Pulmonary hypertension

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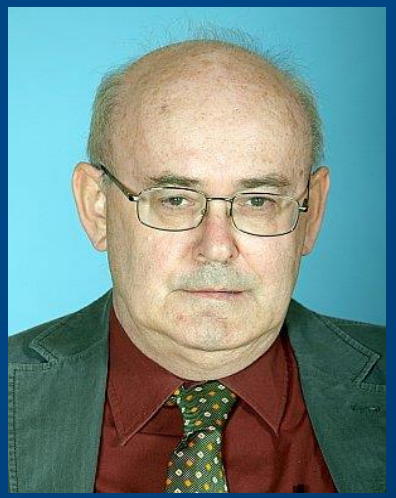
Prof Widimsky

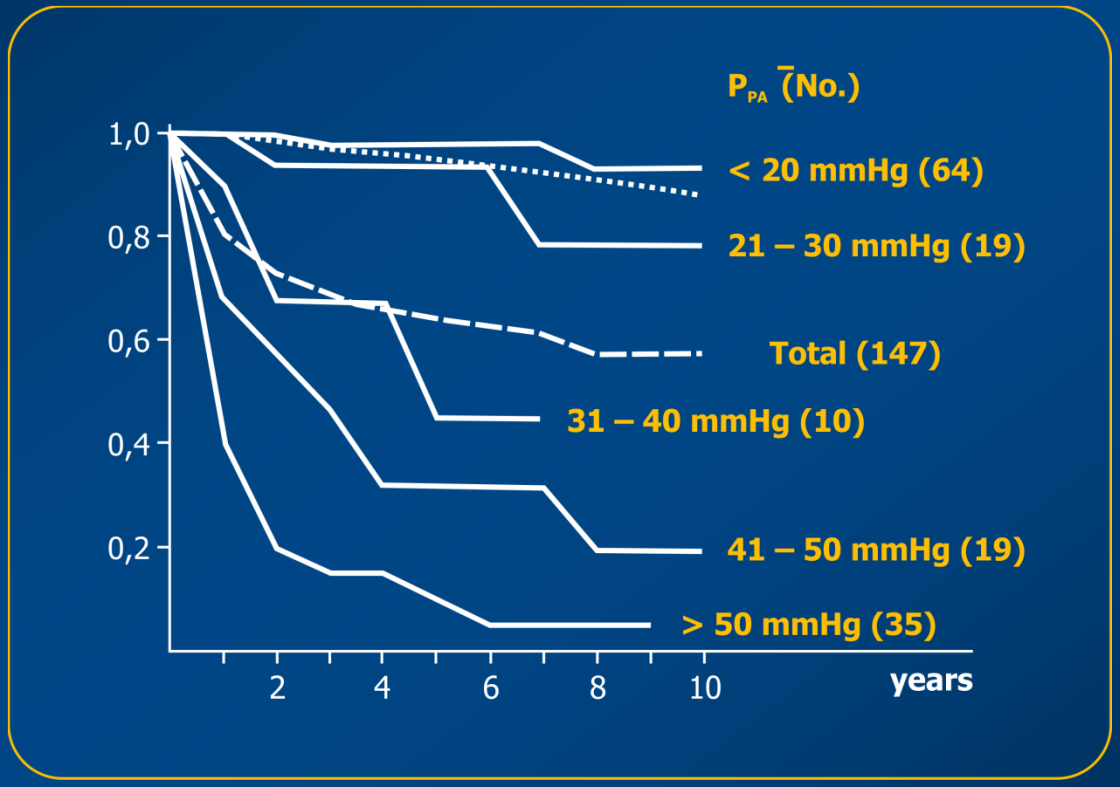


Prof Herget

Groverova award- ATS

One of the most quoted publications – destiny of post-PE patients depending on PH

Cumulative survival



Cumulative survival curves according to the initial PPA. Dotted line represents predicted survival among men 40-50 years old.

Riedel M, Staněk V, Widimský J, Přerovský I. Chest 1982

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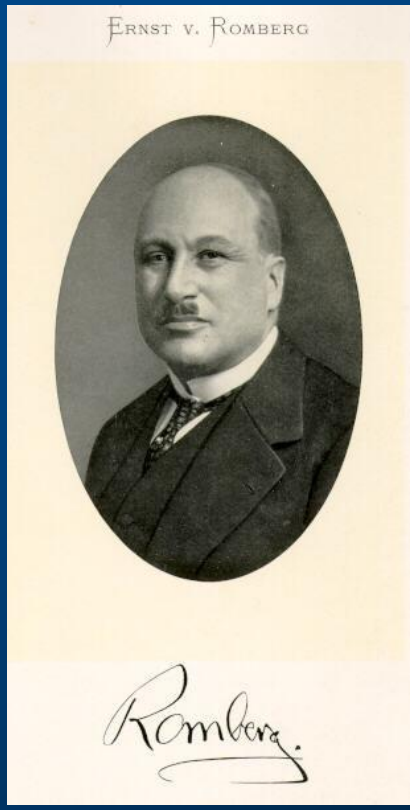
History of pulmonary hypertension

1891	Ernst von Romberg „Uber Sklerose der Lungen Arterie“
1901	Abel Ayerza of Argentina „ cardiacos negros“
1951	Dresdale „PRIMARY PULMONARY HYPERTENSION“
1967	aminorex fumarate – epidemy of PAH
1973	WHO symposium – Geneva – 1st classification
1981	US National Institute of Health: PPH
1998	WHO Evian
2003	WHO Venice
2008	WHO Dana Point
2015	**US, ESC guidelines**

Case Report Described by Romberg

First symptoms

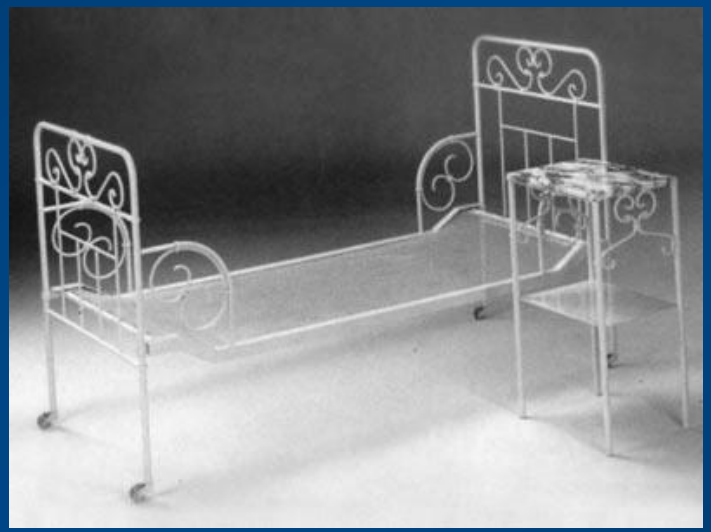
- 24-year old man, occupation: gardener
- First symptoms 1 ¼ years before presentation
- Increasing shortness of breath
- Headaches, often dizziness
- Swollen liver and spleen
- Cyanosis on exertion
- No edema
- At work till admission to hospital



Romberg, Deutsches Archiv für Klinische Medizin 1891

Treatment Strategy 1891

- Bed rest
- Digitalis



Digitalis purpurea L.

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M

„Nice Classification“ of pulmonary hypertension

1. PAH

- **1.1 idiopathic**
- **1.2 hereditary**
- **1.3 caused by medicines and toxines**
- **1.4 associated with:**
  - ***Connective tissue disease***
  - ***HIV infection***
  - ***Portal hypertension***
  - ***Congenital heart defect***
  - ***Chronic hemolytic anemia***
- **1.5 Chronic pulmonary hypertension – children**
- **1.6 Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis**

2. Pulmonary hypertension by left ventricular failure

3. Pulmonary hypertension by pulmonary parenchyma or hypoxic

4. Chronic thromboembolic pulmonary hypertension

5. Multifactorial pulmonary hypertension

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Schema of PH according to hemodynamic examination

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

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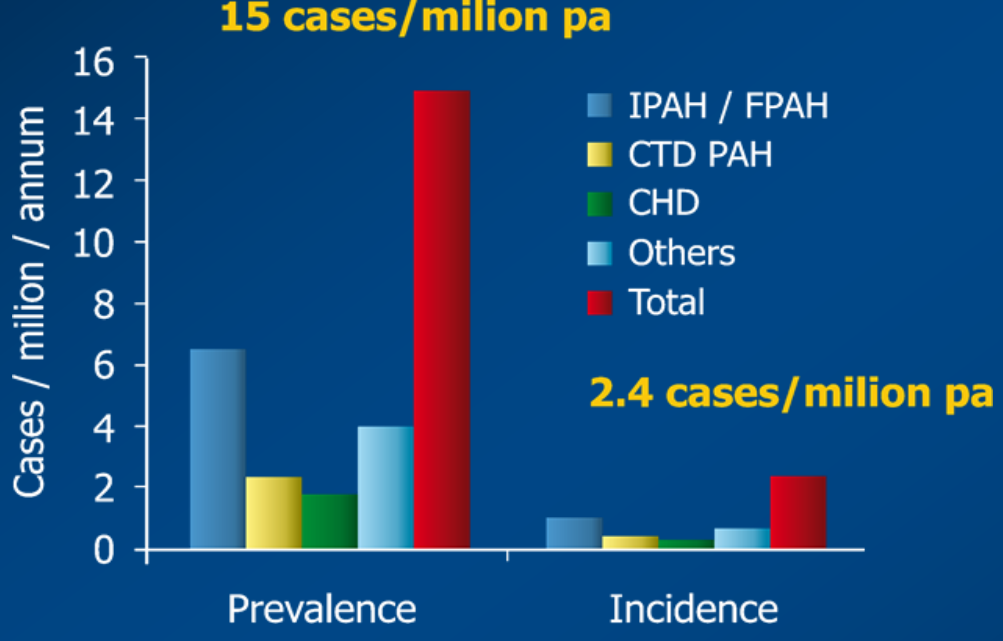
PAH epidemiology

Number of patients : 686 PAH (all types)



Age* (years)	50 ± 15
Women	65.1%
Man	34.9%

*11.4 % are older than 70 years

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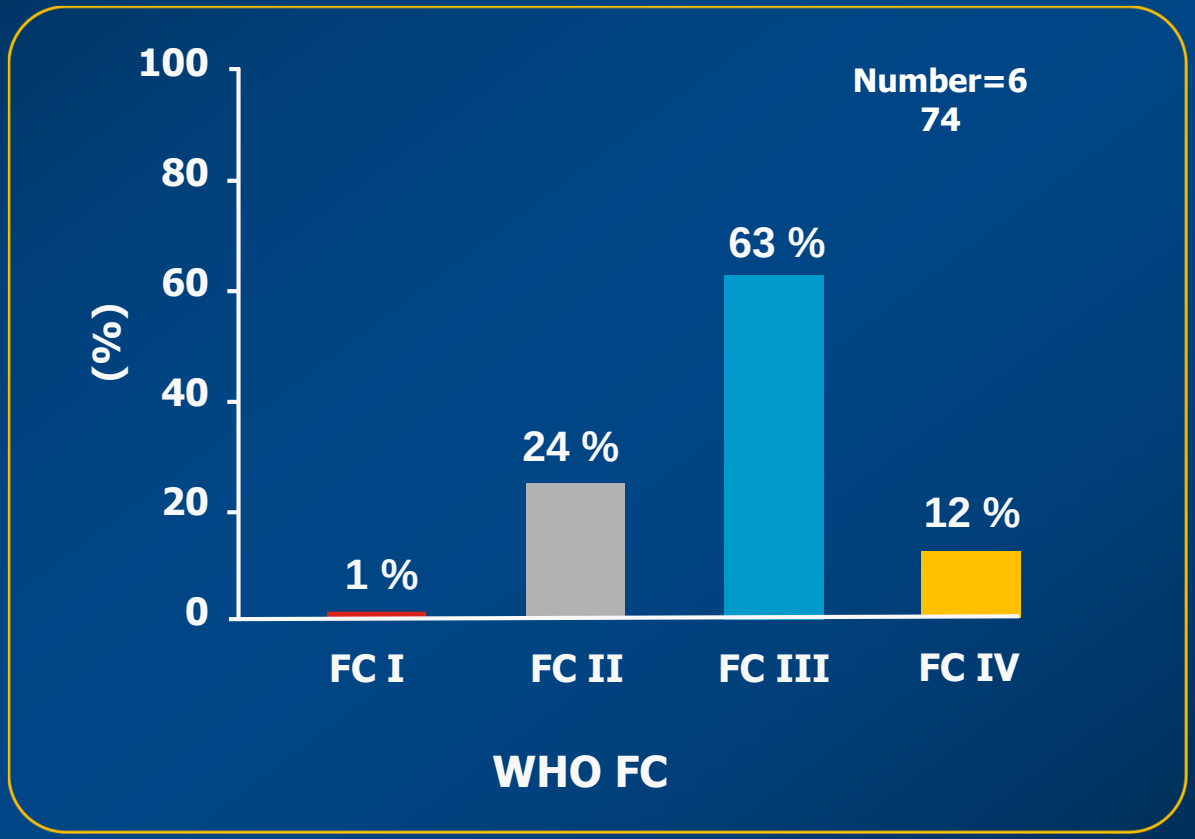
PH diagnosis is often late

French National Registry (2002 – 2003)



Humbert 2006

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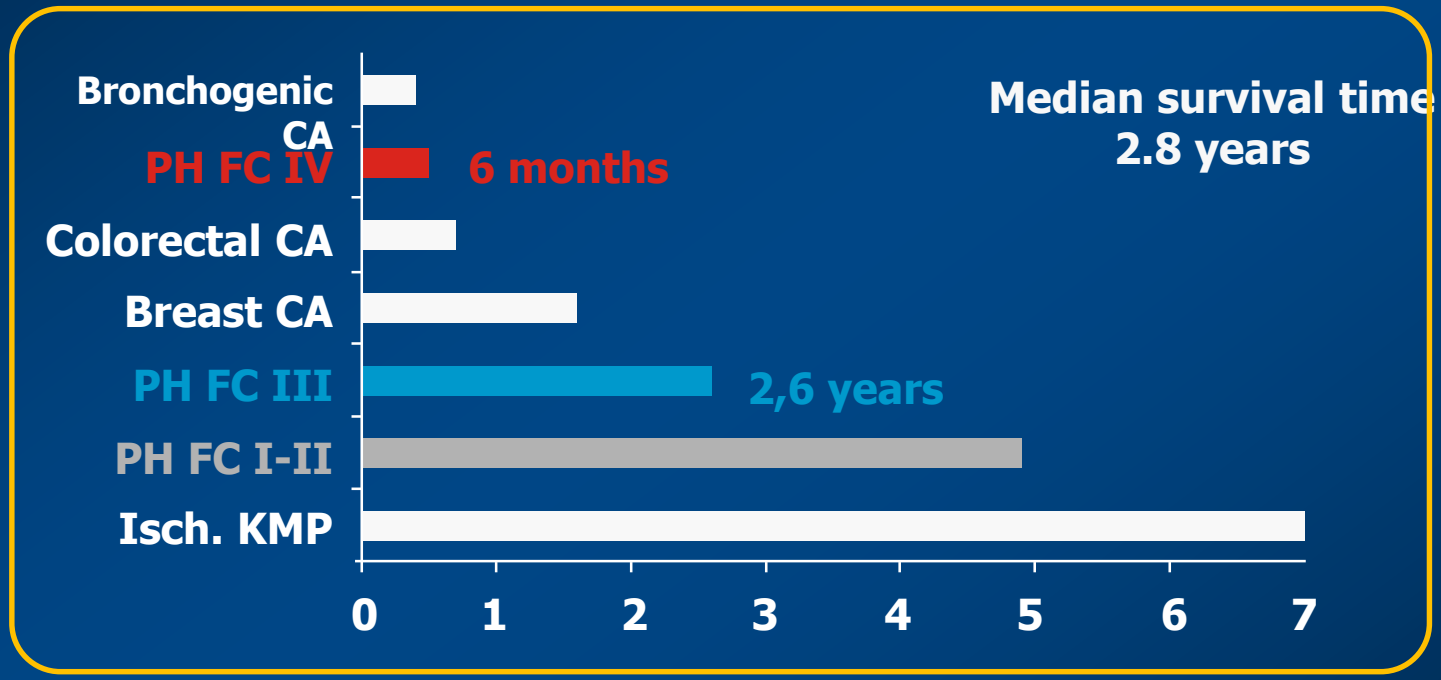
PAH prediction in relation to WHO FC



- Early diagnosis of PAH may help patients to survive.

D´Alonzo, 1991
Kato 2001
Bjoraker 1998

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Prognostic factors for survival of patients with PAH

Functional capacity

- NYHA / WHO degree

Exercise tolerance

- 6 - minute walk test

Hemodynamics

- mRAP, CI, AP

Echo/Doppler

- Tei index, pericardial exsudate, index excentricity, RA area

Sitbon et al. JACC 2002;40:780; Tei et al. J Am Soc Echocardiogr 1996:9:838

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Median survival

according to NYHA classification prior to modern treatment development Ann Intern Med 1991

	months	years
NYHA I a II	58,6	4,9
NYHA III	31,5	2,6
NYHA IV	6	0,5

PAH Prognosis

Ann Intern Med 1991, 343-9

1 year	**68 %**
3 years	**48 %**
5 years	**25 - 30 %**

Medium pulmonary artery pressure	55 mm Hg:	48 months
	85 mm Hg:	12 months
Pressure in right ventricle	10 mm Hg:	46 months
	20 mm Hg:	1 month
Heart index	CI>4l/min/m^2:	43 months
	CI<2l/min/m^2:	17 months

Hemodynamics and FC

	I / II (173)	III (423)	IV (84)	Total (680)
Data available from catheterization	94 %	96 %	93 %	95 %
RAP (mmHg)	6 ± 4	9 ± 5	11 ± 7	8 ± 5
mPAP (mmHg)	51 ± 17	56 ± 15	57 ± 13	55 ± 15
Cardiac output (l/min)	5,0 ± 1,6	4,2 ± 1,4	3,5 ± 1,5	4,3 ± 1,5
SvO_2 (%)	67 ± 8	62 ± 8	54 ± 9	63 ± 9
TPR (W.u.)	9,5 ± 6,8	13,0 ± 6,9	16,2 ± 8,2	12,5 ± 7,3

Humbert 2006

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PAH level of risk

Low risk	Prediction factors	High risk
No	Clinical manifestation of insufficiency at RV (right ventricle)	Yes
Progressive	Progression	Rapid
II,III	WHO classification	IV
More than > 400 m	6 MWT	Less than < 300 m
Minimally increased	BNP	Significantly increased
Not extensive RV disorder	ECHO	Pericardial effusion, disorder of RV
Normal or almost normal	Hemodynamics	↑ PS, ↓CI

McLaughlin 2008.

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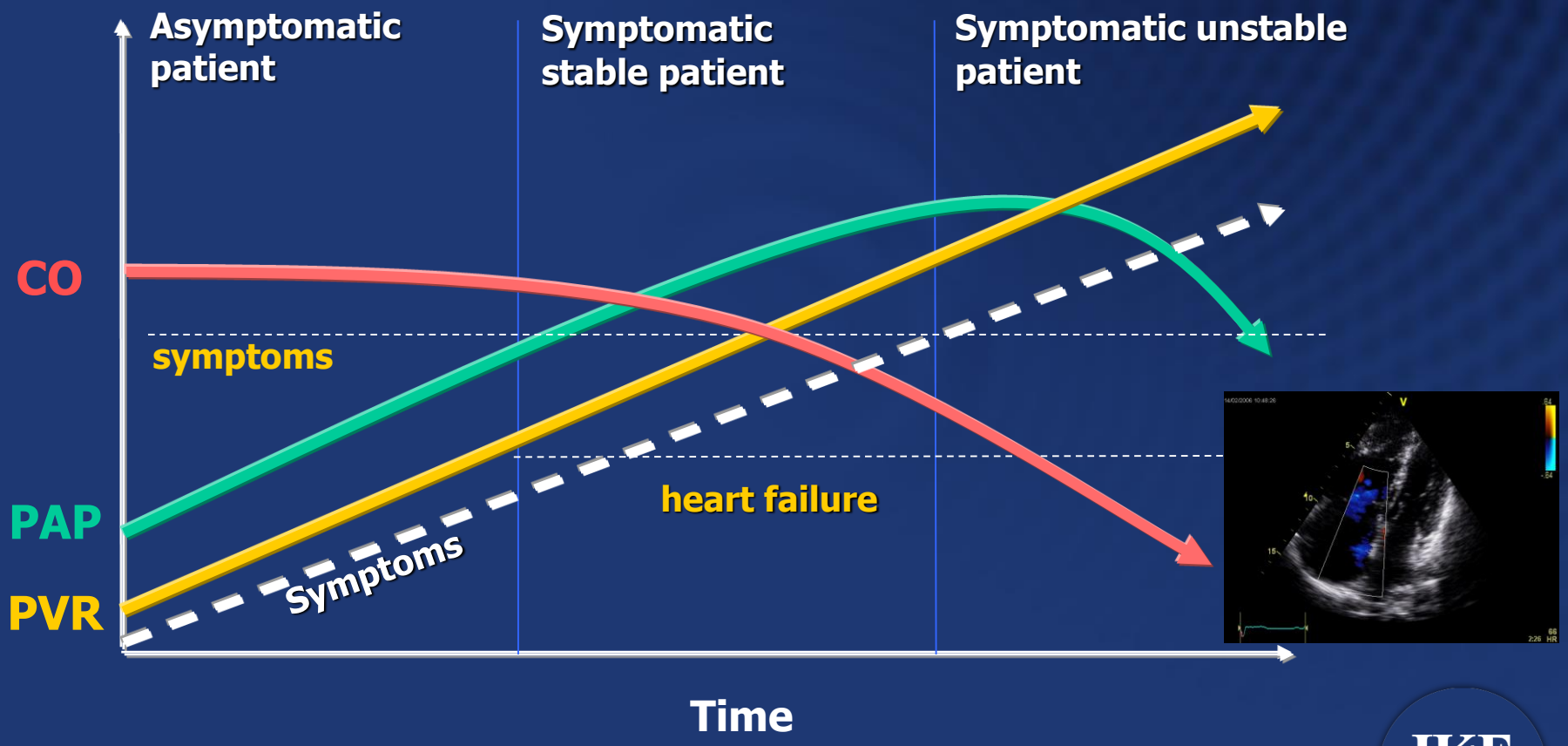
Progression of Pulmonary Hypertension



Rich, Harrison's Principles of Internal Medicine. 15th ed. 2001:1506-1507

Examination methods

EKG

Hypertrophy of right ventricle in 87 % and right - hand axis in 79 % patients with idiopathic pulmonary arterial hypertension (IPAH)

sensitivity 55 %

specificity 70 %

Normal EKG

does not exclude PH

Examination methods

Thorax X-ray

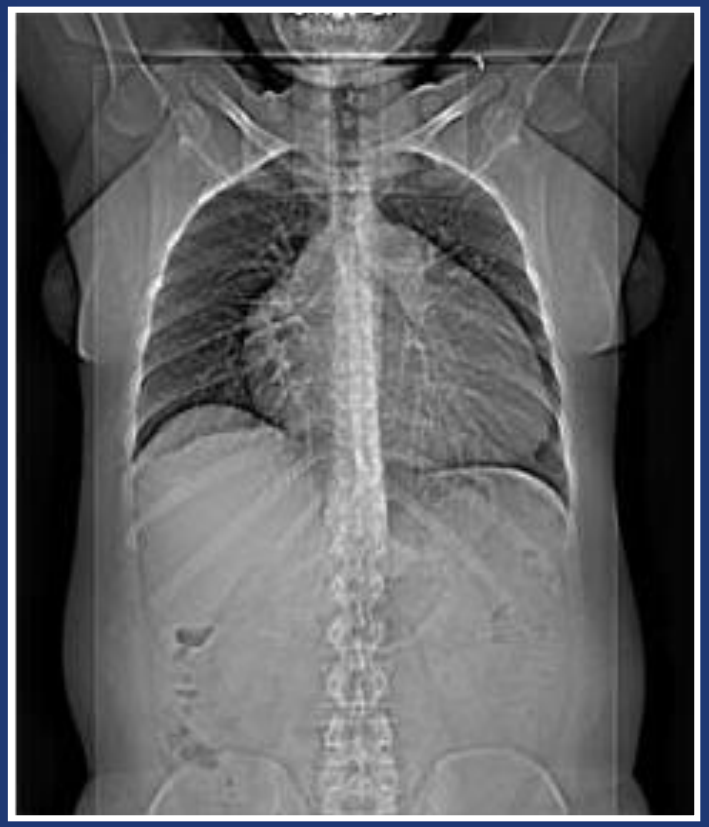
Abnormal X-ray picture in

90 % patients at the time of IPAH diagnosis

- aortic root dilatation, faded peripheral vessel drawing

-right chamber and ventricle dilatation

Normal X-ray picture does not exclude light post - capillar pulmonary hypertension



Examination methods

Echocardiographic examination

Doppler echocardiography is an excellent non-invasive method for PH-suspected patients

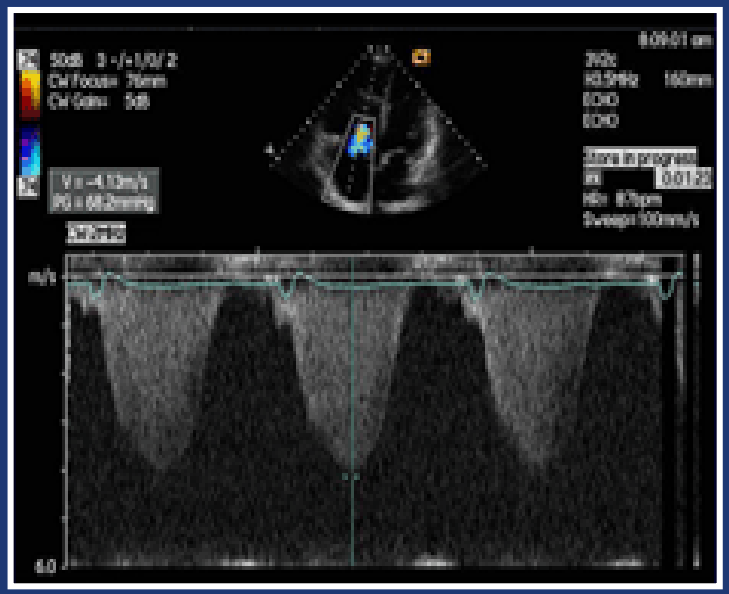
Flow curve in a. pulmonalis – acceleration time (I.,II.,III types (W))

Peak and telediastolic gradient on pulmonal regurgitation

Max. gradient on tricuspidal regurgitation

PH consequences

- dilatation, ventricle hypertrophy
- paradoxical movement of interventricular septum
- right ventricle has a D-shape
- dilatation of PM

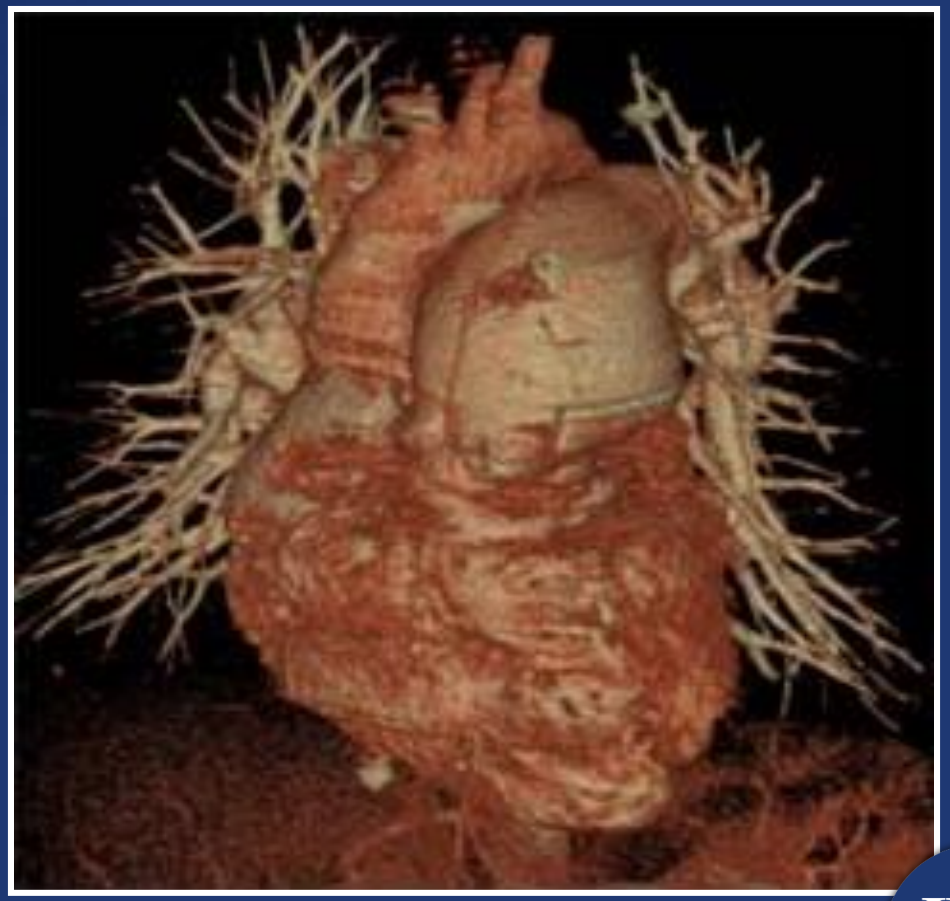


Diagnostics of PAH: clinical + echo

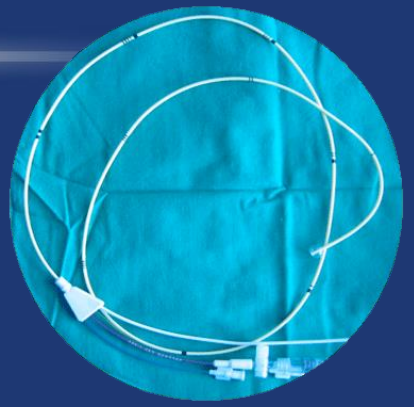
- **Exclude passive pulmonary hypertension caused by:**
  - valve diseases
  - left-sided heart failure on systolic dysfunction of left ventricle and / or diastolic dysfunction of left ventricle
- **Exclude cardiomyopathy**
- **Exclude pericardial disease**

CT angiography

In patients, whose V/P scintigraphy shows segmental or subsegmental defects of perfusion with normal ventilation.

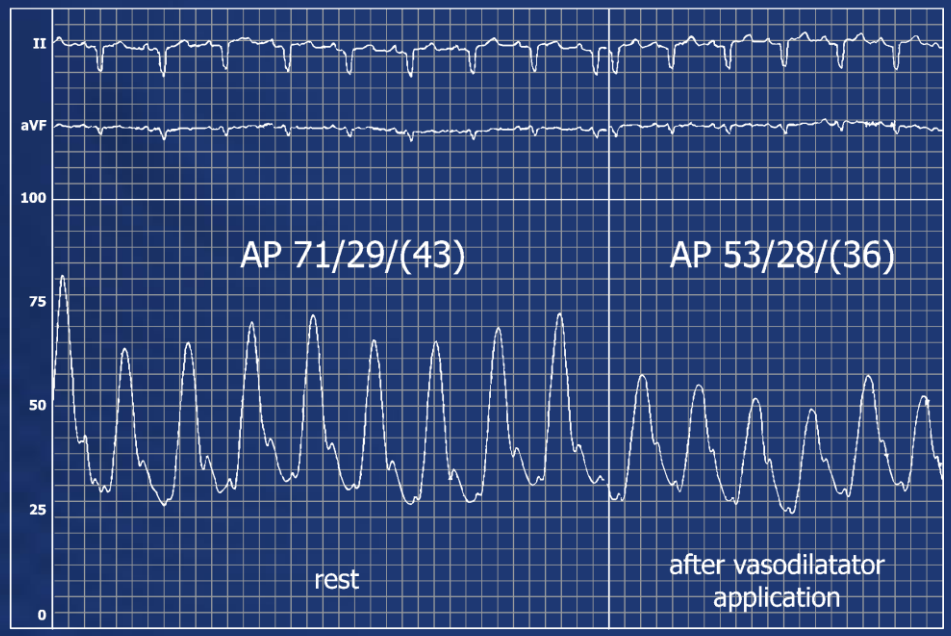


Right - sided heart catheterization



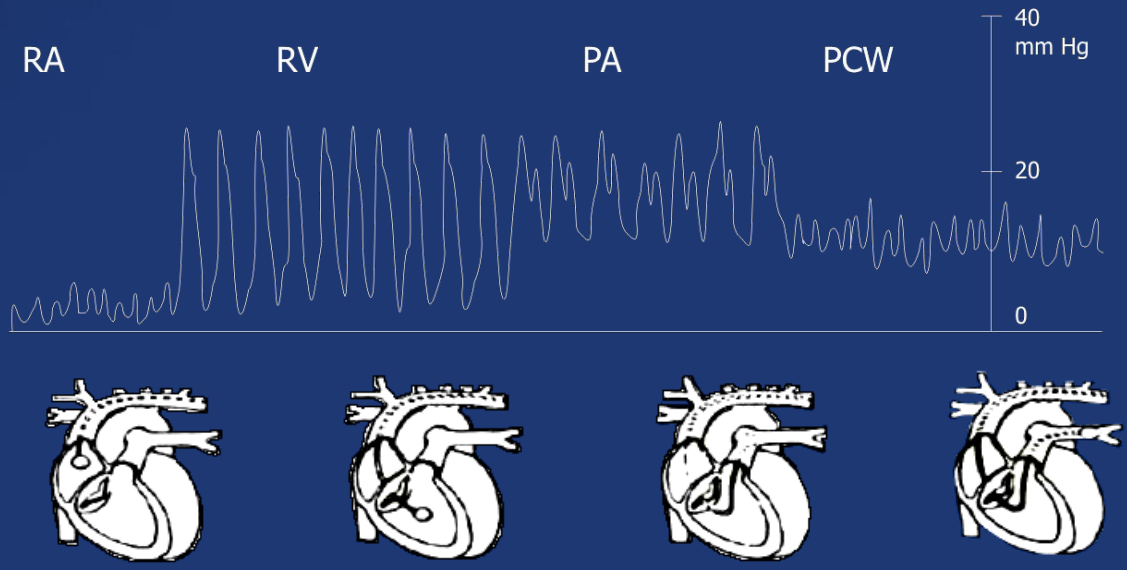
1) Presence of pulmonary hypertension
2) Type of pulmonary hypertension
3) Vasodilatation testing
4) Prognosis

pressure curve of pulmonary artery



Breakdown by hemodynamic examination

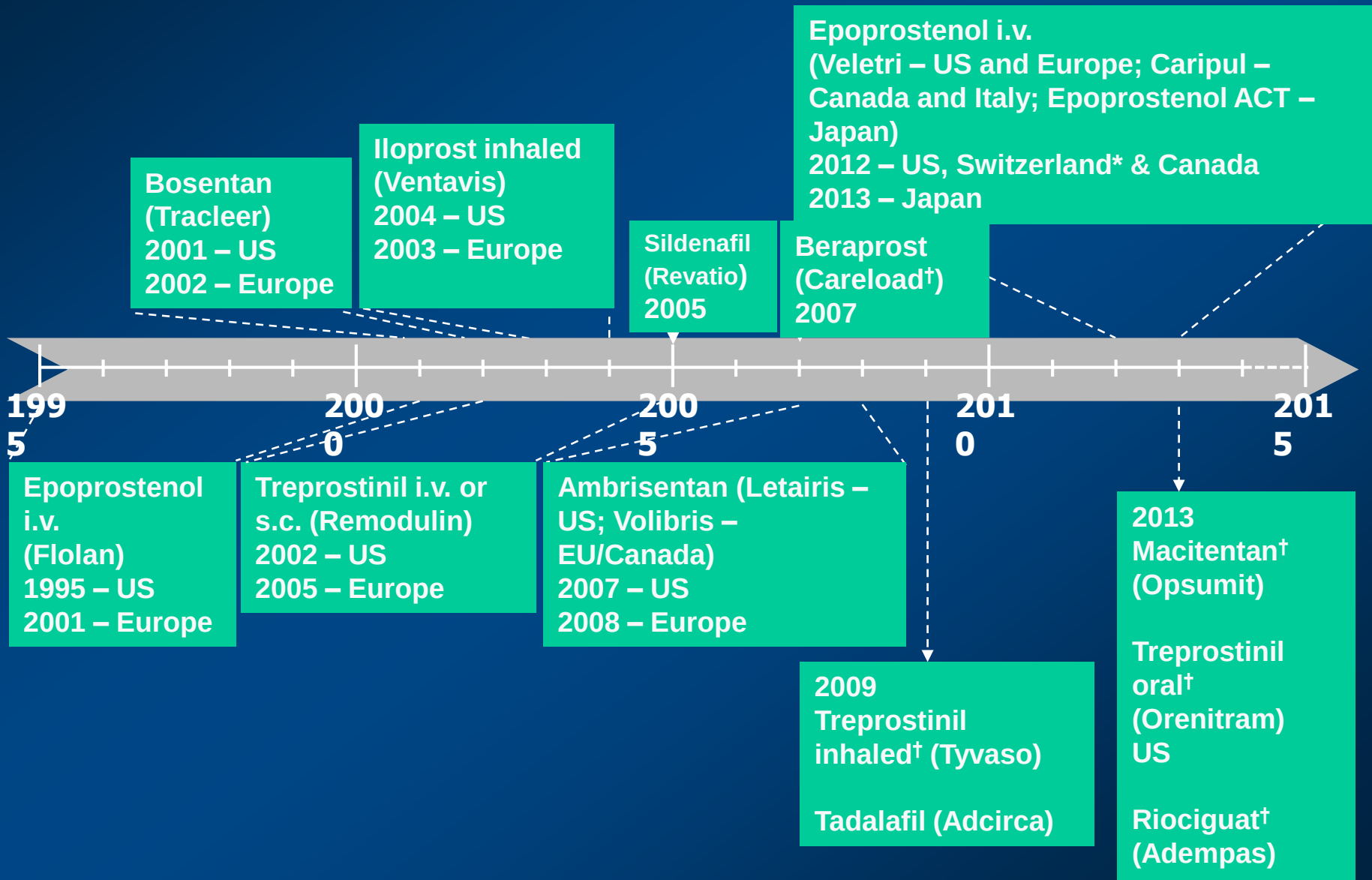
(mmHg)	mPAP	sPAP
LIGHT	26-35	36-45
MEDIUM	36-45	46-60
HEAVY	> 45	> 60

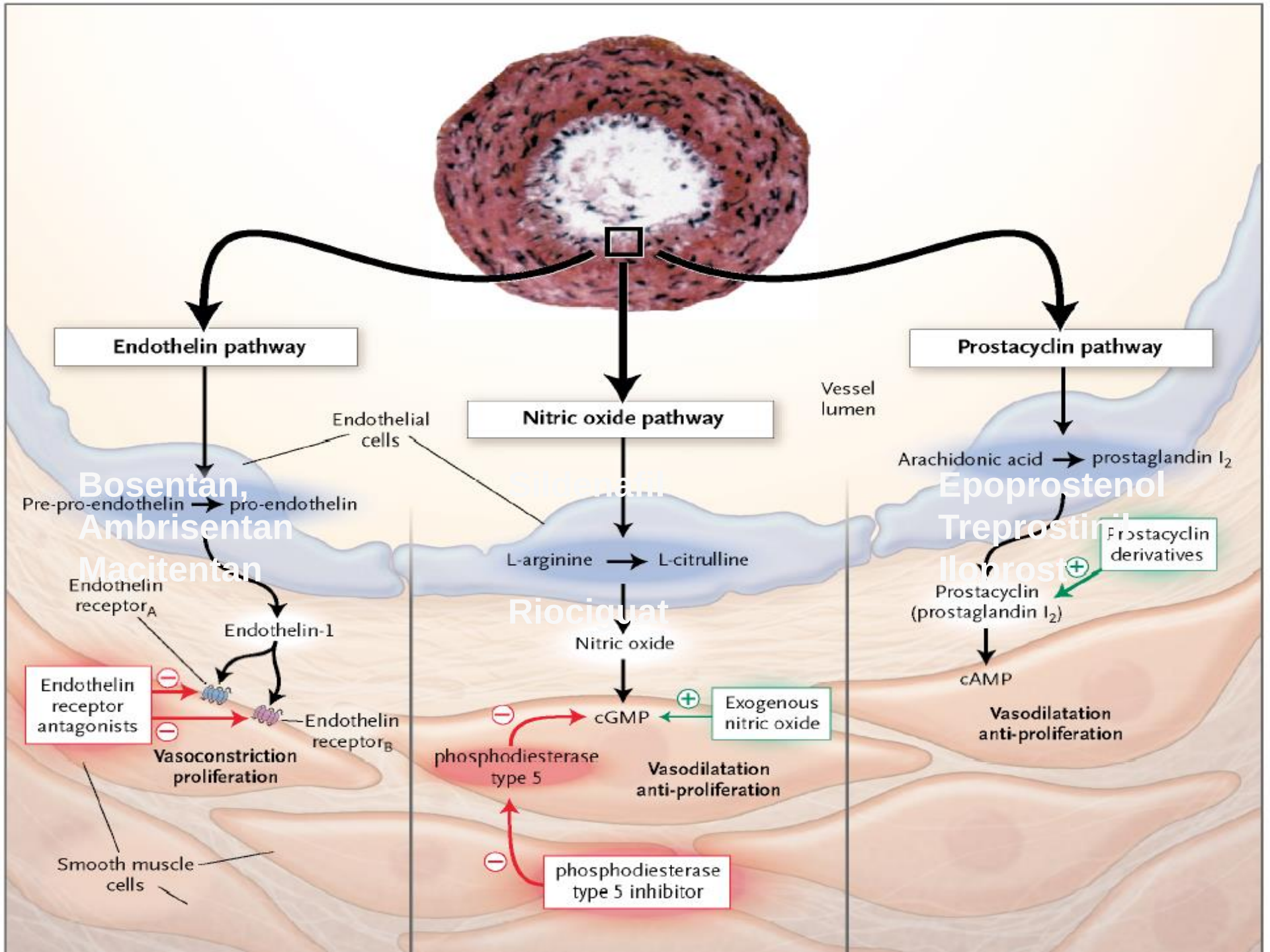


Vazodilatators used for testing

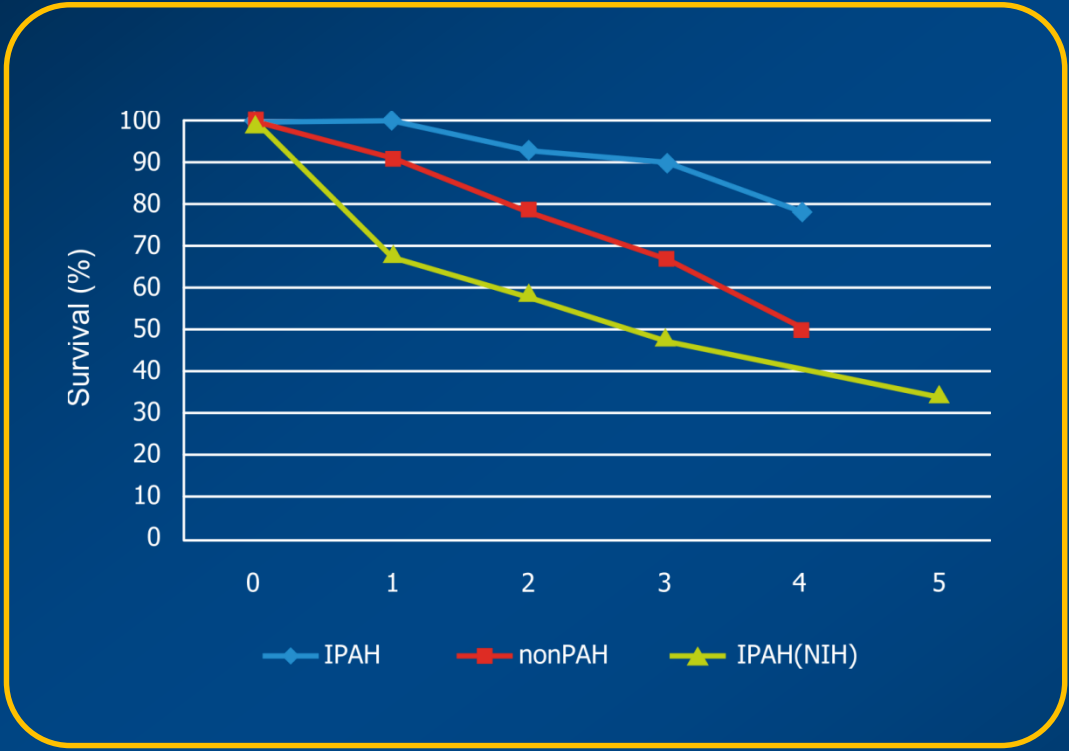
Substance	Initial dose	Maximum dose	Protocol
Nitric oxide inhalation	10 ppm	80 ppm	Increase dose by 10 ppm every 5 minutes
Prostacyclin i.v.	2 ng/kg/min.	16 ng/kg/min.	Increase dose by 2 ng/kg/min. every 10 minutes
Adenosin i.v.	10 µg/kg/min.	50 µg/kg/min.	Increase dose by 10 µg/kg/min. every 10 minutes

Treatment terapie PAH




Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Vessel lumen
Endothelial cells
Bosentan,
Ambrisentan
Macitentan
Sildenafil
Epoprostenol
Treprostinil
Iloprost
Riociguat
Pre-pro-endothelin
pro-endothelin
Arachidonic acid
prostaglandin I2
Prostacyclin derivatives
L-arginine
L-citrulline
Endothelin receptorA
Endothelin-1
Prostacyclin (prostaglandin I2)
Nitric oxide
cAMP
Endothelin receptor antagonists
Endothelin receptorB
Vasoconstriction proliferation
cGMP
Exogenous nitric oxide
Vasodilatation anti-proliferation
phosphodiesterase type 5
Vasodilatation anti-proliferation
phosphodiesterase type 5 inhibitor
Smooth muscle cells

Situation in Czech Republic to date, IKEM facility – Mortality of group



Mortality after 1 year	**1,5 %**
Mortality after 2 years	**9,8 %**
Mortality after 3 years	**11,9 %**
Mortality after 4 years	**21,2 %**

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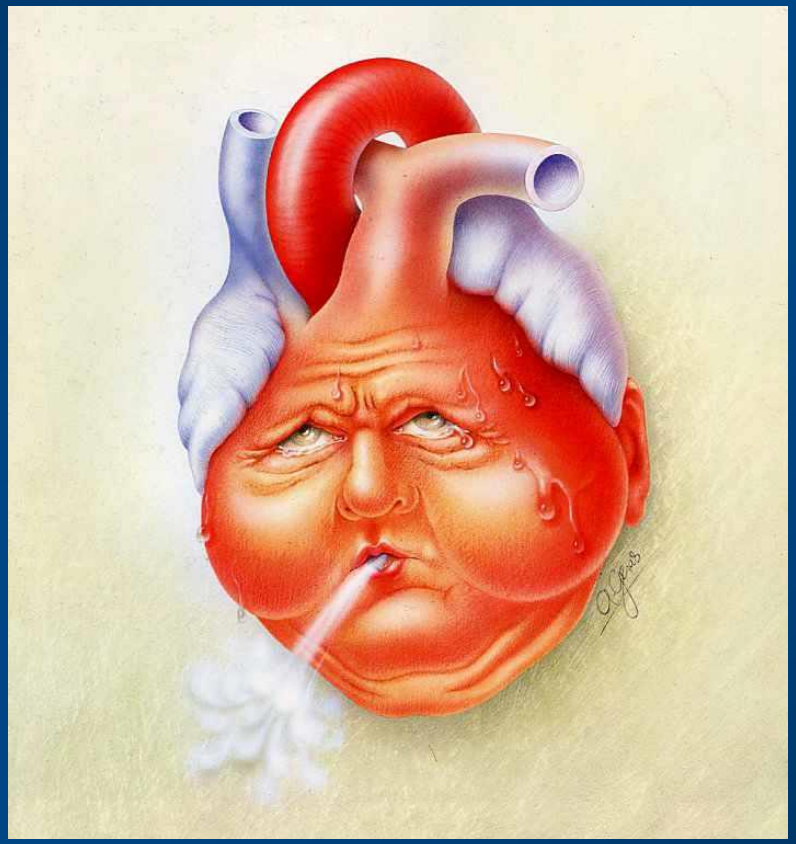
Pulmonary Hypertension and Chronic Heart Failure



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PH occurrence in CHF and predisposing factors

320 patients		**28 %**	**36 %**	**17 %**	**19 %**	
	Overall	**PVR (WU) <1.5**	**PVR (WU) 1.5-2.49**	**PVR (WU) 2.5-3.49**	**PVR (WU) >3.5**	**p**
Age (yr)	52 + 10	49 ± 12	53 ± 09	52 ± 10	53 ± 11	NS
LVEF (%)	23 ± 9	24 ± 07	23 ± 08	24 ± 13	21 ± 7	NS
NYHA %						
2	34	36	31	33	35	
3	44	45	41	44	43	NS
4	22	19	28	23	22	
IHD (%)	51	49	55	50	52	NS
DCM (%)	49	51	45	50	48	

DCM - dilated cardiomyopathy; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; NS = nonsignificant; NYHA = New York Heart Association Classification; PVR = pulmonary vascular resistance; WU = Wood Units.

Butler 1999

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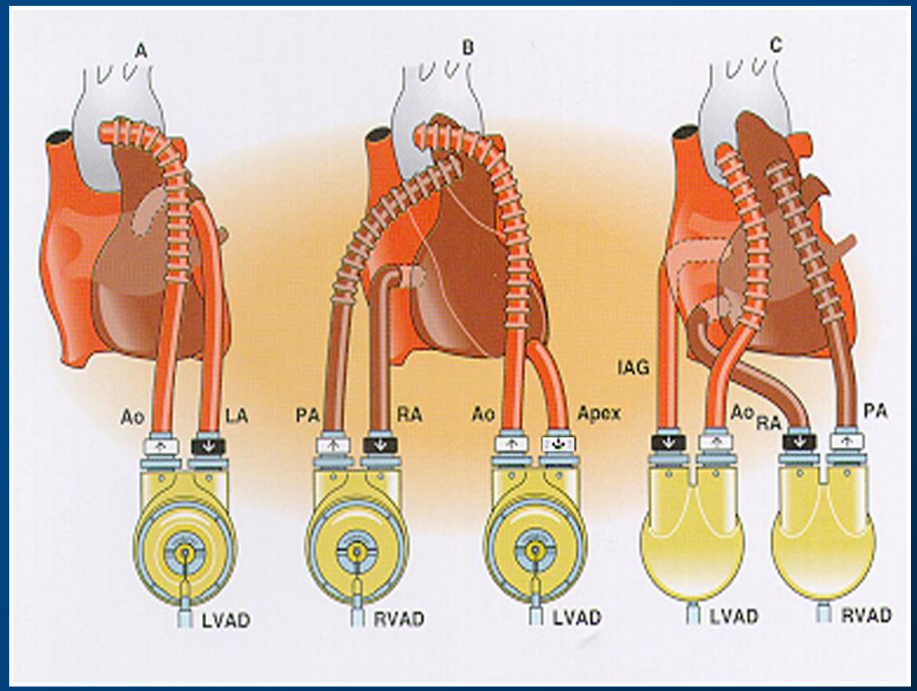
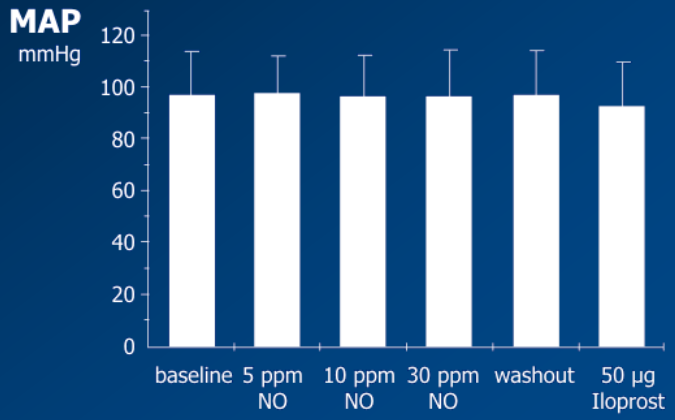
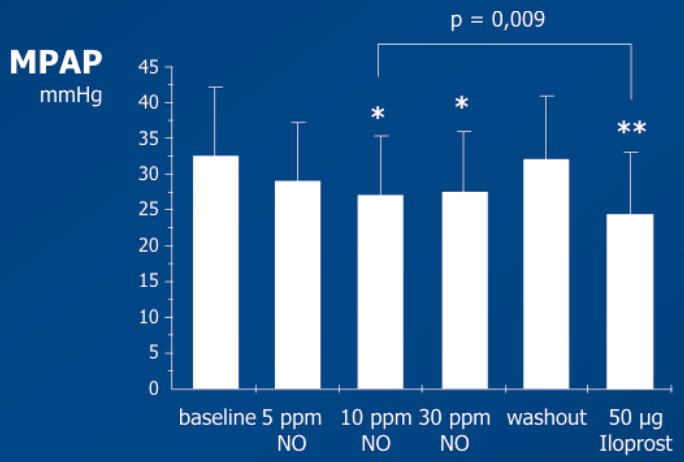
New Approaches to PH in CHF

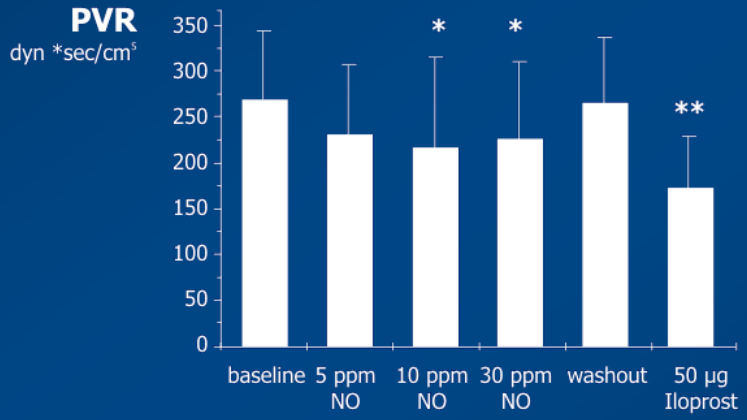
- Prostacyclin?
- Sildenafil?
- Mechanical support?

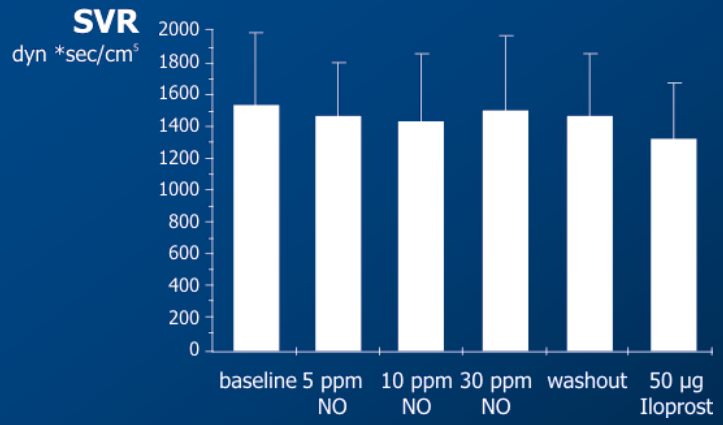


PH Reversibility Testing - iloprost









Sablotzki 2002

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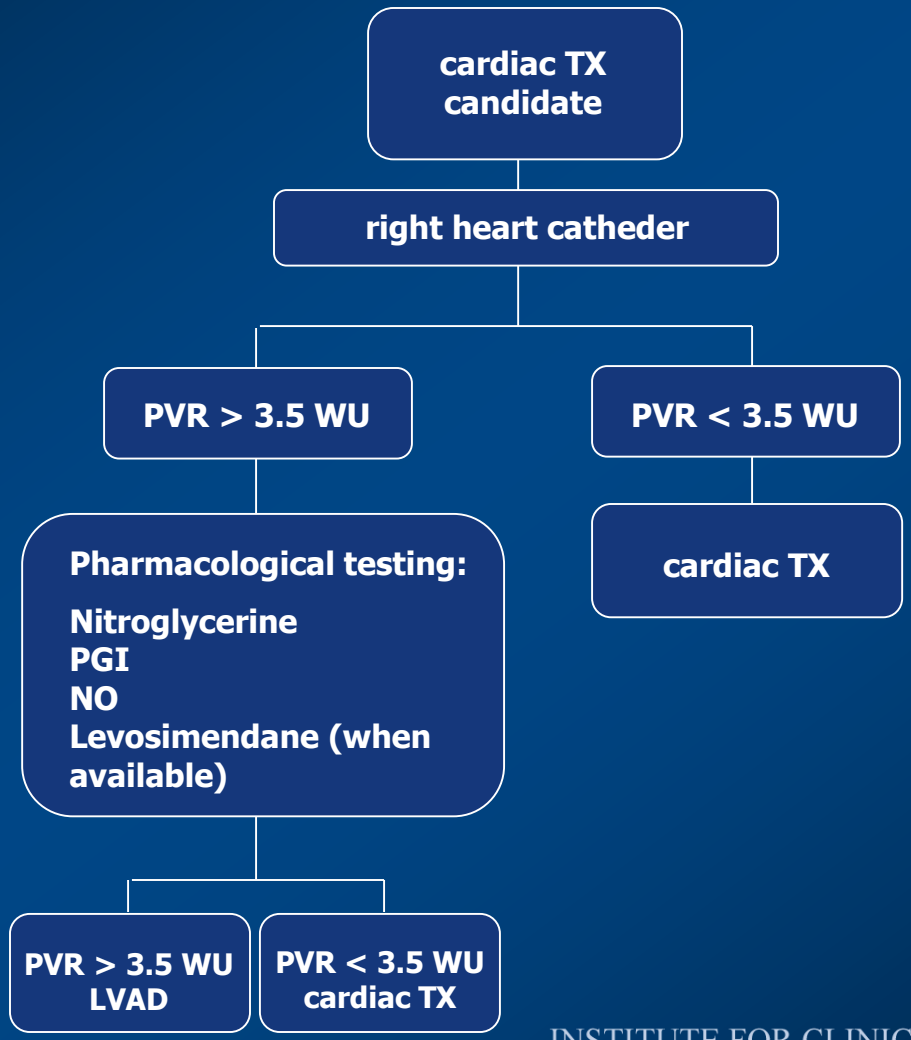
Mechanical support and CHF



Zimpfler 2007

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Mechanical support and CHF

Variable	All patients	*P* value*	Continuous flow†	Pulsatile flow‡	*P* value§
n	35		27	8	
PVR					
Baseline	5.1 ± 2.6	—	5.3 ± 2.7	5.1 ± 3.5	.976
3-d FUP	2.9 ± 1.3	<.0001	2.7 ± 1.2	3.2 ± 1.3	.310
6-wk FUP	2.0 ± 0.8	<.0001	2.1 ± 0.8	1.9 ± 0.9	.905
After testing	4.5 ± 2.1	—	—	—	—
PAsyst					
Baseline	63.2 ± 9.3	—	65.2 ± 13.0	65.3 ± 10	.976
3-d FUP	39.6 ± 10.6	<.0001	37.6 ± 9.4	43.4 ± 12.5	.175
6-wk FUP	26.7 ± 3.6	<.0001	29.6 ± 6.5	28.1 ± 7.5	.236
After testing	36 ± 10.2	—	—	—	—
PAmean					
Baseline	44.0 ± 6.2	—	45.5 ± 6.8	43.0 ± 8.4	.397
3-d FUP	28.6 ± 7.3	<.0001	28.1 ± 7.5	29.6 ± 6.5	.604
6-wk FUP	18.4 ± 4.3	<.0001	19.0 ± 4.2	17.8 ± 5.1	.571
After testing	30.2 ± 6.8	—	—	—	—
PCWP					
Baseline	28.1 ± 6.0	—	29.0 ± 5.7	27.1 ± 7.0	.439
3-d FUP	12.0 ± 5.7	<.0001	11.9 ± 4.4	13.0 ± 8.3	.641
6-wk FUP	10.0 ± 3.6	<.0001	10.1 ± 13.7	9.1 ± 3.7	.572
After testing	15.8 ± 1.9	—	—	—	—
CO					
Baseline	3.1 ± 0.8	—	3.0 ± 0.6	2.6 ± 0.7	.601
3-y FUP	5.7 ± 0.7	<.0001	6.2 ± 1.1	5.1 ± 0.8	.375
6-wk FUP	4.0 ± 0.9	.002	4.2 ± 0.8	4.6 ± 0.4	.453
After testing	3.2 ± 7	—	—	—	—

Zimpfler 2007

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Acute hemodynamic effect sildenafil in heart transplant candidates with severe pulmonary hypertension

From January 2007 through December 2007, we performed a total of

263 RHC

↓

16 patient

(TPG > 15 mmHg and/or PAR > = 3 W.u)

↓

PGE 1 was administered at a dose of 200 ug/kg/min

↓

sildenafil citrate 40 mg p.o.

↓

and after 1 hour we measure hemodynamic parameters

Al-Hiti, Melenovsky Chest 2008

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Acute hemodynamic effect sildenafil in heart transplant candidates with severe pulmonary hypertension

Results

	rest	Δ PGE 1	Δ sildenafil	p Δ sil.vs. ΔPGE1
HR	82.6±	-0.3±6.8	-7.0±8.0	0.088
TK	86.2±11.6	-10.3±5.9	-10.6±15.4	0.092
MPAP	49.6±5.4	-6.3±7.5	-12.3±7.1	0.019
PCW	25.5±3.7	-4.9±6.1	-2.6±5.8	0.471
TPG	24.1±6.0	-1.4±9.9	-9.7±3.7	0.016
CO	3.5±0.8	-0.4±1.2	0.8±0.7	0.318
PVR	7.1±2.2	-1.6±2.3	-3.5±1.6	0.027

Al-Hiti, Melenovsky Chest 2008

Conclusion

- Untreated PAH is a fast killing disease.
- Upon diagnosis setting, most patients are not indicated for treatment with Calcium channel blockers.
- Definitive diagnosis and treatment decision belongs to the hands of specialist centers.
- Patients with suspected PAH should be referred to a specialist centre, whenever:
  - A. PG max tric. reg. = 30 - 40 mmHg, progressing, or symptoms are present
  - B. PG max tric. reg. > 40 mmHg also in asymptomatic patients

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