Pulmonary hypertension in CHD – what’s new in the guidelines

Prof. Dr. Markus Schwerzmann / Zentrum für angeborene Herzfehler
WHAT'S NEW?

NOT MUCH...
Outline of this talk

- PAH associated with congenital heart disease
  - classification
- PH due to left heart disease
  - new diagnostic criteria
- Risk assessment
- Recommendations regarding pulmonary vasodilators
- General measures in PH patients
  - role of oral anticoagulation
## Comprehensive clinical classification

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<tbody>
<tr>
<td>1.</td>
<td>Pulmonary arterial hypertension</td>
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<tr>
<td>1.1.</td>
<td>Idiopathic</td>
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<td>1.2.</td>
<td>Hereditary</td>
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<td>1.3.</td>
<td>Drugs and toxin induced</td>
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<td>1.4.</td>
<td>associated with .... CTD, HIV, <strong>Congenital heart disease</strong></td>
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<td>1‘.</td>
<td>Pulmonary veno-occlusive disease / persistent PH of the new born</td>
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<td>2.</td>
<td>PH due to left heart disease</td>
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<td>3.</td>
<td>PH due to lung disease and/or hypoxia</td>
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<td>4.</td>
<td>CTEPH and other pulmonary artery obstructions</td>
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<td>5.</td>
<td>PH with unclear and/or multifactorial mechanisms</td>
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### 1.4. PAH associated with CHD

<table>
<thead>
<tr>
<th>1. Eisenmenger syndrome</th>
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<tr>
<td>large intra- or extracardiac defects, shunt reversal or bi-directional shunting; cyanosis, secondary erythrocytosis, multiple organ involvement</td>
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<tr>
<th>2. PAH with systemic-to-pulmonary shunts</th>
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<tr>
<td>correctable / non correctable no cyanosis at rest</td>
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<tr>
<th>3. PAH with small / coincidental defects</th>
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<tr>
<td>VSD &lt; 1 cm, ASD &lt; 2 cm; closing the defect is contraindicated</td>
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<th>4. PAH after defect correction</th>
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<tr>
<td>persists or recurs/develops after correction in the absence of other hemodynamic lesions</td>
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Clinical classification

Eisenmenger

PAH after repair

PAH with small defects

PAH with shunts

Reversibility
Reversibility of pulmonary vascular disease

2. PH due to left heart disease

PH (mean PAP ≥ 25 mmHg)

Postcapillary PH
PCWP > 15 mmHg

Precapillary PH
PCWP ≤ 15 mmHg

Isolated postcapillary PH
DPG < 7 mmHg
and/or
PVR ≤ 3 WU

Combined post- and precapillary PH
DPG ≥ 7 mmHg
and/or
PVR > 3 WU

Terms „Transpulmonary gradient“ + „Out-of-proportion“ have been abolished; Controversy regarding definition of Cpc-PH: and/or
Pulmonary Hypertension in Heart Failure
Epidemiology, Right Ventricular Function, and Survival

Mario Gerges¹, Christian Gerges¹, Anna-Maria Pistritto², Marie B. Lang¹, Pia Trip³, Johannes Jakowitsch¹, Thomas Binder¹, and Irene M. Lang¹

Survival curves

Systolic HF

Diastolic HF

A

B

Cumulative survival SHF

Cumulative survival DHF

Time to last contact (months)

Mean pulmonary artery wedge pressure (mmHg)

Mean pulmonary artery wedge pressure (mmHg)

p=0.024

p=0.004

0 24 48 72 96 120 144 188

0 24 48 72 96 120 144

0 10 20 30 40 50

0 10 20 30 40 50 60 70

50 40 30 20 10

50 40 30 20 10
Effect of Pulmonary Hypertension Hemodynamic Presentation on Clinical Outcomes in Patients With Severe Symptomatic Aortic Valve Stenosis Undergoing Transcatheter Aortic Valve Implantation
Insights From the New Proposed Pulmonary Hypertension Classification

(Circ Cardiovasc Interv. 2015;8:e002358. DOI: 10.1161/CIRCINTERVENTIONS.114.002358.)
PH due to left heart disease

True combined post-and pre-capillary PH:
DPG ≥ 7mmHg AND PVR > 3 WU.

ERJ 2016; in press
PH due to left heart disease

Therefore there is no new evidence supporting the use of PAH therapies in PH-LHD, due in part to the absence of studies specifically stratifying patients for PH and/or targeting this specific condition.

## Risk assessment Group 1

<table>
<thead>
<tr>
<th>Determinants of prognosis* (estimated 1-year mortality)</th>
<th>Low risk &lt;5%</th>
<th>Intermediate risk 5–10%</th>
<th>High risk &gt;10%</th>
</tr>
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<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
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<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncope()</td>
<td>Repeated syncope()</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;440 m</td>
<td>165–440 m</td>
<td>&lt;165 m</td>
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<tr>
<td>Cardiopulmonary exercise testing</td>
<td>PeakVO(_2) &gt;15 ml/min/kg (&gt;65% pred.) VE/VCO(_2) slope &lt;36</td>
<td>PeakVO(_2) 11–15 ml/min/kg (35–65% pred.) VE/VCO(_2) slope 36–44.9</td>
<td>PeakVO(_2) &lt;11 ml/min/kg (&lt;35% pred.) VE/VCO(_2) slope ≥45</td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt;50 ng/l NT-proBNP &lt;300 ng/l</td>
<td>BNP 50–300 ng/l NT-proBNP 300–1400 ng/l</td>
<td>BNP &gt;300 ng/l NT-proBNP &gt;1400 ng/l</td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt;18 cm(^2) No pericardial effusion</td>
<td>RA area 18–26 cm(^2) No or minimal, pericardial effusion</td>
<td>RA area &gt;26 cm(^2) Pericardial effusion</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>RAP &lt;8 mmHg CI ≥2.5 l/min/m(^2) SvO(_2) &gt;65%</td>
<td>RAP 8–14 mmHg CI 2.0–2.4 l/min/m(^2) SvO(_2) 60–65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 l/min/m(^2) SvO(_2) &lt;60%</td>
</tr>
</tbody>
</table>

Low risk: FC I or II, no signs of clinically relevant RV dysfunction
Intermediate risk: FC III, RV dysfunction but no RV failure
High risk: FC III or IV, severe RV dysfunction or RV failure
Pulmonary vasodilators in PH-CHD

Data available for
• Breathe-5 trial: Bosentan RCT in Eisenmenger
• Sildenafil, Tadalafil, Epoprostenol
• Add on Sildenafil (in addition to Bosentan)

New drugs
• Macitentan (Seraphin trial; NEJM 2013): PAH with repaired CHD
• Riociguat (Patent trial; NEJM 2013): PAH with repaired CHD
• Selexipag (Griphon trial; NEJM 2015): PAH with repaired CHD

Can we use these drugs in all PH-CHD subclasses?
Pulmonary vasodilators in PH-CHD

Yes, we can... 

Treatment recommendations identical for all Group 1 indications 

New approach: Consider up-front combination therapy
Immortality bias

Diller GP et al., Heart 2014; 100: 1366-40.

Conclusions The current analysis challenges the traditional view of benign survival prospects of patients with Eisenmenger syndrome. In addition, survival prospects do not seem to have considerably improved over the last decades in untreated patients. These results support a proactive treatment strategy including a more aggressive approach trying to avoid the development of the condition.
Survival in PH-CHD

The American Journal of Cardiology (www.ajconline.org)

Four-Year Survival Estimate ± SE
78% ± 4%
77% ± 3%
76% ± 5%
74% ± 1%

No. at Risk:
Repaired CHD 105 103 98 93 88 83 80 76 70
Unrepaired ES 132 124 120 113 111 106 100 94 87
Unrepaired No ES 91 90 86 81 78 67 60 58 53
IPAH/HPAH 1626 1544 1470 1391 1303 1164 1086 999 912

Am J Cardiol 2014; 113:147-
Oral anticoagulation in PAH

(Circulation. 2014;129:57-65.)

Anticoagulation and Survival in Pulmonary Arterial Hypertension
Results From the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)

iPAH
n=800
66% OAC

not iPAH
n=483
43% OAC
Oral anticoagulation in PAH

Effect of Warfarin Treatment on Survival of Patients With Pulmonary Arterial Hypertension (PAH) in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL)

(Circulation. 2015;132:2403-2411. DOI: 10.1161/CIRCULATIONAHA.115.018435.)

iPAH or PAH due to CTD
Recommendations for general measures

• Oral anticoagulation should ☑️ may be considered for IPAH, HPAH and PAH due to anorexins (II a ☑️ II b) Not recommended any more for other PAH subgroups, including PAH-CHD.

• The use of ACE inhibitors, ARBs, beta-blockers and ivabradine is not recommended in patients with PAH unless required by co-morbidities (i.e. high blood pressure, coronary artery disease or left heart failure) (new Class III)
The end...
Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups

90 Eisenmenger
48 PAH – systemic to PA s
10 PAH – small defects
44 PAH – repaired defects
PATHOPHYSIOLOGY AND NATURAL HISTORY

CONGENITAL HEART DISEASE

Isolated atrial septal defect with pulmonary vascular obstructive disease — long-term follow-up and prediction of outcome after surgical correction

PETER M. STIEFEL, M.B.B.S. (HONS), VALENTIN FUSTER, M.D., MARC COHEN, M.D., DONALD G. RITTER, M.D., AND DWIGHT C. McGOON, M.D.

ABSTRACT We examined the cases of 702 patients found to have isolated atrial septal defect of the secundum or sinus venosus type at catheterization from 1953 to 1978. Forty patients (69%), 34 women and six men, had pulmonary vascular obstructive disease, with a total pulmonary resistance greater than 7 U*m²; of these patients 26 (mean age 47 years) underwent surgical closure and 14 (mean age 44 years) received medical treatment. All patients were followed for at least 4 years, with a median follow-up of 12 years. At the most recent follow-up, 17 of the 40 patients were dead. Of the 22 surgically treated patients with total pulmonary resistance less than 15 U*m², 19 were alive with significant regression of symptoms. All four surgically treated patients with total pulmonary resistance greater than or equal to 15 U*m² were dead. Of the five medically treated patients with total pulmonary resistance less than 15 U*m², four had died, and one was alive with significant progression of symptoms. Of the nine medically treated patients with total pulmonary resistance greater than or equal to 15 U*m², six had died and the three survivors had progression of symptoms. In the surgically treated group, the following variables correlated with survival: total pulmonary resistance (p < 0.0001), pulmonary arteriolar resistance (p < 0.0001), pulmonary-to-systemic resistance ratio (p = 0.001), systemic arterial oxygen saturation (p = 0.05), and pulmonary arterial oxygen saturation (p = 0.007). In conclusion: (1) Atrial septal defect with high total pulmonary resistance is uncommon and predominates in adult female patients. (2) Total pulmonary resistance (or pulmonary arteriolar resistance) is the best predictor of surgical outcome. In patients with total pulmonary resistance less than 15 U*m², surgical treatment is advised. (3) In patients with borderline total pulmonary resistance, the systemic arterial oxygen saturation provides a good prediction of surgical outcome.


PATIENTS with moderate or large congenital ventricular septal defects become symptomatic and develop pulmonary hypertension with an increased pulmonary vascular resistance in childhood. In contrast, patients with an isolated atrial septal defect (of ostium secundum or sinus venosus type) usually do not become symptomatic until middle or old age. A fraction of these patients go on to develop pulmonary vascular obstructive disease.1-2 Surgical correction, in patients with isolated atrial septal defect, is usually recommended when there is a significant shunt (pulmonary-to-systemic flow ratio of at least 1.5:1) and no evidence of severe pulmonary vascular obstructive disease.3 Furthermore, in the absence of significant pulmonary vascular obstructive disease, many studies have reported good surgical results even in the elderly.4 It has often been stated that the risks and benefits of surgery depend mainly on the presence of pulmonary hypertension;5-6 but the point at which surgery should be avoided remains uncertain. No large studies have reported on the long-term follow-up of patients with atrial septal defect and pulmonary vascular obstructive disease and the effect of surgery. This study addressed that question with particular reference to the prediction of outcome after surgical correction.

Methods

Study patients: Between 1953 and 1978, 702 patients at the Mayo Clinic were found to have isolated atrial septal defect of the ostium secundum or sinus venosus type at cardiac catheterization. Of these 702 patients, 69% had pulmonary vascular obstructive disease, defined as a total pulmonary resistance of
• 22 pts. developing pulmonary hypertension 12 years after shunt closure (13 ASD, 6 VSD, 1 PDA, 1 ASD+VSD, 1 AVSD).

• At baseline:
  – 8/22 pts. had PVR > 5 WU
  – 21/22 had PVRi > 6WU*m²
  – 21/22 had PVR/SVR ratio > 0.33
  – 11/22 had a Qp:Qs < 1.5, and 2/22 had Qp:Qs > 2
None of the patients had residual PH on echo
Reversibility of pulmonary vascular disease

- Recommendations regarding shunt closure are definitively on the “safe side“, probably too much on the safe side

- The larger the Qp:Qs, the lower the PVR the more we are sure that the patient will benefit

- “Treat-and-repair“ approach not supported by guidelines; no recommendations regarding re-evaluation after therapy are given