = ventricular.

Somerville J. Int J Cardiol 1998;63:1-8
Sudden Death in ES

Dilatation of pulmonary trunch in pt with ES
Emodinamic e prognosis in CHD-PAH

Pulmonary vasoreactivity predicts long-term outcome in patients with Eisenmenger syndrome receiving bosentan therapy

Michele D’Alto, Emanuele Romeo, Paola Argiento, Giuseppe Santoro, Berardo Sarubbi, Giampiero Gaiò, Christian Mélot, Maria Giovanna Russo, Robert Naeije, Raffaele Calabro

Heart 2010 96: 1475-1479

38 CHD-PAH: vasoreactivity test

**Conclusion** Pulmonary vasoreactivity is a significant predictor of clinical worsening in patients with CHD-PAH.
Conclusion

Sudden death and refractory heart failure were the causes of death in our Eisenmenger population.

An higher functional class at first observation, clinical deterioration during the follow-up, signs of heart failure and a lower ΔPVR during acute vasoreactivity test are of prognostic value in terms of mortality for Eisenmenger patients.