LÉČBA PLICNÍ HYPERTENZE U SRDEČNÍHO SELHÁNÍ

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	Nemám konflikt zájmů	Mám konflikt zájmů	Specifikace konfliktu (vyjmenujte subjekty, firmy či instituce, se kterými Vaše spolupráce může vést ke konfliktu zájmů)
Zaměstnanecký poměr	X		
Vlastník / akcionář	X		
Konzultant	X		
Přednášková činnost	X		
Člen poradních sborů (advisory boards)	X		
Podpora výzkumu / granty	X		
Jiné honoráře (např. za klinické studie či registry)	X		

J. Widimský*, H. Dixon**

Normal values of central haemodynamics at rest and during exercise

A preliminary report of a retrospective WHO study

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** Dept. of Statistics, World Health Organisation, Geneva, Switzerland

Table 1b - Number of persons by centre

Centre	At rest	Exercise
Basel	105	101
Berne	44	44
Birmingham	39	28
Boston	45	—
Denver	46	22
Düsseldorf	49	48
Kobe	5	—
Lyon	30	30
Prague	48	41
Sendai	9	—
Stockholm	16	15
Yamagouchi	2	—
Wisconsin	30	—
La Paz	61	23
List of participating centres enclosed.	**529**	**352**

178

Table 5 - Normal data at rest, supine position, age 20-29

	mean	range	SD
PAm	13.7	6 - 21	3.0
PW	7.8	1 - 14	2.8
LVd	8.2	2 - 15	2.8
RVs	24.7	11 - 42	5.3
RVd	5.1	0 - 14	2.9
PAR	0.8	0.1 - 2	0.3

Table 6 - Normal data at rest, supine position, age 30-39

	mean	range	SD
PAm	14.5	7 - 23	3.2
PW	8.3	3 - 15	2.5
LVd	8.8	5 - 15	3.4
RVs	24.5	16 - 35	5.1
RVd	4.8	0 - 10	2.4
PAR	0.9	0.2 - 2.3	0.5

Table 7 - Normal data at rest, supine position, age 40-49

	mean	range	SD
PAm	15.0	6 - 24	4.3
PW	7.8	0 - 15	3.2
LVd	5.9	3 - 8	2.1
RVs	22.6	15 - 32	4.8
RVd	4.0	0 - 9	2.1
PAR	1.0	0.3 - 2.5	0.5

Table 8 - Normal data at rest, supine position, age 50-59

	mean	range	SD
PAm	16.2	8 - 22	3.7
PW	8.3	2 - 13	2.9
RVs	24.6	21 - 30	3.0
RVd	3.0	0 - 6	2.1
PAR	1.3	0.4 - 2.2	0.5

Table 9 - Normal data at rest, supine position, age 60-69

	mean	range	SD
PAm	15.9	9 - 22	2.7
PW	9.1	3 - 16	2.8
RVs	27.0	22 - 37	3.8
RVd	6.1	2 - 14	2.8
PAR	1.1	0.5 - 2.1	0.4

Normální hodnoty hemodynamického vyšetření

$\bar{P}_{pa}$ mmHg	14.0 ± 3.3
Systolic P_{pa} mmHg	20.8 ± 4.4
Diastolic P_{pa} mmHg	8.8 ± 3.0
P_{paw} mmHg	8.0 + 2.9
Cardiac output $L \cdot min^{-1}$	7.3 ± 2.3
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	4.1 ± 1.3
PVR $dyn \cdot s \cdot cm^{-5}$	74 ± 30

Obdobné hemodynamické parametry jako WHO studie 1980

Kovacs G., eta al Eur Respir J 2009

Pulmonary hypertension

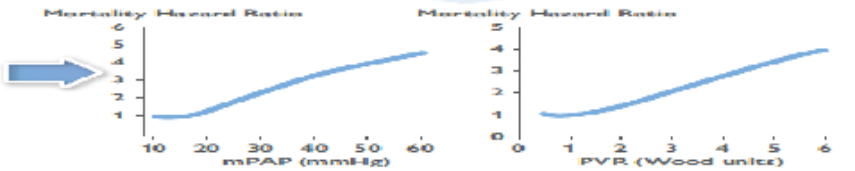
Prevalence

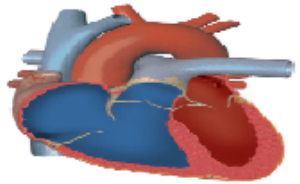
1%

Global population

Pulmonary congestion in post-capillary PH

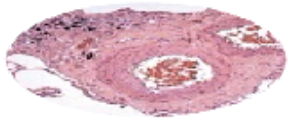
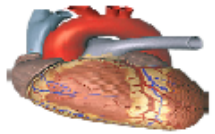
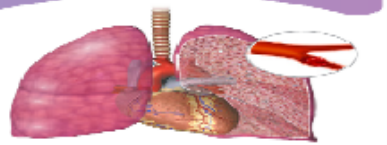
Pulmonary vascular disease / obstruction in pre-capillary PH





Right heart failure

Clinical Classification

Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
				
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematologic disorders • Systemic disorders
Prevalence				
Rare			Rare	Rare
Therapeutic Stra				
Medical therapy • PAH drugs • CCB in responders Lung transplantation	**IpcPH:** • Treatment of LHD[a] **CpcPH:** • Treatment of LHD[a] • Potentially: PAH drugs (trials)	**PH-lung disease:** • Optimized care of underlying lung disease **Severe PH:** • Potentially: PAH drugs (trials)	Surgical therapy: • PEA Interventional: • BPA Medical therapy: • PH drugs	Optimized treatment of underlying disease • Potentially: PAH drugs (trials)

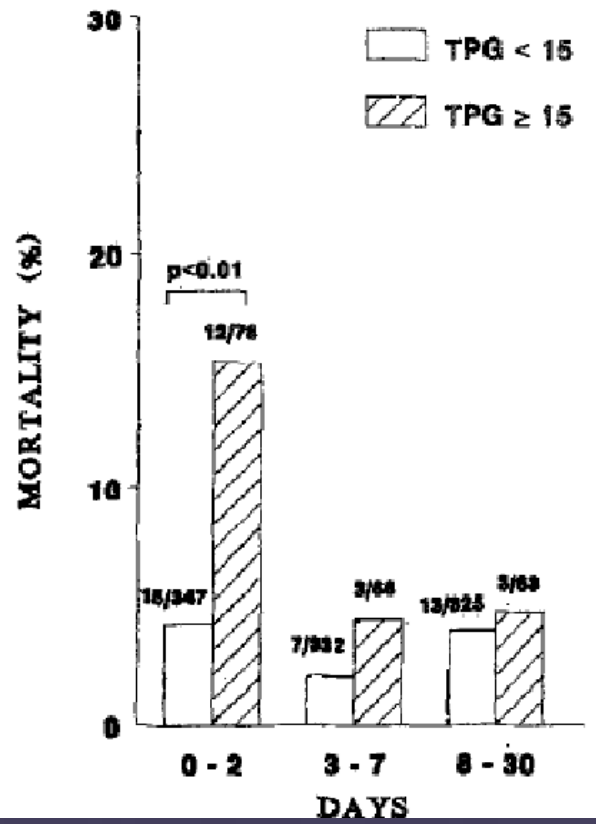
ESC ERS

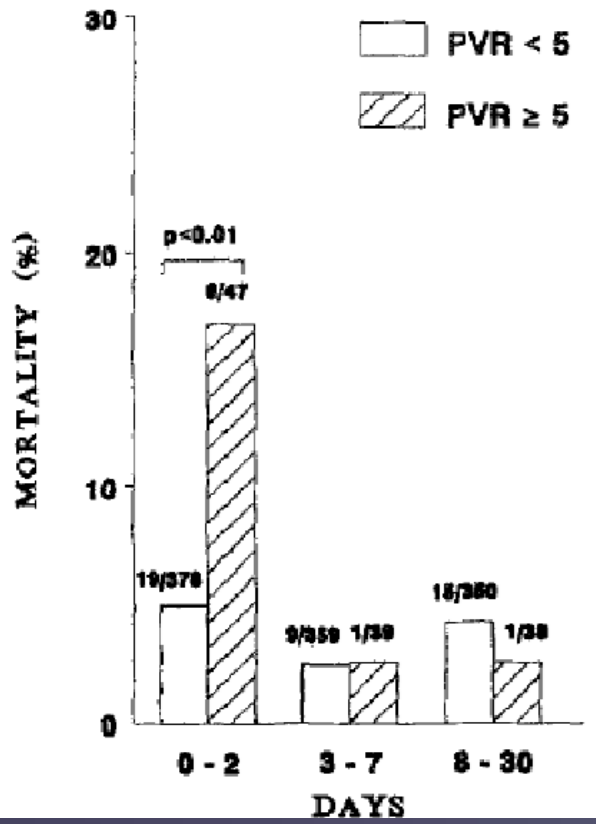
Rozdělení PH dle hemodynamického vyšetření

Definice	Charakteristika	Klinická skupina
Plicní hypertenze (PH)	Střední tlak v AP > 20 mmHg	Všechny skupiny
Prekapilární PH	Střední tlak v AP > 20 mmHg PAWP ≤ 15 mmHg PAR > 2 W.j.	1. PAH 3. PH hypoxická 4. CTEPH 5. PH nejasné etiologie
Postkapilární PH Isolovaná postkapilární PH Kombinovaná PH	Střední tlak v PAP >20 mmHg PAWP > 15 mmHg PAR ≤ 2W.j. ??????? PAR >2 W.j. ???????	2. PH při CHSS

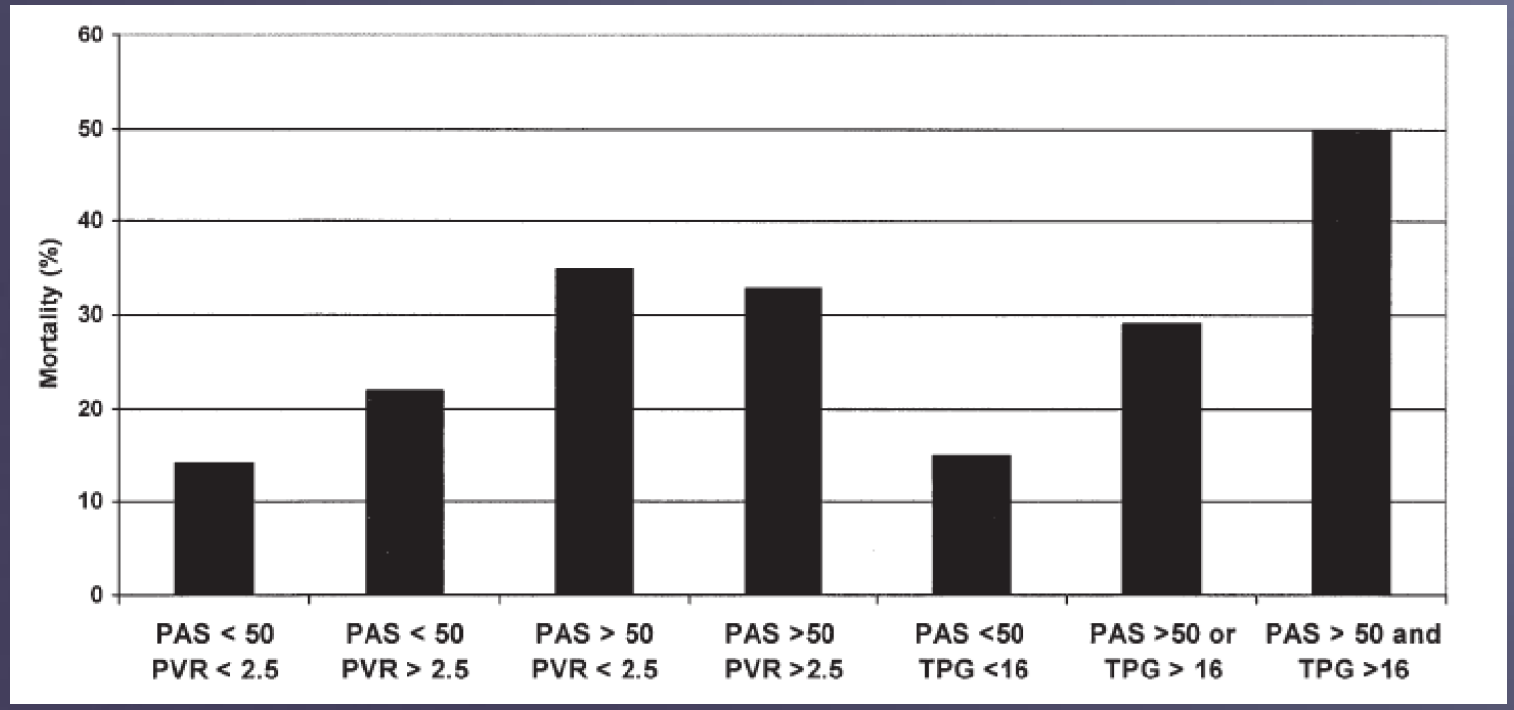
Transpulmonální gradient (TPG) = AP střed - PAWP
Plicní arteriální rezistence (PAR) = TPG/srdeční výdej

Humbert M. et al.:European Heart Journal (2022) 00, 1–114


30
20
10
0
MORTALITY (%)
TPG < 15
TPG ≥ 15
p<0.01
12/78
16/347
3/44
7/332
13/325
3/69
0 - 2
3 - 7
8 - 30
DAYS

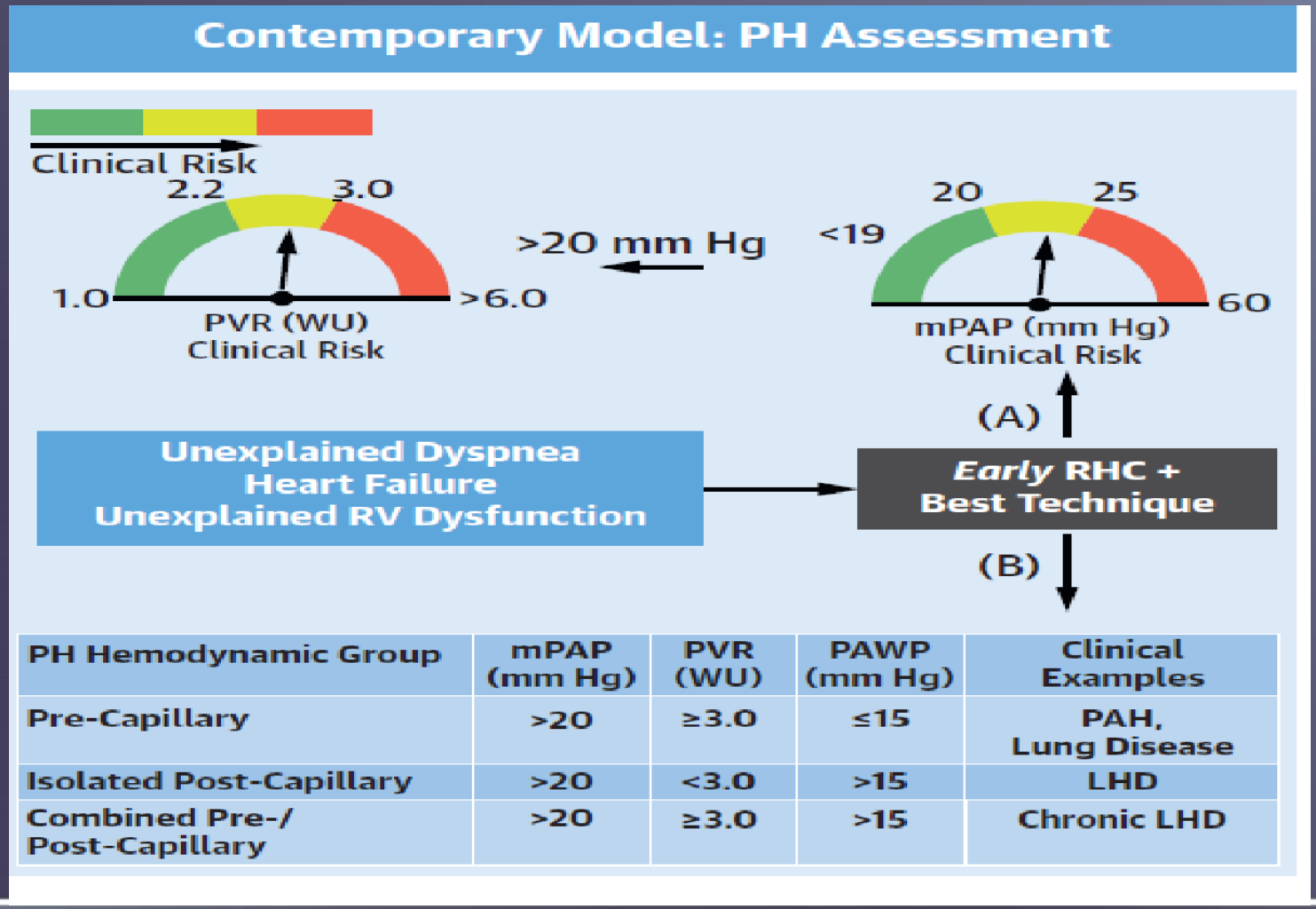

30
20
10
0
MORTALITY (%)
PVR < 5
PVR ≥ 5
p<0.01
8/47
19/378
9/359
1/38
15/380
1/38
0 - 2
3 - 7
8 - 30
DAYS

Predikce mortality po Tx srdce na základě hodnoty TPG



Butler J. et al.: The Journal Heart and Lang Transplantation 2005

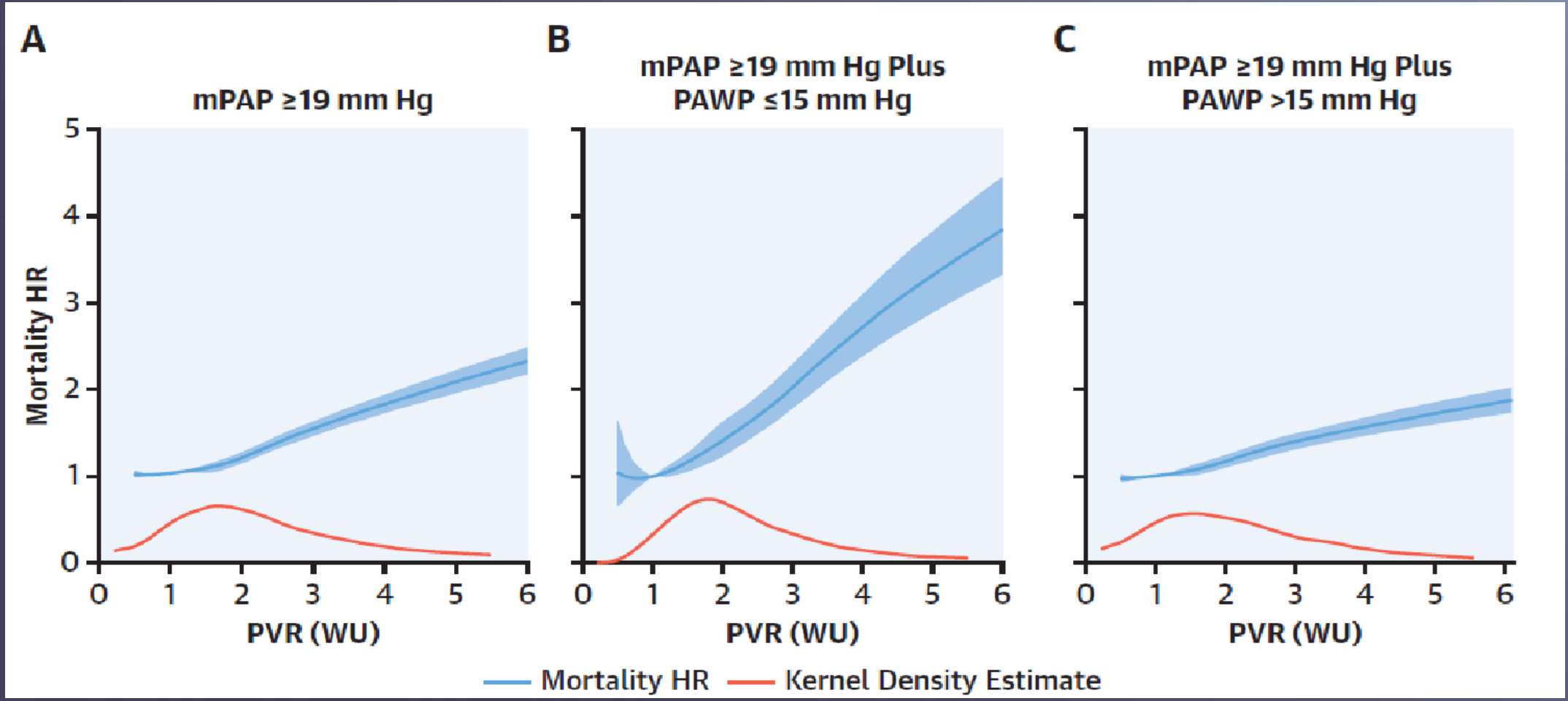
Analýza více než 40 000 nemocných se srdečním selháním



PH Hemodynamic Group	mPAP (mm Hg)	PVR (WU)	PAWP (mm Hg)	Clinical Examples
Pre-Capillary	>20	≥3.0	≤15	PAH, Lung Disease
Isolated Post-Capillary	>20	<3.0	>15	LHD
Combined Pre-/ Post-Capillary	>20	≥3.0	>15	Chronic LHD

Maron JACC VOL.76,NO.22,2020

Analýza více než 40 000 nemocných se srdečním selháním



Marlon JACC VOL.76,NO.22,2020

Testování reverzibility PH

Podávávají se:

nitroprussid

NO

Levosimendan

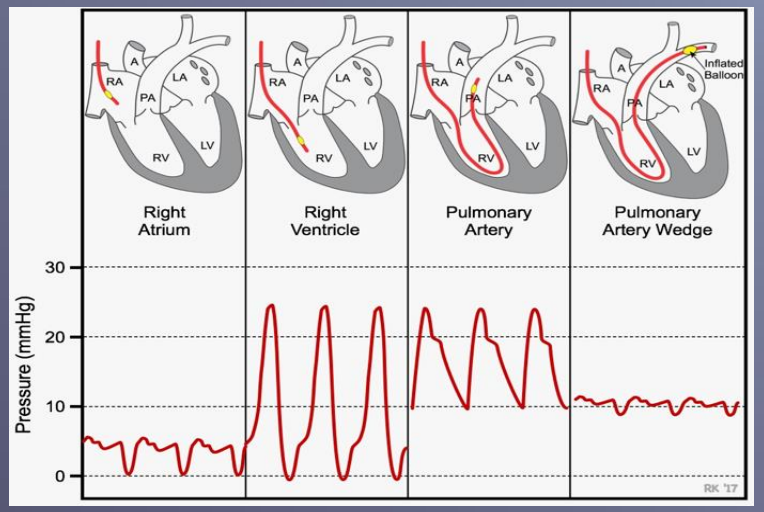
iPDE-III

PGE I /na našem pracovišti od r. 95-2015/

iPDE-V / od roku 2015/

Indikace k testování:

TPG ≥ 15 mmHg a/nebo PAR ≥ 3 W.j



International Society for Heart and Lung Transplantation - PAR >5 W.j. a/nebo TPG >15 mmHg je relativní kontraindikací srdeční transplantace

Mehra M.R. et al.: J Heart Lung Transplant 2006;25:1024 – 42

538 RHC (od roku 2017- 2018)
26 pacientů (4.8%) indikováno k testování reversibility PH, sildenafil 20 mg i.v.
(TPG>15 mmHg or PAR >3 W.j. při euvolemii)

	rest	sildenafil	delta
Heart rate, /min	79 ± 18.7	77 ± 18.3	-1.5
PA mean, mmHg	42 ± 7.4	30.4 ± 8.5	-11.6
PA wedged pressure, mmHg	25 ± 5.7	19 ± 7.1	-6
Cardiac output, l/min	3.6 ± 0.9	4.2 ± 1	0.65
Pulmonary vascular resistance, W.u	4.9 ± 1.6	2.8 ± 5.8	-2.09
Total systemic resistance, w.u.	29 ± 9.6	15.2 ± 8.2	-7.85
TSR/PVR	4.7 ± 1.9	7.0 ± 13.1	2.29

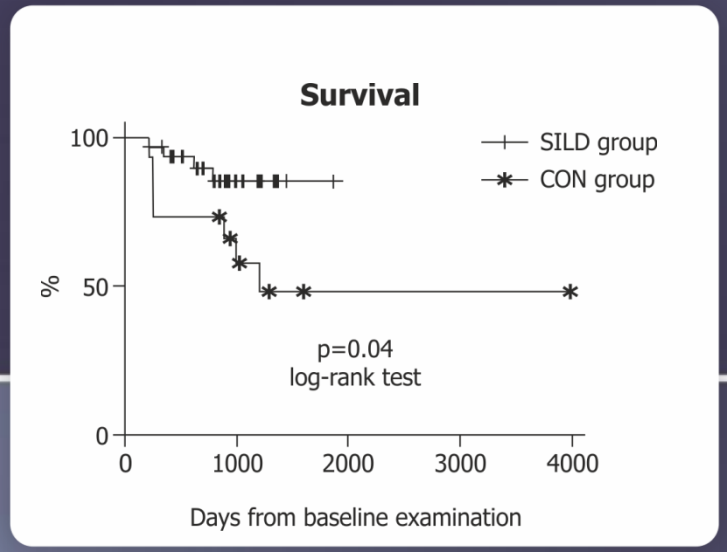
Nové přístupy k PH u CHSS

Prostacyklin ?

ERA ?

PDE5

Mechanická podpora



Léčba PH asociovaná onemocnění levého srdce

Základem léčby je léčba vyvolávajícího onemocnění, tj. léčba levostranného srdečního selhání, léčba chlopňových vad srdečních

First author or study [ref.]	Study drug	Dose	Subjects n	Duration	Population	Primary outcome	Result
Guazzi [74]	Sildenafil	50 mg 3 times a day	44	12 months	HFpEF	PVR, RV performance, CPET	Improvement
LEPHT [75]	Riociguat	0.5, 1 or 2 mg 3 times a day	201	16 weeks	HFrEF	mPAP *versus* placebo	No change
Hoendermis [73]	Sildenafil	60 mg 3 times a day	52	12 weeks	HFpEF	mPAP *versus* placebo	No change
SIOVAC [77]	Sildenafil	40 mg 3 times a day	231	24 weeks	VHD	Composite clinical score#	Worsening in active group
MELODY-1 [76]	Macitentan	10 mg once daily	48	12 weeks	HF (EF >30%); 75% HFpEF	Safety and tolerability	+10% fluid retention in active group

Table 2. Long-term, Placebo-Controlled Studies in Patients With Heart Failure and Pulmonary Hypertension

Study	Drug	Duration	Population	N	Results
Lewis 2007[67]	Sildenafil (25 to 75 mg TID)	12 wk	NYHA class II–IV, LVEF <40%, mPAP >25 mm Hg	34	Sildenafil increased peak Vo_2 and cardiac output and reduced PVR with exercise; no effect on PCWP, blood pressure, or heart rate; improved 6-MWT distance and reduced HF admissions; higher incidence of headache
Kaluski 2008[68]	Bosentan (8–125 mg BID)	20 wk	NYHA class IIIB-IV, LVEF <35%, RVSP ≥40 mm Hg (echo), supine SBP ≥100 mm Hg	94	No difference from baseline to week 20 in RVSP (0.1±11.5 mm Hg, *P*=0.97) or other echocardiographic parameter; more SAEs in the bosentan arm
Guazzi 2011[69]	Sildenafil (50 mg TID)	1 yr	LVEF ≥50%, RVSP ≥40 mm Hg (echo)	44	Sildenafil reduced mean PAP by 42.0±13.0%, improved right-ventricular function, and reduced right-atrial pressure by 54.0±7.2% and PCWP by 15.7±3.1%
Guazzi 2012[70]	Sildenafil (50 mg TID)	1 yr	LVEF <45%, mean PAP 25-35 mm Hg	32	Sildenafil increased peak Vo_2 and exercise ventilation efficiency, and decreased PCWP, mean PAP, and pulmonary vascular resistance

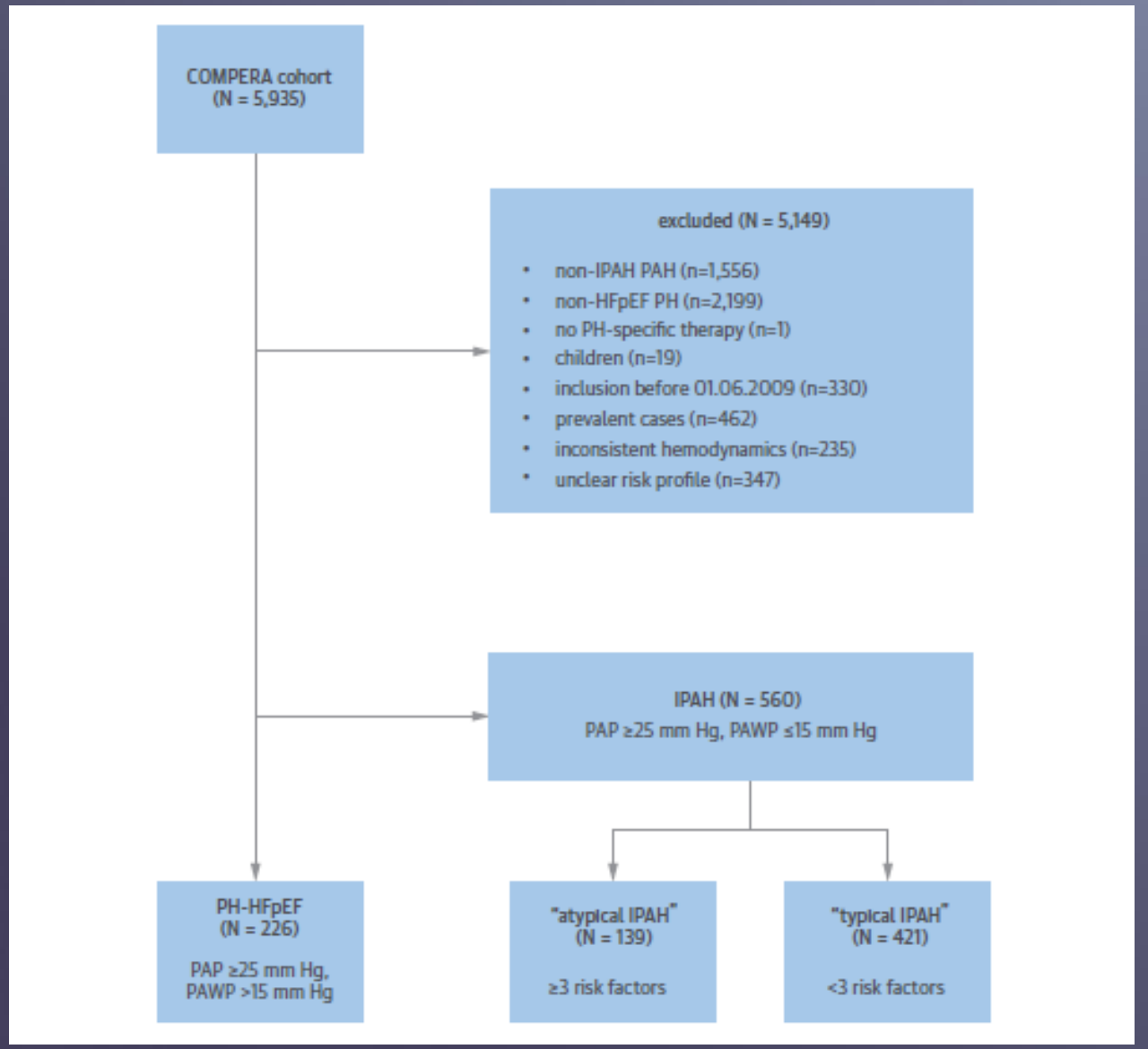


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TABLE 1 Baseline Characteristics

	All Patients (N = 786)	Typical IPAH (n = 421)	Atypical IPAH (n = 139)	Typical vs. Atypical IPAH p Value	PH-HFpEF (n = 226)	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
Age, yrs	66.6 ± 15.0	61.5 ± 17.3	71.3 ± 9.2	<0.001	73.2 ± 8.3	<0.001	0.434
Female	467 (59.4)	250 (59.4)	77 (55.4%)	1.000	140 (61.9)	1.000	0.686
BMI, kg/m^2	28.1 (24.5-32.6)	26.0 (23.3-29.8)	32.2 (28.3-36.0)	<0.001	29.6 (25.7-34.0)	<0.001	0.002
WHO-FC				0.089		<0.001	0.315
I/II	91 (11.8)	71 (17.4)	12 (8.8)		8 (3.6)		
III	540 (70.3)	275 (67.6)	96 (70.6)		169 (75.1)		
IV	137 (17.8)	61 (15.0)	28 (20.6)		48 (21.3)		
6MWD, m	289.5 ± 121.8	319.0 ± 123.5	250.5 ± 104.2	<0.001	260.0 ± 115.0	<0.001	0.787
RAP, mm Hg	9.8 ± 5.4	8.5 ± 5.2	8.9 ± 4.8	0.615	12.9 ± 4.8	<0.001	<0.001
PAPm, mm Hg	46.0 ± 11.9	46.9 ± 13.3	43.9 ± 10.7	0.025	45.7 ± 9.4	0.437	0.326
PAWP, mm Hg	12.5 ± 6.0	9.3 ± 3.4	10.0 ± 3.6	0.186	19.9 ± 4.4	<0.001	<0.001
TPG, mm Hg	33.5 ± 13.1	37.6 ± 13.6	33.9 ± 11.1	0.006	25.8 ± 9.1	<0.001	<0.001
Cardiac index, l/min/m^2	2.2 ± 0.8	2.3 ± 0.8	2.2 ± 0.8	0.629	2.2 ± 0.7	0.653	0.988
PVR, Wood Units	9.6 ± 6.7	10.8 ± 6.0	9.8 ± 10.6	0.309	7.0 ± 3.4	<0.001	<0.001
SvO_2, %	62.2 ± 9.0	62.1 ± 9.9	62.7 ± 9.0	0.804	62.1 ± 6.9	0.999	0.863
BNP, pg/ml	269 (127-541)	287 (119-543)	200 (115-469)	1.000	310 (186-638)	0.963	0.312
NT-proBNP, pg/ml	1,738 (621-3,891)	1,435 (541-3,888)	1,683 (478-2,815)	1.000	2,196 (1,125-4,285)	0.021	0.066
Arterial hypertension	66.5	43.2	98.6	<0.001	91.9	<0.001	0.021
CAD	32.0	15.7	59.7	<0.001	46.4	<0.001	0.049
Diabetes mellitus	30.6	10.7	74.8	<0.001	41.2	<0.001	<0.001
AF	28.9	10.7	42.4	<0.001	54.4	<0.001	0.187
BMI >30 kg/m^2	37.6	23.5	65.2	<0.001	47.1	<0.001	0.002

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TABLE 4 Response to Targeted PH Therapy

	Typical IPAH	Atypical IPAH	Typical vs. Atypical IPAH p Value	PH-HFpEF	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
6MWD, m						
Baseline	320 (234 to 417)	250 (175 to 332)	<0.001	270 (165 to 345)	<0.001	1.000
12 months	414 (324 to 460)	310 (240 to 379)	<0.001	330 (194 to 380)	<0.001	1.000
Change from baseline in 6MWD, m						
Mean ± SD	52 ± 101	58 ± 84	1.000	33 ± 82	0.453	0.904
Median (IQR)	50 (1 to 00)	60 (10 to 75)		29 (−10 to 74)		
WHO-FC I/II						
Baseline	17.4	8.8	0.056	3.6	<0.001	0.164
12 months	39.5	26.2	0.208	23.0	0.026	1.000
Improvement of WHO-FC	34.5	36.9	1.000	36.8	1.000	1.000
Change from baseline in NT-proBNP/BNP, %	−42.6 (−77.1 to 17.4)	−35.9 (−69.9 to 13.8)	1.000	−13.7 (−40.6 to 32.2)	0.031	0.248

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Závěr

1) Zásadním vyšetřením před Tx srdce je pravostranná katetrizace a hodnoty TPG a PAR
2) V současné době je schválena jako jediná možnost ovlivnění PH před Tx srdce cestou MSP
3) Bude potřeba nových studií u nemocných s HF a PH k ovlivnění TPG a PAR.