Pulmonary Hypertension: Follow-up in adolescence and adults

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Pulmonary hypertension: Follow-up in adolscence and adults

Prevalence reported in ACHD up to 28%, defined by sPAP>40

Table 9 Arbitrary criteria for estimating the presence of PH based on tricuspid regurgitation peak velocity and Doppler-calculated PA systolic pressure at rest (assuming a normal right atrial pressure of 5 mmHg) and on additional echocardiographic variables suggestive of PH

	Class[a]	Level[b]
Echocardiographic diagnosis: PH unlikely		
Tricuspid regurgitation velocity ≤2.8 m/s, PA systolic pressure ≤36 mmHg, and no additional echocardiographic variables suggestive of PH	I	B
Echocardiographic diagnosis: PH possible		
Tricuspid regurgitation velocity ≤2.8 m/s, PA systolic pressure ≤36 mmHg, but presence of additional echocardiographic variables suggestive of PH	IIa	C
Tricuspid regurgitation velocity 2.9–3.4 m/s, PA systolic pressure 37–50 mmHg with/without additional echocardiographic variables suggestive of PH	IIa	C
Echocardiographic diagnosis: PH likely		
Tricuspid regurgitation velocity >3.4 m/s, PA systolic pressure >50 mmHg, with/without additional echocardiographic variables suggestive of PH	I	B
Exercise Doppler echocardiography is not recommended for screening of PH	III	C

[a]Class of recommendation.

Table 3 Haemodynamic definitions of pulmonary hypertension[a]

Definition	Characteristics	Clinical group(s)[b]
Pulmonary hypertension (PH)	Mean PAP ≥25 mmHg	All
Pre-capillary PH	Mean PAP ≥25 mmHg PWP ≤15 mmHg CO normal or reduced[c]	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥25 mmHg PWP >15 mmHg CO normal or reduced[c]	2. PH due to left heart disease
Passive Reactive (out of proportion)	TPG ≥12 mmHg TPG >12 mmHg	

[a]All values measured at rest.
[b]According to Table 4.
[c]High CO can be present in cases of hyperkinetic conditions such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anaemia.

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Pulmonary hypertension: Follow-up in adolscence and adults

Table 4 Updated clinical classification of pulmonary hypertension (Dana Point, 2008[1])

1 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3 Pulmonary hypertension due to lung diseases and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4 Chronic thromboembolic pulmonary hypertension

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 = activin receptor-like kinase 1 gene; APAH = associated pulmonary arterial hypertension; BMPR2 = bone morphogenetic protein receptor, type 2; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

Table 6 Clinical classification of congenital, systemic-to-pulmonary shunts associated with pulmonary arterial hypertension

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.

B. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts

In these patients with moderate to large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest.

C. Pulmonary arterial hypertension with small[a] defects

In cases with small defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH.

D. Pulmonary arterial hypertension after corrective cardiac surgery

In these cases, congenital heart disease has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant post-operative residual congenital lesions or defects that originate as a sequela to previous surgery.

[a]The size applies to adult patients.
PAH = pulmonary arterial hypertension; I

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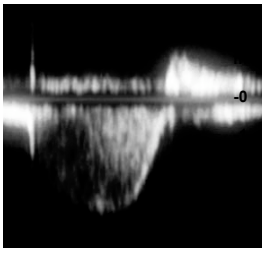
Tricuspid Regurgitation: Estimation of Pulmonary Artery Prerssure



CW Doppler measurement of peak TR velocity

Δ **p = 4v²**

$4Vmax_{TI}^2$ = RVPsyst - RAP

$4Vmax_{TI}^2$ + RAP = RVPsyst

RVPsyst = PAPsyst
If no obstruction between RV and PA (DCRV, subv. PS, valv. PS, periph. PS)

Pulmonary hypertension - Echocardiography Following adolscence and adults with CHD

- Detection of elevated PAP or progression of PH:
  - unoperated shunt lesions
    - + newly diagnosed ASD
    - + VSD considered too small for closure
  - „left" (systemic) heart disease
    - + systemic AV valve regurgitation (surgery in asympt. pts with PAP>50)
    - + severe systemic ventricle dysfunction (eligibilty for transplantation)
- Follow-up after repair: recognition of PH
- Follow-up of pts. with severe PAH and Eisenmenger syndrome
  prognostic parameters for treatment decisions (targeted therapy, transplant)

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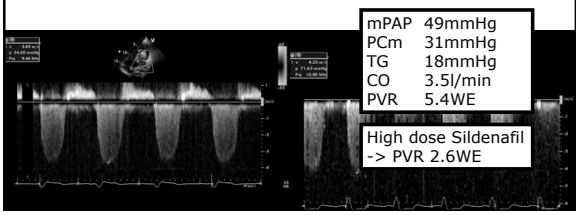
Female 39 yrs TGA, Mustard



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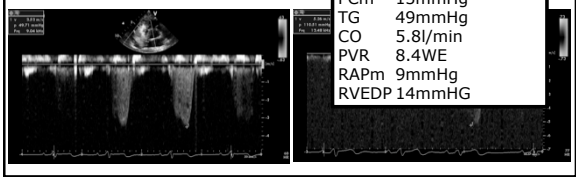
Male, 17 yrs VSD closure 1993



PAP	80/46/62mmHg
PCm	13mmHg
TG	49mmHg
CO	5.8l/min
PVR	8.4WE
RAPm	9mmHg
RVEDP	14mmHG

Pulmonary hypertension - Echocardiography Following adolscence and adults with CHD

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  - prognostic parameters for treatment decisions (targeted therapy, transplant)

Pulmonary hypertension: Follow-up in adolscence and adults

Table 16 Suggested assessments and timing for the follow-up of patients with PAH

	At baseline (prior to therapy)	Every 3–6 months[a]	3–4 months after initiation or changes in therapy	In case of clinical worsening
Clinical assessment WHO-FC ECG	✓	✓	✓	✓
6MWT[b]	✓	✓	✓	✓
Cardio-pulmonary exercise testing[b]	✓		✓	✓
BNP/NT-proBNP	✓	✓	✓	✓
Echocardiography	✓		✓	✓
RHC	✓[c]		✓[d]	✓[d]

[a]Intervals should to be adjusted to individual patients needs.
[b]Usually one of the two exercise tests is performed.
[c]Is recommended (*Table 11A*).
[d]Should be performed (*Table 11A*).
BNP = brain natriuretic peptide; ECG= electrocardiogram; RHC = right heart catheterization; 6MWT = 6-minute walking test; WHO-FC =WHO functional class.

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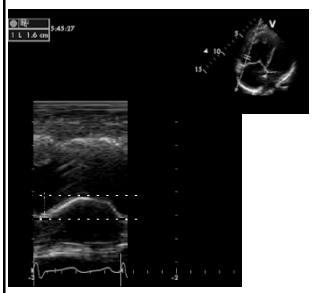
Table 15 Parameters with established importance for assessing disease severity, stability and prognosis in PAH (adapted from McLaughlin and McGoon[84])

Better prognosis	Determinants of prognosis	Worse prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of progression of symptoms	Rapid
No	Syncope	Yes
I, II	WHO-FC	IV
Longer (>500 m)[a]	6MWT	Shorter (<300 m)
Peak O_2 consumption >15 mL/min/kg	Cardio-pulmonary exercise testing	Peak O_2 consumption <12 mL/min/kg
Normal or near-normal	BNP/NT-proBNP plasma levels	Very elevated and rising
No pericardial effusion TAPSE[b] >2.0 cm	Echocardiographic findings[b]	Pericardial effusion TAPSE[b] <1.5 cm
RAP <8 mmHg and CI >2.5 L/min/m^2	Haemodynamics	RAP >15 mmHg or CI <2.0 L/min/m^2

[a]Depending on age.
[b]TAPSE and pericardial effusion have been selected because they can be measured in the majority of the patients.
BNP = brain natriuretic peptide; CI = cardiac index; 6MWT = 6-minute walking test; RAP = right atrial pressure; TAPSE = tricuspid annular plane systolic excursion; WHO-FC = WHO functional class.

Echo findings reported with best prognostic value:
pericardial effusion, indexed RA area, LV eccentricity index,
RV Doppler index, tricuspid annular plane systolic excursion (TAPSE)

PAH – RVF and TAPSE



Pulmonary hypertension: Follow-up in adolscence and adults

- When to start targeted therpay?
- When to change targeted therapy?
- When to consider HLTX?

Table 22 Definition of inadequate response to PAH treatments (see also section 7.2.5 and 7.2.6)

Inadequate clinical response for patients who were initially in WHO-FC II or III:
(1) Resulting clinical status defined as stable and not satisfactory
(2) Resulting clinical status defined as unstable and deteriorating
Inadequate clinical response for patients who were initially in WHO-FC IV:
(1) No rapid improvement to WHO-FC III or better
(2) Resulting clinical status defined as stable and not satisfactory

Recommendations for Targeted Pulmonary Arterial Hypertension Therapy in Congenital Heart Disease

	Class[a]	Level[b]
• Targeted PAH therapy in CHD should only be performed in specialized centres	I	C
• The ERA bosentan should be initiated in WHO-FC III* patients with Eisenmenger syndrome	I	B
• Other ERAs, phosphodiesterase type-5 inhibitors and prostanoids should be considered in WHO-FC III* patients with Eisenmenger syndrome	IIa	C
• Combination therapy may be considered in WHO-FC III patients with Eisenmenger syndrome	IIb	C
• The use of calcium channel blockers should be avoided in patients with Eisenmenger syndrome	III	C

a = class of recommendation. b = level of evidence.
*Although recent data support the use of ERA such as bosentan also in WHO-FC II, in pts with idiopathic PAH and PAH associated with connective tissue diseases such data are currently not available for Eisenmenger pts. Because of marked differences in the natural history between these groups, the results cannot simply be applied to GUCH and further studies are required before recommendations.

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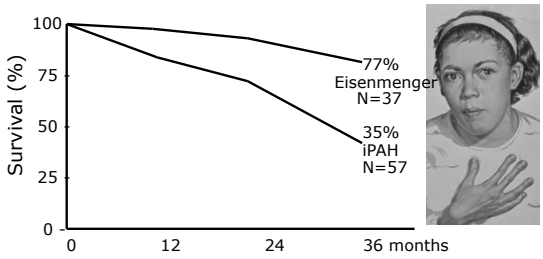
iPAH vs. Eisenmenger

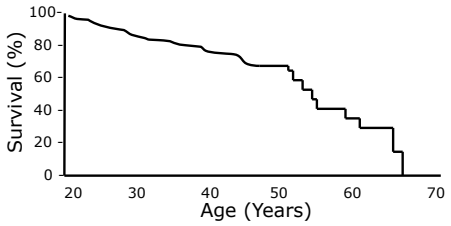
Outcome of Eisenmenger patients vs. iPAH



Hopkins WE et al J Heart Lung Transplant 1996;15:100-105

Survival of Adult Eisenmenger Patients

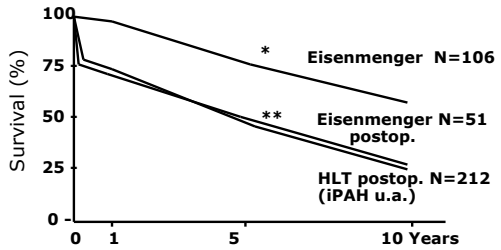
N = 109 (>18 yrs at entry)
Simple anatomy: 66 complex anatomy: 43



9 transplants (4 deaths), 33 additional deaths
median survival 52.6 yrs (age at death 37±13 yrs)

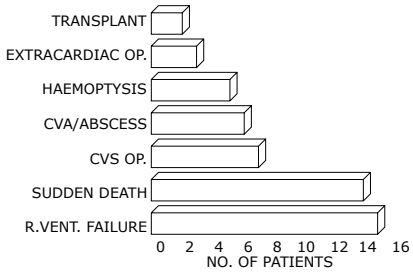
Cantor WJ et al Am J Cardiol 1999;84:677-81

Natural history of Eisenmenger vs. transplantation in Eisenmenger / iPAH



***** *Nagaya OH et al Am Heart J 2002;143:739-44*
*** Stoica SC et al Ann Thorac Surg 2001;72:1887-91*

Eisenmenger: Causes of Death



Somerville J: Int J Cardiol 1998;63:1-8

Eisenmenger: Predictors of outcome

- NYHA functional class, early presentation, complex anatomy
- RV dysfunction, elevated RAP, decreased systemic flow
- SV arrhythmias, RVH ECG index
- Noncardiac surgery, pregnancy
- Renal dysfinction
- But not: Syncope, haemoptysis, cerebral events

Cantor WJ et al Am J Cardiol 1999;84:677-81 (N=109)
Nagaya OH et al Am Heart J 2002;143:739-44 (N=106)
Daliento L et al Eur Heart J 1998;19:1845-55 (N=188)

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[a]Depending on age.
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BNP = brain natriuretic peptide; CI = cardiac index; 6MWT = 6-minute walking test; RAP = right atrial pressure; TAPSE = tricuspid annular plane systolic excursion; WHO-FC = WHO functional class.

Echo findings reported with best prognostic value:
pericardial effusion, indexed RA area, LV eccentricity index, RV Doppler index, tricuspid annular plane systolic excursion (TAPSE)

Eisenmenger: FU of RVF

RV Function, normal

systolic

Table 4 Systolic function

Variable	Studies	n	LRV (95% CI)	Mean (95% CI)	URV (95% CI)
TAPSE (mm) (Figure 17)	46	2320	16 (15-18)	23 (22-24)	30 (29-31)
Pulsed Doppler velocity at the annulus (cm/s)	43	2139	10 (9-11)	15 (14-15)	19 (18-20)
Color Doppler velocities at the annulus (cm/s)	5	281	6 (5-7)	10 (9-10)	14 (12-15)
Pulsed Doppler MPI (Figures 16 and 18)	17	686	0.15 (0.10-0.20)	0.28 (0.24-0.32)	0.40 (0.35-0.45)
Tissue Doppler MPI (Figure 18)	8	590	0.24 (0.16-0.32)	0.39 (0.34-0.45)	0.55 (0.47-0.63)
FAC (%) (Figure 8)	36	1276	35 (32-38)	49 (47-51)	63 (60-65)
RV EF (%) (Figure 8)	12	596	44 (38-50)	58 (53-63)	71 (66-77)
3D RV EF (%)	9	524	44 (39-49)	57 (53-61)	69 (65-74)
IVA (m/s^2)	12	389	2.2 (1.4-3.0)	3.7 (3.0-4.4)	5.2 (4.4-5.9)

CI, Confidence interval; *EF*, ejection fraction; *FAC*, fractional area change; *IVA*, isovolumic acceleration; *LRV*, lower reference value; *MPI*, myocardial performance index; *RV*, right ventricular; *TAPSE*, tricuspid annular plane systolic excursion; *3D*, three-dimensional; *URV*, upper reference value.

diastolic

Table 6 Diastolic function

Variable	Studies	n	LRV (95% CI)	Mean (95% CI)	URV (95% CI)
E (cm/s)	55	2866	35 (33-37)	54 (52-56)	73 (71-75)
A (cm/s)	55	3096	21 (19-24)	40 (38-41)	58 (55-60)
E/A ratio*	56	2994	0.8 (0.7-0.9)	1.4 (1.4-1.5)	2.1 (2.0-2.2)
Deceleration time (ms)	25	1284	120 (105-134)	174 (163-186)	229 (214-243)
IVRT (ms)	23	1241	23 (16-30)	48 (43-53)	73 (66-80)
E′ (cm/s)	40	1688	8 (7-9)	14 (13-14)	20 (19-21)
A′ (cm/s)	37	1575	7 (6-8)	13 (12-14)	20 (19-21)
E′/A′ ratio	29	1053	0.5 (0.4-0.6)	1.2 (1.1-1.3)	1.9 (1.7-2.0)
E/E′ ratio	3	359	2 (1-2)	4 (4-4)	6 (5-7)

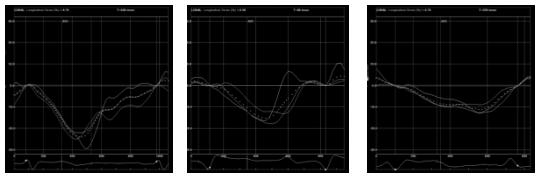
CI, Confidence interval; *IVRT*, isovolumic relaxation time; *LRV*, lower reference value; *URV*, upper reference value.
*Age-dependent: average E/A ratio = 1.6 in the third decade of life, decreasing by 0.1 for every subsequent decade.

summary

Variable	Unit	Abnormal
Chamber dimensions		
RV basal diameter	cm	>4.2
RV subcostal wall thickness	cm	>0.5
RVOT PSAX distal diameter	cm	>2.7
RVOT PLAX proximal diameter	cm	>3.3
RA major dimension	cm	>5.3
RA minor dimension	cm	>4.4
RA end-systolic area	cm^2	>18
Systolic function		
TAPSE	cm	<1.6
Pulsed Doppler peak velocity at the annulus	cm/s	<10
Pulsed Doppler MPI	–	>0.40
Tissue Doppler MPI	–	>0.55
FAC (%)	%	<35
Diastolic function		
E/A ratio	–	<0.8 or >2.1
E/E′ ratio	–	>6
Deceleration time (ms)	ms	<120

Rudski LG et al J Am Soc Echocardiogr. 2010;23:685-713
ASE/EAE/CSE Guidelines for the echocardiographic assessment of the right heart in adults

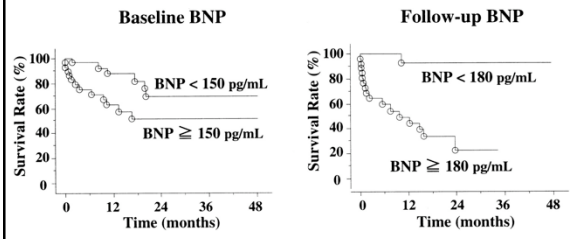
Speckle Tracking – RV Longitudinal Strain



NORMAL Eisenmenger 2 Eisenmenger 3

BNP in PPH (iPAH)

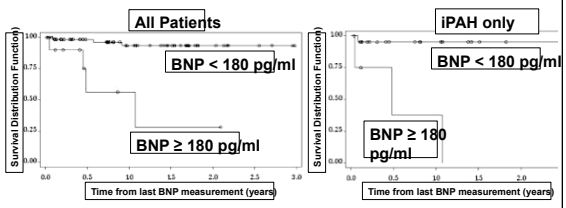
N = 60, Measurements repeated after 3mo (mean FU) in 53
49 pts. received i.v. or oral prostacyclin; mean clinical FU 2yrs



Nagaya N et al Circuation 2000;102:865-870

BNP in Pediatric Patients with Pulmonary Arterial Hypertension

N=78 No strong correlation of BNP with echo and hemodynamics, but of change in BNP and change in hemodynamics



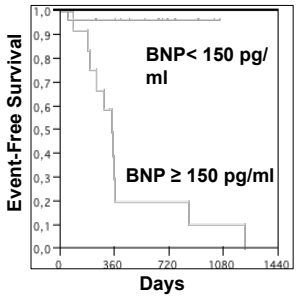
Bernus A et al Chest 2009;135:745-751

50 children with PHT (i or assoc., 23 CHD): BNP >130pg/ml predicted death or TX
However, 6 of 14 had values lower than that *Lammers AE et al IJC 2009;135:21*

BNP - Predictor of Outcome in CHD

RESULTS: Pts. with PHT

Event-Free Survival: BNP <150 vs BNP ≥150



48 pts.
CHD, PAP >50mmHg

FU 15±11 yrs

Events:
Death
Hosp. for CHF
Transplantion

Gabriel H et al Circulation 2002 (Suppl) / AHA

Pulmonary hypertension - Echocardiography Following adolscence and adults with CHD

- Careful noninvasive assessment of PAP in all adults with CHD at FU visit
  - detect elevation of PAP and progression
- In pts. with severe PAH / Eisenmenger 3 – 6 months evaluation:
  - signs of right heart failure
  - functional status
  - 6MWT (CPET)
  - Echo (RVF, pericardial effusion)
  - BNP / NT-proBNP plasma levels

Thank you for your attention!