Síndrome de Eisenmenger
Algo más que hipertensión pulmonar

Rafael Alonso González
Adult Congenital Heart Centre & Centre for Pulmonary Hypertension
Royal Brompton Hospital (London)
I.
Die angeborenen Defecte der Kammerscheidewand des Herzens.

Von
Dr. Victor Eisenmenger.

(Hierauf Tafel L)

1.
Durch die Untersuchungen Rokitansky's is der Lehre von der Entstehung angeborener Defecte des Septum ventriculorum eine Basis gegeben, die nicht mehr verlassen werden darf.

Alle vorkommenden Formen entstehen durch Entwicklungshemmung und die überaus grösste Mehrzahl hat ihren Grund in abnormen Theilungsvorgängen des Truncus arteriosus communis.

Trotzdem tauchen immer wieder auf's neue Theorien auf, die in dem mechanismischen Moment des strömenden Blutes die Ursache für viele Entwicklungsfehler und -- in neuester Zeit -- sogar für die normale Evolution des Herzens suchen.

Hunter* und Morgagni sind die Begründer dieser Theorien.

Hunter lehrt: Wenn beim Fötus ein Hinderniss für den Blutstrom in der Lungenarterie erwächst, so lange die Kammerscheidewand nicht fertig ist, muss zwischen beiden Ventrikeln eine Oeffnung fortbestehen. Der kräftige Widerstand des Blutstrooms, der von einer Kammer in die andere fließt, hindert die Kammerscheidewand sich auszubilden.

Ahnlich Morgagni.

Diese Lehren fanden eifrige Verfechter. Lebert gestattet sich auf Grund derselben sogar den Schluss, dass in zwei von Bouillaux und

1) Rokitansky, Die Defecte der Scheidewände des Herzens. Wien 1875.
3) Morgagni, Cit. bei Barresi, Sperimentale. Bd. 46.


Z. Klin. Med 1897

Victor Eisenmenger
1864 - 1932

FIGURE 2. Left to right: Baron Bronn, Archduke Francis Ferdinand, Victor Eisenmenger, Count Cavriani.
THE EISEMENGER SYNDROME
OR PULMONARY HYPERTENSION WITH REVERSED CENTRAL SHUNT* 

BY

PAUL WOOD, O.B.E., M.D., F.R.C.P.
Director, Institute of Cardiology; Physician, National Heart Hospital; Physician-in-Charge, Cardiothoracic Department, Brompton Hospital, London

Distinctive Characteristics of Individual Members of the Eiseimenger Group

Patent Ductus.—(1) The catheter passed through the duct more easily than through any other central communication between the two circulations. It did so in 90% of cases, and usually took an anterograde course to enter the descending aorta. (2) The duct was wholly reversed in more than 40% of cases, and was reversed in 10% with other defects. (3) Patent ductus was the only lesion which was occasionally associated with no lesion in either direction. (4) Differential oxygen desaturation between right brachial and femoral samplings was pathognomonic of patent ductus, and occurred in all but two cases in which there was no duct in either direction. (5) Oxygen saturation of samples from the right brachial artery averaged 96.2%, range 81 to 96.5%, and from the descending aorta or femoral artery 77.7% (range 65 to 88%).

Aorto-Pulmonary Septal Defect.—(1) When the catheter passed through the defect it entered the ascending aorta from the pulmonary artery. (2) In other respects the findings were similar to those of patent ductus with bidirectional shunt but no differential desaturation.

Eisenmenger's Complex.—(1) Passage of the catheter via the defect (24%) into the ascending aorta followed a characteristic medial course as in Fallo's tetralogy. (2) An appreciable left-to-right shunt at the aortic level, as described by Bing et al. (1947), could be detected in all but two cases, in both of which the diagnosis was subsequently proved at necropsy. (3) Pulmonary artery samples were always higher (i.e., 50%) and more saturated than aortic or mixed samples.

Single Ventricle.—In all respects but one these cases resembled Eiseimenger's complex. The increase in oxygen saturation at the aortic level was 16%. The one distinctive feature was the similarity of aortic to arterial pulmonary oxygen saturation and venticular samples. The arterial oxygen saturation was lower than in other members of the Eisenmenger group, averaging 87%. Three such cases were proved at necropsy.

Transposition of the Great Vessels.—These cases differed from Eiseimenger's complex in all major respects but one. The distinctive feature was the higher oxygen saturation of the pulmonary artery compared with those from the aorta and right ventricle. In the three cases studied the difference was 12, 17, and 5%. The rise in oxygen saturation at the ventricular level averaged 20%. Three cases in the series resembled Eiseimenger's complex in all respects except that the catheter took a left aortic lateral course except as it entered the ascending aorta (Plate, Fig. 1). This Journal, September 20, facing p. 790, characteristic of one type of corrected transposition. The pulmonary artery is 80% regularly entered in such cases.

Pulmonary Arteries.—There were three characteristic features in the two cases studied. (1) The physiological situation was similar to that in aortic-pulmonary septal defect with the addition of a second left-to-right shunt at the ventricular level. As the catheter passed from the right atrium, through the right ventricle, into the truncus, the oxygen saturation of respective samples rose first by 10 and 15%, then by a further 10 and 14%. (2) The catheter entered the pulmonary arteries from the "aorta," instead of vice versa as in aortic-pulmonary septal defect. (3) Samples from the "aorta" and pulmonary arteries were identical.

Atrial Septal Defect.—(1) The catheter passed through the defect in two-thirds of 18 proved cases. (2) The pulmonary arterial pressure was less than the systemic pressure on average of 25.34 mm Hg in 70% of the cases; in 10%, it was higher; and in the remainder about the same. When the mean pressure was similar the pulse pressure was usually greater in the pulmonary artery, the systolic pressure being higher and the diastolic lower than in the systemic arteries. Agents affecting pulmonary or systemic flow or resistance selectively usually altered the pressure relationship between the two circulations. (3) A direct shunt at atrial level was demonstrated in 84% of the cases, right atrial samples being on the average 13%, more desaturated than samples from the superior vena cava (range 6 to 21%). (4) The oxygen saturation of left atrial samples averaged 91% in the eight cases in which they were obtained (range 72 to 88%). Left ventricular samples were similar when sucked; arterial and venous samples likewise (average 82%; range 78 to 88%).

Primary Pulmonary Hypertension.—The physiological findings in four cases could not be distinguished from a combination of low atrial septal defect and ventricular septal defect, there being bidirectional shunts at both atrial and ventricular levels. The rise in oxygen saturation averaged 10%, in the right atrium and 7.5% in the right ventricle. The line of the catheter when it entered Fallo's tetralogy in both groups is that in Fallo's tetralogy and Eisenmenger's complex.

Common Anterior Venous Canal.—A single proved case that came to necropsy had virtually both a single atrium and single ventricle. The rise in oxygen saturation resulting from the left-to-right shunt of the bidirectional shunt occurred at atrial level and measured 22%, those from the common ventricle, pulmonary artery, and femoral artery were similar at around 80% saturated.

Atypical Pulmonary Venous Drainage.—As a cause of the Eisenmenger reaction both total and hemimembranous pulmonary venous drainage must be rare, for no case was recognized amongst the 127 studied in this paper. One of

"pulmonary hypertension at systemic level due to high pulmonary vascular resistance with reversed bi-directional shunt" - "...it matters very little where the shunt happens to be. The distinguishing feature is not anatomy, but the physiological behaviour of the pulmonary circulation."
Guidelines for the diagnosis and treatment of pulmonary hypertension

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

A. Eisenmenger’s syndrome

Eisenmenger’s syndrome includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis, and multiple organ involvement are present.
### Clasificación anatómica-fisiopatológica de los cortocircuitos asociados con hipertensión pulmonar

<table>
<thead>
<tr>
<th>TIPO DE LESIÓN</th>
<th>TAMAÑO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortocircuito pre-tricuspideo simple</strong></td>
<td><strong>Hemodinámico (Qp/Qs)</strong></td>
</tr>
<tr>
<td>• CIA</td>
<td>• Restrictivo</td>
</tr>
<tr>
<td>• Drenaje venoso pulmonar anómalo</td>
<td>• No restrictivo</td>
</tr>
<tr>
<td><strong>Cortocircuito post-tricuspideo simple</strong></td>
<td><strong>Anatómico</strong></td>
</tr>
<tr>
<td>• CIV</td>
<td>• Pequeño o moderado (CIA ≤ 2cm, CIV ≤ 1 cm)</td>
</tr>
<tr>
<td>• Ductus persistente</td>
<td>• Grande (CIA &gt; 2cm, CIV &gt; 1 cm)</td>
</tr>
<tr>
<td><strong>Cortocircuitos combinados</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiopatías congénitas complejas</strong></td>
<td></td>
</tr>
<tr>
<td>• Canal AV completo</td>
<td></td>
</tr>
<tr>
<td>• Truncus arteriosus</td>
<td></td>
</tr>
<tr>
<td>• Ventrículo único sin obstrucción al flujo pulmonar</td>
<td></td>
</tr>
<tr>
<td>• Transposición de grandes vasos + CIV/DAP</td>
<td></td>
</tr>
<tr>
<td>• Otras</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DIRECCIÓN DEL CORTOCIRCUITO</th>
<th>ANOMALÍAS CARDIACAS/EXTRACARDIACAS ASOCIADAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sistémico-pulmonar (I-D)</strong></td>
<td><strong>REPARADO</strong></td>
</tr>
<tr>
<td><strong>Pulmonar-sistémico (D-I)</strong></td>
<td><strong>No operado</strong></td>
</tr>
<tr>
<td><strong>Bidireccional</strong></td>
<td><strong>Cirugía paliativa</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Cirugía correctora</strong></td>
</tr>
</tbody>
</table>

Riesgo de desarrollar HAP en pacientes con cortocircuitos

Cortocircuito

\[ \text{Estrés parietal} \rightarrow \text{Remodelado vascular} \rightarrow \text{Disfunción endotelial} \rightarrow \text{Cortocircuito I-D} \]

\[ \text{↑ Flujo pulmonar} \]

\[ \text{Cortocircuito D-I} \rightarrow \text{RVP} \]
I-RVP
Bidireccional/cortocircuito D-I

Endotelio
Ligera
Moderada
Severa

Estrés parietal
Remodelado vascular
Disfunción endotelial

I-D

I
II
III
IV-V

Síndrome de Eisenmenger
RVP
Cortocircuito derecha-izquierda
Capacidad de ejercicio

% predicted peak oxygen consumption

- Severely impaired
- Moderately impaired
- Mildly impaired
- Borderline
- Normal

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>q25</th>
<th>med.</th>
<th>q75</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1375</td>
<td>49</td>
<td>65</td>
<td>81</td>
</tr>
<tr>
<td>Simple lesions</td>
<td>214</td>
<td>54</td>
<td>70</td>
<td>87</td>
</tr>
<tr>
<td>Valvular lesions</td>
<td>166</td>
<td>56</td>
<td>73</td>
<td>86</td>
</tr>
<tr>
<td>Repaired TOF</td>
<td>378</td>
<td>57</td>
<td>71</td>
<td>85</td>
</tr>
<tr>
<td>AVSD</td>
<td>40</td>
<td>56</td>
<td>69</td>
<td>86</td>
</tr>
<tr>
<td>Systemic RV</td>
<td>150</td>
<td>47</td>
<td>64</td>
<td>80</td>
</tr>
<tr>
<td>Ebstein's anomaly</td>
<td>67</td>
<td>47</td>
<td>59</td>
<td>72</td>
</tr>
<tr>
<td>Fontan</td>
<td>92</td>
<td>45</td>
<td>56</td>
<td>69</td>
</tr>
<tr>
<td>Complex cyanotic</td>
<td>63</td>
<td>34</td>
<td>42</td>
<td>54</td>
</tr>
<tr>
<td>Eisenmenger</td>
<td>80</td>
<td>31</td>
<td>39</td>
<td>46</td>
</tr>
</tbody>
</table>

Capacidad de ejercicio

Afectación del sistema hematológico
<table>
<thead>
<tr>
<th><strong>HAEMOGLOBIN</strong></th>
<th><em>19.0 g/dL</em></th>
<th>11.5 - 15.1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCV</strong></td>
<td><em>0.61</em></td>
<td>0.34 - 0.45</td>
</tr>
<tr>
<td><strong>RBC</strong></td>
<td><em>7.35 10^{12}/L</em></td>
<td>3.73 - 4.92</td>
</tr>
<tr>
<td><strong>MCV</strong></td>
<td><em>83 fL</em></td>
<td>84 - 98</td>
</tr>
<tr>
<td><strong>MCH</strong></td>
<td><em>25.8 pg</em></td>
<td>28.3 - 33.3</td>
</tr>
<tr>
<td><strong>MCHC</strong></td>
<td><em>31.2 g/dL</em></td>
<td>32.4 - 35.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PLATELETS</strong></th>
<th><em>91 10^{9}/L</em></th>
<th>147 - 397</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBC TOTAL</strong></td>
<td><em>3.7 10^{9}/L</em></td>
<td>5.1 - 11.4</td>
</tr>
<tr>
<td>Neutrophils</td>
<td><em>2.3 10^{9}/L</em></td>
<td>2.6 - 7.9</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td><em>1.0 10^{9}/L</em></td>
<td>1.3 - 3.7</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.3 10^{9}/L</td>
<td>0.3 - 1.0</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.1 10^{9}/L</td>
<td>0.1 - 0.5</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.0 10^{9}/L</td>
<td>0.0 - 0.2</td>
</tr>
</tbody>
</table>
- **Aumento fisiológico del número de eritrocitos como consecuencia de la hipoxemia**
- **Aumento de la hemoglobina y del hematocrito**
  - Aumenta el aporte tisular de oxígeno
  - Aumento de la viscosidad
- **Tipos de eritrocitosis secundaria**
  - Compensada
  - Descompensada
A. Whole Blood Viscosity vs. Hematocrit (Low Shear)

Viscosity (mPa.s, log scale)

- Iron Replete: $r=0.78^*$
- Iron Deficient: $r=0.50^*$

<table>
<thead>
<tr>
<th>SÍNTOMAS DE HIPERVISCOSIDAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolores de cabeza</td>
</tr>
<tr>
<td><strong>Mareo, inestabilidad</strong></td>
</tr>
<tr>
<td>Disminución del estado de alerta</td>
</tr>
<tr>
<td><strong>Dificultad para la concentración</strong></td>
</tr>
<tr>
<td>Alteraciones visuales (visión borrosa, doble)</td>
</tr>
<tr>
<td><strong>Parestesias de labios y dedos</strong></td>
</tr>
<tr>
<td><strong>Tinnitus</strong></td>
</tr>
<tr>
<td><strong>Cansancio, fatiga</strong></td>
</tr>
<tr>
<td>Dolores musculares, torácico o abdominal</td>
</tr>
</tbody>
</table>
Relación entre Hb y SatO₂

Relación entre Hb y SatO₂

\[ y = -0.444x + 57.5 \]

Hb predicha = 61 - \( \frac{O_2Sat}{2} \)

Riesgo de ACV aumentado en presencia de:

HTA, FA, **historia previa de sangrías** y **microcitosis** (p = 0.005)
Déficit de hierro

**Change in total Camphor score**

20.7±10.9 vs 16.2±10.4, p=0.001

**Change in 6MWT distance**

371.7±84.7 vs 402.8±74.9, p=0.001
Assess annually
Anaemia history
Symptoms of hyperviscosity
SatO₂
Laboratory measures

Serum ferritin ≤15μg/l
Transferrin saturation ≤ 15%

Patient iron-deficient
Iron supplementation
Address others causes

Reassess symptoms
Repeat laboratory test
Stop iron if iron replete
Regularly reassess symptoms and laboratory test

Serum ferritin >15μg/l
Transferrin saturation > 15%

Patient iron-replety
No symptoms of hyperviscosity

Resolution of symptoms
Iron-replete
Reassess every 6-12 months

Patient iron-replety
Symptoms of hyperviscosity

Assess for other causes
Hypovolaemia
Brain abscess
Hypothyroidism

Hyperviscosity symptoms
Packed cell volume > 65%

Phlebotomy with fluid replacement
• **Trombocitopenia**
  - <130.000, factor predictor de mortalidad a largo plazo

• **Déficit de factores de la coagulación**
  - Vitamina K dependientes (II, VII, IX y X)
    - Hematomas espontáneos
  - Factor V
  - Déficit del factor von Willebrand
  - Aumento de la actividad fibrinolítica
    - Hematomas espontáneos
    - Sanguinorría gingival
    - Epistaxis
    - Menorragia
    - Hemoptisis (11%)

• **Perioperatoria**
Diátesis hemorrágica
Eventos tromboembólicos

- Incidencia de hemoptisis: 11%
- Incidencia de trombosis: 20%
- Más frecuente:
  - Pacientes mayores
  - Disfunción biventricular
  - Arteria pulmonar dilatada
  - Flujo pulmonar lento

No thrombus

Thrombus

Right ventricle

Left ventricle

Ventricular ejection fraction (%)

0

10

20

30

40

50

60

70

ANP

BNP

Serum neuropeptide level (pmol/l)

0

10

20

30

40

50

60

70

80

90

100

* p<0.05

Peak VO₂

Peak exercise O₂ consumption

0

2

4

6

8

10

12

14

16

18

20

### Table 25  Recommendations for PAH associated with congenital cardiac shunts

<table>
<thead>
<tr>
<th>Statement</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>The ERA bosentan is indicated in WHO-FC III patients with Eisenmenger’s syndrome</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Other ERAs, phosphodiesterase type-5 inhibitors, and prostanoids should be considered in</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

In the absence of significant haemoptysis, oral anticoagulant treatment should be considered in patients with PA thrombosis or signs of heart failure.
Eventos cerebrovasculares

- 14% de los pacientes
- Factores de riesgo:
  - Vías periféricas
  - Hipertensión
  - Microcitosis
- Abceso cerebral: 3,7%

ALTERACIONES ESTRUCTURALES
- Engrosamiento de la membrana basal
- Aumento de la matriz mesangial
- Dilatación de los capilares glomerulares
- Esclerosis segmentaria

ALTERACIONES FUNCIONALES
- Proteinuria
- Aumento de las resistencias vasculares
- Disminución del flujo plasmático
- Disminución de la fracción de filtración
- Aumenta la reabsorción tubular de ácido úrico

Alteraciones de la función renal

Alteraciones de la función renal

![Graph showing cumulative mortality over time for different GFR levels: GFR < 60 ml/min/1.73 m² (black), GFR = 60-89 ml/min/1.73 m² (gray), GFR ≥ 90 ml/min/1.73 m² (light gray). The graph indicates significantly higher mortality for GFR < 60 ml/min/1.73 m² compared to GFR ≥ 90 ml/min/1.73 m².](image)

Supervivencia

Hopkins et al. Journal of Heart & Lung Transplant, 1996
Supervivencia

Causa de muerte

- Transplant
- Extracardiac surgery
- Haemoptysis
- CVA/Abscess
- CV surgery
- Sudden cardiac death
- RV failure

<table>
<thead>
<tr>
<th>Classical Predictors of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex congenital heart disease</td>
</tr>
<tr>
<td>Syncope</td>
</tr>
<tr>
<td>Younger age at presentation or symptoms</td>
</tr>
<tr>
<td>Poor functional class</td>
</tr>
<tr>
<td>Signs of heart failure</td>
</tr>
<tr>
<td>Presence of right ventricular dysfunction</td>
</tr>
<tr>
<td>Supraventricular arrhythmias</td>
</tr>
<tr>
<td>RAP &gt; 7 mmHg</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Serum uric acid</td>
</tr>
<tr>
<td>Long QRS</td>
</tr>
<tr>
<td>Down syndrome</td>
</tr>
</tbody>
</table>

Daliento et al. Eur Heart J 1998  
Cantor WJ et al. Am J Cardiol 1999  
Oya H et al. Heart 2000  
Oya H et al. Am Heart J 2002  
Diller GP. Eur Heart J 2006
<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP (per 100 pg/ml)</td>
<td>1.68 (1.40 to 2.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6 min walk test distance (per 10 m)</td>
<td>0.93 (0.87 to 0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>Resting oxygen saturation (%)</td>
<td>0.87 (0.78 to 0.98)</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine (per 10 µm/l)</td>
<td>1.15 (1.07 to 1.25)</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Non-Down patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP (per 100 pg/ml)</td>
<td>1.63 (1.30 to 2.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6 min walk test distance (per 10 m)</td>
<td>0.92 (0.87 to 0.98)</td>
<td>0.006</td>
</tr>
<tr>
<td>Resting oxygen saturation (%)</td>
<td>0.83 (0.71 to 0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine (per 10 µm/l)</td>
<td>1.49 (1.20 to 1.75)</td>
<td>0.0001</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>1.51 (1.04 to 2.20)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>1.06 (1.01 to 1.10)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Down patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP (per 100 pg/ml)</td>
<td>3.81 (1.87 to 7.78)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

BNP: brain natriuretic peptide; CI: confidence interval.
BNP factor pronóstico

Expected mortality (%)

Median follow-up 3.3 years
Interquartile range 2.2–4.4 years

BNP (pg/ml)

BNP factor pronóstico

BNP factor pronóstico

**WHO Class I-III**
- Oral CC B (B)
- Sustained response (WHO I-II)

**WHO Class II**
- ERA (A) or PDE-5 I (A)

**WHO Class III**
- ERA (A) o PDE-5 (A)
- Iloprost inhalado (A)
- Treprostinil SC (B)
- Epoprostenol IV (A)
- Iloprost IV (C)
- Treprostinil IV (C)
- Beraprost (C)

**WHO Class IV**
- Epoprostenol IV (A)
- Iloprost IV (C)
- Treprostinil IV (C)
- Iloprost inhalado (B)
- Treprostinil SC (B)
- ERA (B)
- PDE-5 (B)

**Inadequate clinical response**
- Combination therapy
  - + (B) Prostanoïds
  - + (B) PDE-5 I ERA

**Evitar ejercicio extenuante**
- Anticoncepción
- Soporte psicosocial
- Prevenir infecciones

**Referir a un centro de referencia**

* To maintain O2 at 92%
Galie N et al. Circulation 2006;112:48-54
Pulmonary vascular resistance

Placebo (n=17)

Bosentan (n=37)

-472 din·s·cm$^5$

p = 0.038

Galie N et al. Circulation 2006;112:48-54
BREATHE-5 OLE

Change in 6-Minute Walking Distance (m)

Bosentan
Ex-bosentan
Ex-placebo
Placebo

Basal BREATHE-5
Basal BREATHE-5 OLE
Final BREATHE-5 OLE

n = 26
n = 9

33.2 m
61.3 m

Bosentan en CHD-PAH

Disease targeting therapies in patients with Eisenmenger syndrome: Response to treatment and long-term efficiency

Gerhard-Paul Diller a,b,1, Rafael Alonso-Gonzalez a,1, Konstantinos Dimopoulos a,b, Maria Alvarez-Barredo a, Chiehyang Koo a, Aleksander Kempny a, Carl Harries a, Lisa Parfitt a, Anselm S. Uebing a, Lorna Swan a, Philip S. Marino a,b, Stephen J. Wort a,b, Michael A. Gatzoulis a,b,∗ 1 GPD and RAG contributed equally to this work.

a Adult Congenital Heart Disease Centre and Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, UK
b National Heart and Lung Institute, Imperial College School of Medicine, London, UK

N: 79 patients
Follow-up: 3.3 y [0.2-8.9]
$P=0.009$

$P<0.0001$

Diller GP, Alonso-Gonzalez R et al. Int J Cardiol 2012, Mar 3; [Epub ahead of print]
Disease targeting therapies in patients with Eisenmenger syndrome: Response to treatment and long-term efficiency

Gerhard-Paul Diller a,b,1, Rafael Alonso-Gonzalez a,1, Konstantinos Dimopoulos a,b, Maria Alvarez-Barredo a, Chiehyang Koo a, Aleksander Kempny a, Carl Harries a, Lisa Parfitt a, Anselm S. Uebing a, Lorna Swan a, Philip S. Marino a,b, Stephen J. Wort a,b, Michael A. Gatzoulis a,b,1 GPD and RAG contributed equally to this work.

a Adult Congenital Heart Disease Centre and Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, UK
b National Heart and Lung Institute, Imperial College School of Medicine, London, UK
**Inhibidores de la PDE-5**

**Change in 6MWD (m)**

- **N=12**
- **III/IV**
- **p < 0.001**

**CAMPHOR score**

- **p < 0.001**

Tay EL et al. Int J Cardiol Int J Cardiol 2011;149:372-76
Oral sildenafil treatment for Eisenmenger syndrome: a prospective, open-label, multicentre study

Zhen-Ning Zhang,¹,² Xin Jiang,¹ Rui Zhang,¹ Xin-Li Li,³ Bing-Xiang Wu,⁴ Qin-Hua Zhao,¹ Yong Wang,² Li-Zhi Dai,¹ Lei Pan,² Mardi Gomberg-Maitland,⁵ Zhi-Cheng Jing¹

Table 1  Baseline clinical characteristics (n=84)

<table>
<thead>
<tr>
<th>Characteristics*</th>
<th>ASD (n=25)</th>
<th>VSD and/or PDA (n=59)</th>
<th>Total (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, n (%)</td>
<td>12 (48)</td>
<td>32 (54)</td>
<td>44 (52)</td>
</tr>
<tr>
<td>II, n (%)</td>
<td>13 (52)</td>
<td>20 (34)</td>
<td>33 (39)</td>
</tr>
<tr>
<td>IV, n (%)</td>
<td>0 (0)</td>
<td>7 (12)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>443±92</td>
<td>425±104</td>
<td>430±101</td>
</tr>
<tr>
<td>Borg dyspnoea score</td>
<td>3.4±2.2</td>
<td>3.1±2.0</td>
<td>3.2±1.9</td>
</tr>
<tr>
<td>Hgb, g/l</td>
<td>161±31</td>
<td>172±31</td>
<td>169±32</td>
</tr>
<tr>
<td>UA, μmol/l</td>
<td>372±88</td>
<td>393±109</td>
<td>387±103</td>
</tr>
<tr>
<td><strong>Haemodynamic variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, bpm</td>
<td>81±11</td>
<td>82±12</td>
<td>82±12</td>
</tr>
<tr>
<td>mRAP, mm Hg</td>
<td>6±4</td>
<td>5±5</td>
<td>5±5</td>
</tr>
<tr>
<td>mPCWP, mm Hg</td>
<td>5±5</td>
<td>5±5</td>
<td>5±5</td>
</tr>
<tr>
<td>mSAP, mm Hg</td>
<td>81±11</td>
<td>82±10</td>
<td>82±10</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>70±19</td>
<td>83±18†</td>
<td>79±19</td>
</tr>
<tr>
<td>O2i, L/min/m²</td>
<td>2.4±0.6</td>
<td>2.6±0.8</td>
<td>2.5±0.8</td>
</tr>
<tr>
<td>Qsi, L/min/m²</td>
<td>2.5±0.7</td>
<td>3.1±1.0†</td>
<td>2.9±1.0</td>
</tr>
<tr>
<td>PVRI, dyns×s×cm⁻⁵×m²</td>
<td>2271±879</td>
<td>2711±1267</td>
<td>2580±1177</td>
</tr>
<tr>
<td>SVRI, dyns×s×cm⁻⁵×m²</td>
<td>2639±870</td>
<td>2220±784</td>
<td>2344±828</td>
</tr>
<tr>
<td>PVRI/F SVRI ratio</td>
<td>0.93±0.48</td>
<td>1.27±0.57†</td>
<td>1.17±0.56†</td>
</tr>
<tr>
<td>Resting SaO₂ in room air, %</td>
<td>89.0±3.5</td>
<td>85.0±5.5†</td>
<td>85.9±5.5</td>
</tr>
</tbody>
</table>

Zhang ZN et al. Heart 2011;97:1876-81
Inhibidores de la PDE-5

Zhang ZN et al. Heart 2011;97:1876-81
### Table 2  Percentage changes in clinical and haemodynamic variables at 12 months compared with baseline*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ASD (n=25)</th>
<th>p Value</th>
<th>VSD and/or PDA (n=59)</th>
<th>p Value</th>
<th>Total (n=84)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment effect</td>
<td></td>
<td>Treatment effect</td>
<td></td>
<td>Treatment effect</td>
<td></td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD, m</td>
<td>1.3 (0.3 to 2.3)</td>
<td>0.015</td>
<td>2.8 (2.2 to 3.4)</td>
<td>&lt;0.0001</td>
<td>2.4 (1.2 to 3.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>48 (22 to 74)</td>
<td>0.001</td>
<td>59 (42 to 75)</td>
<td>&lt;0.001</td>
<td>44 (24 to 61)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>−1.2 (−1.9 to −0.5)</td>
<td>0.002</td>
<td>−0.9 (−1.4 to −0.4)</td>
<td>0.001</td>
<td>−0.8 (−1.5 to −0.3)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>−7.3 (−12.2 to −2.4)</td>
<td>0.005</td>
<td>−7.0 (−12.6 to −1.1)</td>
<td>0.02</td>
<td>-6.7 (-12.2 to -0.8)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>−33 (−66 to −1)</td>
<td>0.105</td>
<td>−8 (−34 to 18)</td>
<td>0.556</td>
<td>−15 (−36 to 5)</td>
<td>0.139</td>
</tr>
<tr>
<td>Haemodynamic variables†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, bpm</td>
<td>−2.8 (0 to −7.4 to 1.8)</td>
<td>0.212</td>
<td>−2.2 (−5.5 to 1.1)</td>
<td>0.1</td>
<td>−1.4 (−4.2 to 1.4)</td>
<td>0.323</td>
</tr>
<tr>
<td>mSAP, mm Hg</td>
<td>−1.0 (−6.1 to 4.1)</td>
<td>0.692</td>
<td>−1.4 (−3.9 to 1.0)</td>
<td>0.244</td>
<td>−1.3 (−3.5 to 0.9)</td>
<td>0.248</td>
</tr>
<tr>
<td>mRAP, mm Hg</td>
<td>0.6 (−1.1 to 2.2)</td>
<td>0.492</td>
<td>0.8 (−0.5 to 2.2)</td>
<td>0.222</td>
<td>−0.8 (−3.0 to 1.8)</td>
<td>0.159</td>
</tr>
<tr>
<td>mPCWP, mm Hg</td>
<td>0.1 (−1.8 to 1.9)</td>
<td>0.929</td>
<td>−0.4 (−1.7 to 1.0)</td>
<td>0.608</td>
<td>−0.2 (−1.3 to 0.9)</td>
<td>0.682</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>−5.4 (−10.0 to 0.9)</td>
<td>0.022</td>
<td>−4.4 (−8.0 to −0.9)</td>
<td>0.016</td>
<td>−4.7 (−7.5 to −1.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>PVRi, W/m²</td>
<td>0.4 (0.1 to 0.8)</td>
<td>0.011</td>
<td>0.7 (0.2 to 1.1)</td>
<td>0.009</td>
<td>0.6 (0.2 to 0.9)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>0.1 (0.1 to 0.2)</td>
<td>0.270</td>
<td>0.2 (0.1 to 0.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>−466 (−744 to 189)</td>
<td>0.002</td>
<td>−477 (−677 to −277)</td>
<td>0.027</td>
<td>−475 (−675 to −275)</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>−282 (−629 to 64)</td>
<td>0.452</td>
<td>−70 (−247 to 107)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVRi/FSVRi ratio</td>
<td>−0.07 (−0.31 to 0.17)</td>
<td>0.539</td>
<td>−0.14 (−0.25 to −0.02)</td>
<td>0.027</td>
<td>−0.12 (−0.22 to −0.01)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

*Data from Zhang ZN et al. Heart 2011;97:1876-81*
Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial†

Iversen K et al. Eur Heart J 2010;31:1124-31
Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial $^+$

Iversen K et al. Eur Heart J 2010;31:1124-31
Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial

Iversen K et al. Eur Heart J 2010;31:1124-31
Disease targeting therapies in patients with Eisenmenger syndrome: Response to treatment and long-term efficiency

Gerhard-Paul Diller a,b,1, Rafael Alonso-Gonzalez a,1, Konstantinos Dimopoulos a,b, Maria Alvarez-Barredo a, Chiehyang Koo a, Aleksander Kempny a, Carl Harries a, Lisa Parfitt a, Anselm S. Uebing a, Lorna Swan a, Philip S. Marino a,b, Stephen J. Wort a,b, Michael A. Gatzoulis a,b,* 1 GPD and RAG contributed equally to this work.

a Adult Congenital Heart Disease Centre and Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, UK
b National Heart and Lung Institute, Imperial College School of Medicine, London, UK

Pacientes con tratamiento combinado
Tratamiento de HAP-CHD y supervivencia

Dimopoulos et al. Circulation 2010;120:20-25
The ERA bosentan is indicated in \textbf{WHO-FC III} I B patients with Eisenmenger’s syndrome

Other ERAs, phosphodiesterase type-5 inhibitors, IIa C and prostanoids should be considered in patients with Eisenmenger’s syndrome

- Consistent increase in arterial oxygen saturation and reduces symptoms
- If symptoms of hyperviscosity are present, IIa C phlebotomy with isovolumic replacement should be considered usually when the haematocrit is > 65%
- Combination therapy may be considered in IIb C patients with Eisenmenger’s syndrome
- The use of CCBs is not recommended in patients with Eisenmenger’s syndrome III C
Cuándo empezar a tratar?

<table>
<thead>
<tr>
<th>Characteristics*</th>
<th>ASD (n = 25)</th>
<th>VSD and/or PDA (n = 59)</th>
<th>Total (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>28±9</td>
<td>27±9</td>
<td>28±9</td>
</tr>
<tr>
<td>Gender (female/male; n, %)</td>
<td>20/5 (80)</td>
<td>38/21 (64)</td>
<td>58/26 (69)</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.5±0.1</td>
<td>1.5±0.2</td>
<td>1.5±0.2</td>
</tr>
<tr>
<td>Functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II, n (%)</td>
<td>12 (48)</td>
<td>32 (54)</td>
<td>44 (52)</td>
</tr>
<tr>
<td>III, n (%)</td>
<td>13 (52)</td>
<td>20 (34)</td>
<td>33 (39)</td>
</tr>
<tr>
<td>IV, n (%)</td>
<td>0 (0)</td>
<td>7 (12)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>443±92</td>
<td>425±104</td>
<td>430±101</td>
</tr>
<tr>
<td>Borg dyspnoea score</td>
<td>3.4±2.2</td>
<td>3.1±2.0</td>
<td>3.2±1.9</td>
</tr>
<tr>
<td>Hgb, g/l</td>
<td>161±31</td>
<td>172±31</td>
<td>169±32</td>
</tr>
<tr>
<td>UA, μmol/l</td>
<td>372±88</td>
<td>393±109</td>
<td>387±103</td>
</tr>
<tr>
<td>Haemodynamic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, bpm</td>
<td>81±11</td>
<td>82±12</td>
<td>82±12</td>
</tr>
<tr>
<td>mRAP, mm Hg</td>
<td>6±4</td>
<td>5±5</td>
<td>5±5</td>
</tr>
<tr>
<td>mPCWP, mm Hg</td>
<td>5±5</td>
<td>5±5</td>
<td>5±5</td>
</tr>
<tr>
<td>mSAP, mm Hg</td>
<td>81±11</td>
<td>82±10</td>
<td>82±10</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>70±19</td>
<td>83±18†</td>
<td>79±19</td>
</tr>
<tr>
<td>Qpi, l/min/m²</td>
<td>2.4±0.6</td>
<td>2.6±0.8</td>
<td>2.5±0.8</td>
</tr>
<tr>
<td>Qsi, l/min/m²</td>
<td>2.5±0.7</td>
<td>3.1±1.0†</td>
<td>2.9±1.0</td>
</tr>
<tr>
<td>PVRi, dyn×s×cm⁻⁵×m²</td>
<td>2271±879</td>
<td>2711±1267</td>
<td>2580±1177</td>
</tr>
<tr>
<td>SVRi, dyn×s×cm⁻⁵×m²</td>
<td>2639±870</td>
<td>2220±784</td>
<td>2344±828</td>
</tr>
<tr>
<td>PVRi/F SVRi ratio</td>
<td>0.93±0.48</td>
<td>1.27±0.57</td>
<td>1.17±0.56</td>
</tr>
<tr>
<td>Resting SaO₂ in room air, %</td>
<td>89.0±3.5</td>
<td>85.0±5.5†</td>
<td>85.9±5.5</td>
</tr>
</tbody>
</table>
**EARLY-study**

![Graph showing patients with no clinical worsening over time with Bosentan and Placebo]

- **Patients with no clinical worsening (%)**
  - **Time from start of treatment (weeks)**
    - 0  4  8  12  16  20  24  28  32
  - **Number at risk**
    - **Placebo**
      - 92  90  89  86  84  83  77  18  9
    - **Bosentan**
      - 93  92  87  85  84  83  80  27  15

Galié et al. Lancet 2008; 371: 2093-100
Eisenmenger syndrome

Conventional treatment – Preventive measures

Class (I-) II
- Regular follow-up
  - Role of targeted therapies not defined

Class III
- Bosentan (Sildenafil or ...)
  - Failure
    - Combination therapy?
      - Failure
        - Heart/lung transplant

Class IV
- IV epoprostenol (Bosentan, sildenafil or other targeted therapies)
  - Transplant candidate?
    - Failure
      - Combination therapy?
        - Failure
          - Heart/lung transplant
GRACIAS