FARMAKOTERAPIE A SRDEČNÍ PODPORY U PLICNÍ HYPERTENZE PŘI ONEMOCNĚNÍ LEVÉHO SRDCE

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IKEM

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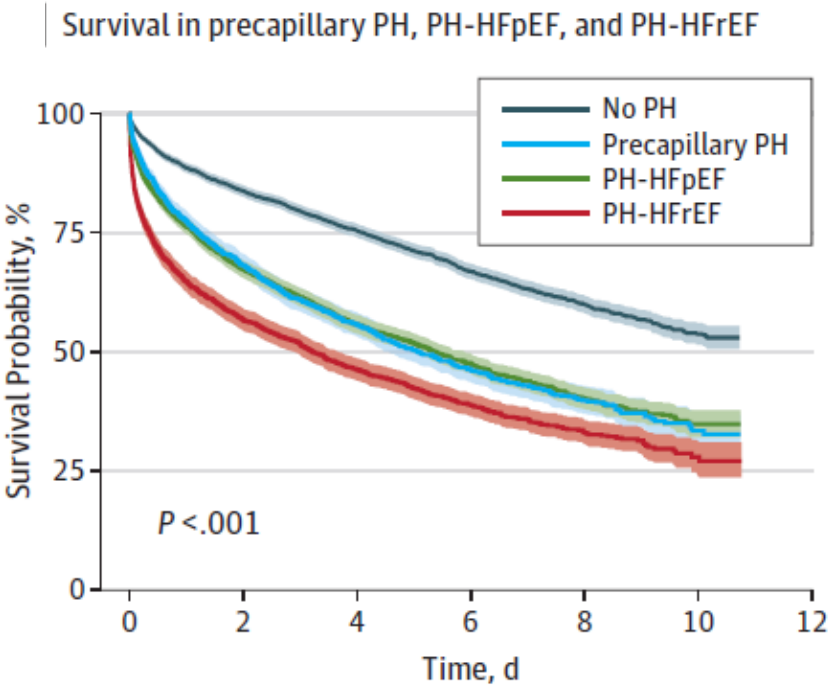
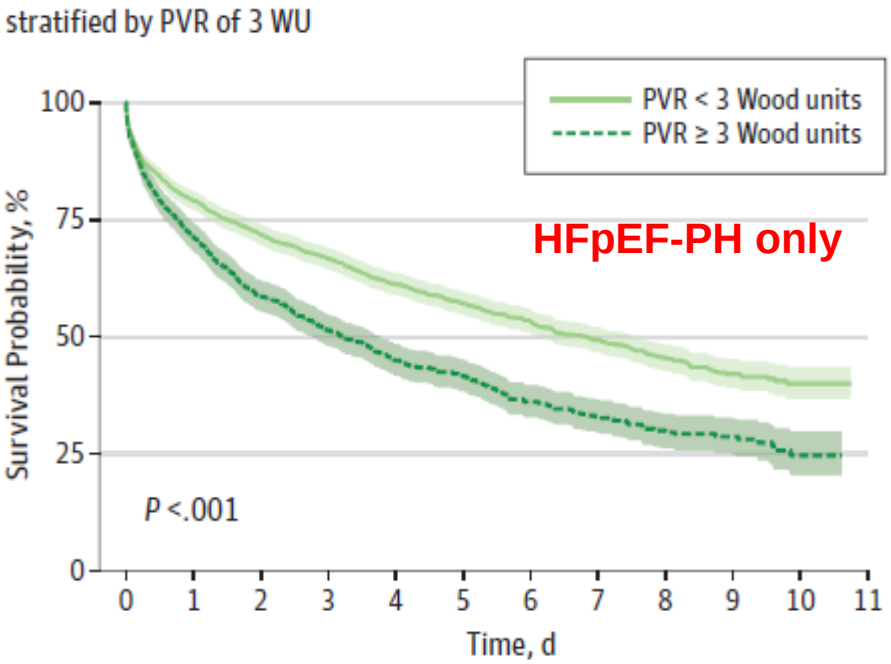
XXVII. VÝROČNÍ SJEZD ČESKÉ KARDIOLOGICKÉ SPOLEČNOSTI 12.–15. května 2019 | Veletrhy Brno

Pacienti s HF a plicní vaskulární nemocí mají horší prognózu

10 023 pacientů s HF nebo PH podstupující pravostrannou katetrizaci, Univ. of Pittsburg

Plicní vaskulární nemoc: plic. vasc. rezistence > 3 w.u.





28% mělo PH-HFpEF
PH-HFpEF má stejně špatnou prognózu jako PAH, ale více hospitalizací

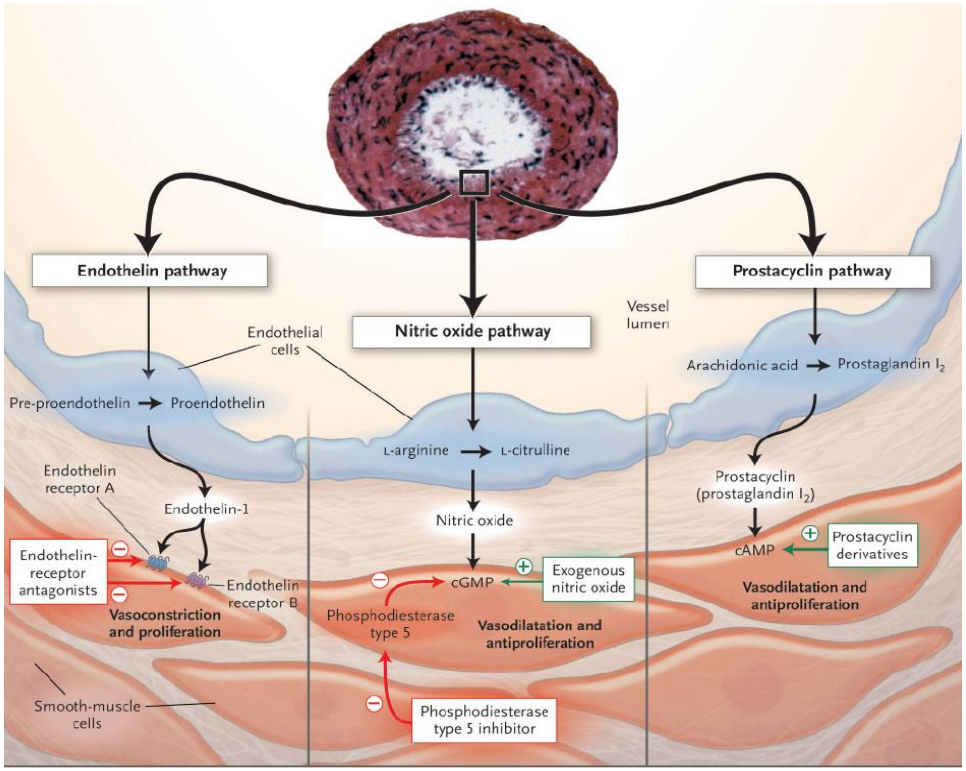
Zvýšená PVR u HFpEF je spojena se zvýšeným rizikem úmrtí

Plicní vaskulární nemoc biologicky relevantní

Vanderpool RR, JAMA Cardiol. 2018 Apr 1;3(4):298-306.

Příčiny plicní vaskulární nemoci u HF

Endotheliální dysfunkce plicní cirkulace



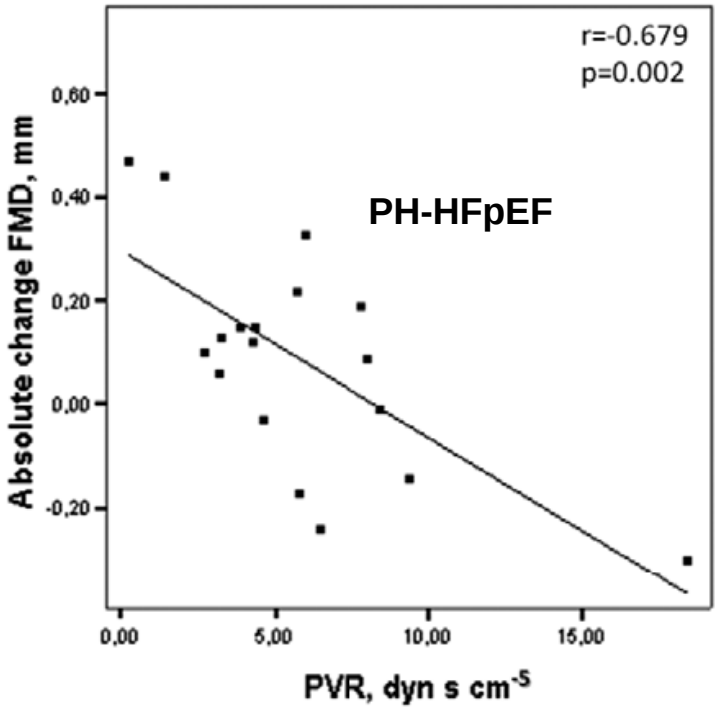
↑ endothelium-derived vasocontrictors: ET-1

↓ endothelium-derived vasorelaxants: PGI_2 , NO

reversible component lof pulmonary vascular disease

Moraes DL, Circ 2000; 102: 1718-23

pulmonary vascular disease is systemic process



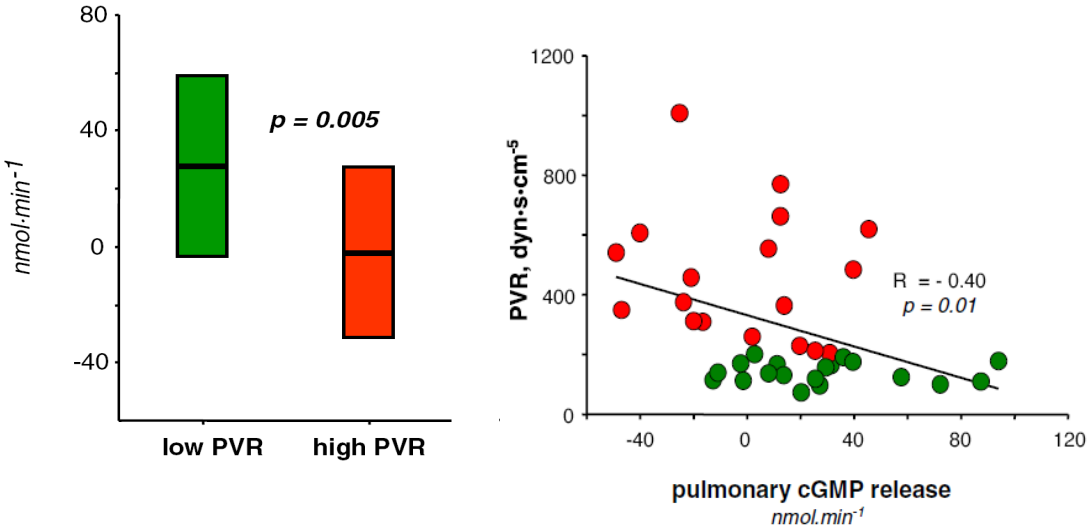
Pulmonary vascular resistance (PVR) correlates with peripheral flow-mediated dilatation (FMD)

Farrero M, Circ HF 2014;7: 791-98

Endoteliální dysfunkce plicní cirkulace

HFrEF

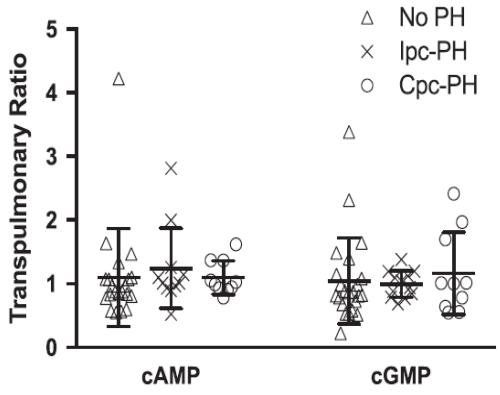
Transpulmonary cGMP release

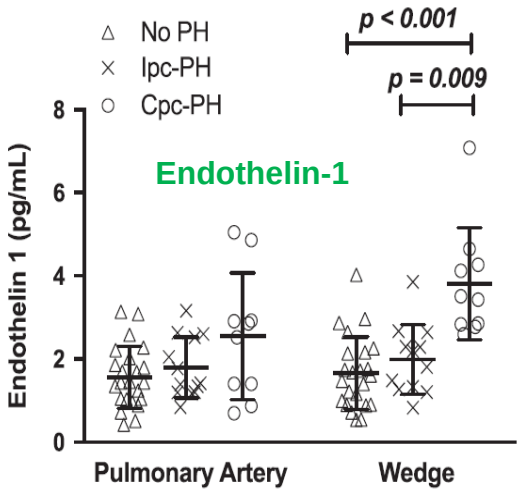


PVR HFpEF: ↓ cGMP pulm. release
↑ cGMP catabolism

Melenovsky V, JACC 2009; 54 (7): 55-600

HFpEF





↔ cGMP pulm. release
(↓ NO availabilty)

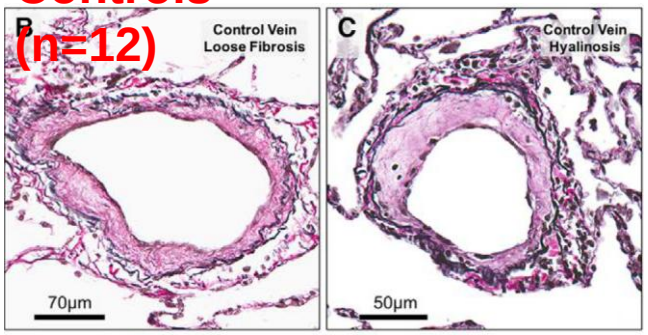
↑ pulmonary release of ET-1
in Cpc-PH HFpEF
contributor or biomarker ?

Meoli DF, Pulm Circ 2018; 8 (1): 1-8

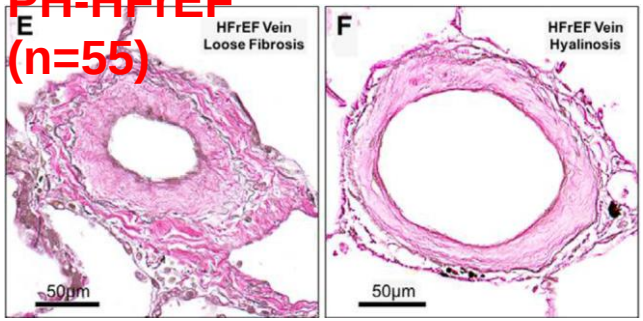
Strukturální změny v plicní cirkulaci u pacientů s HF

Pitevní studie, Mayo clinic

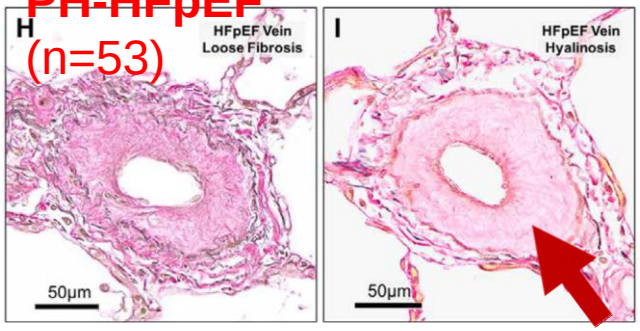
Controls (n=12)



PH-HFrEF (n=55)

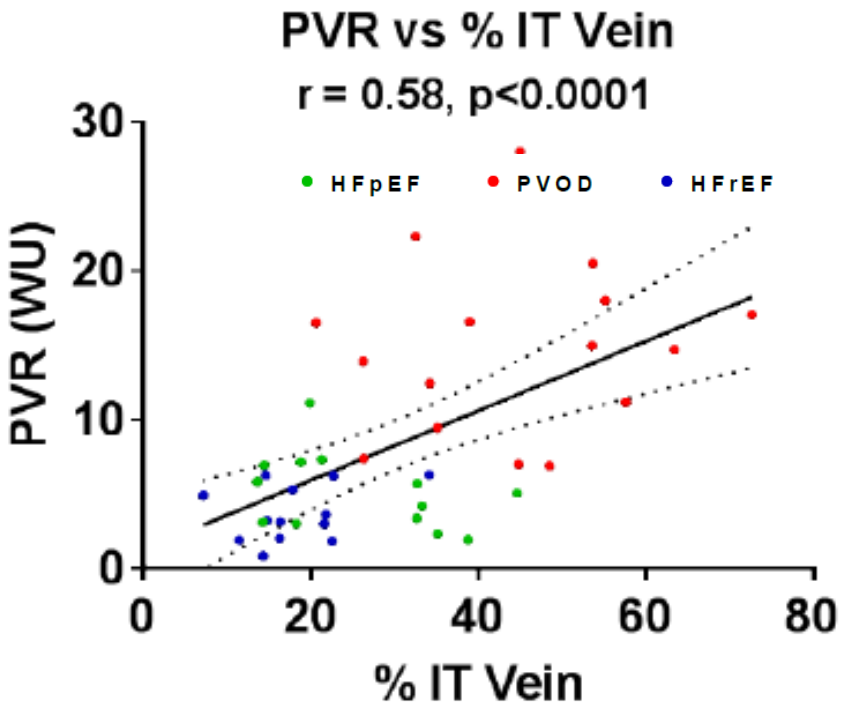


PH-HFpEF (n=53)



Intimal thickening (IT%) in pulmonary veins

related to TPG and PVR better than arteriolar changes
„PVOD-like“ lesions, but less dense



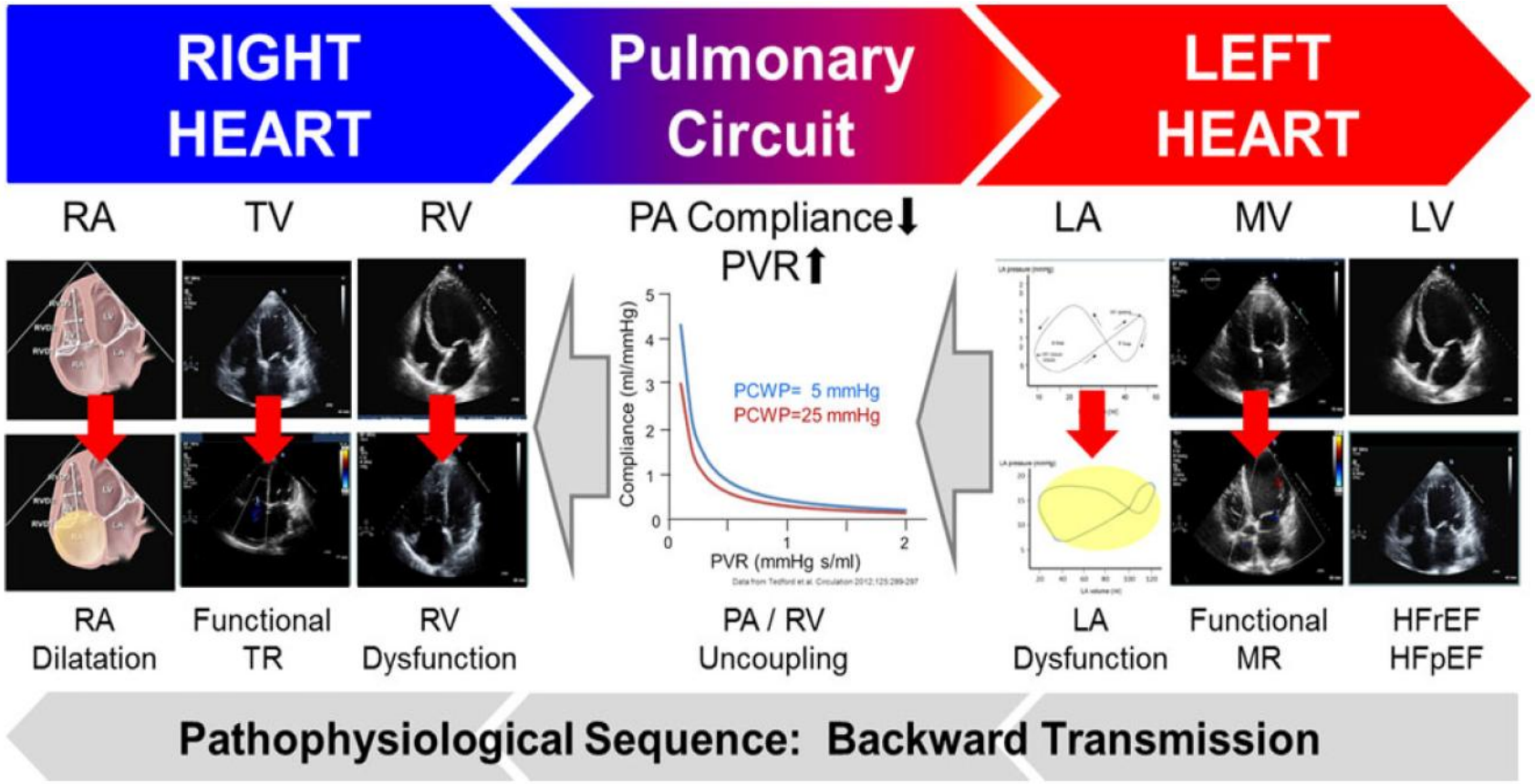
„fixed“ component, but may respond to prolonged LA unloading (LVAD)

trend to more IT thickening in HFpEF vs HFrEF

Loose intimal fibrosis, edema, ECM deposition

Fayyaz AU, Redfield MM. Circulation. 2018 ;137:1796-1810.

Plicní hypertenze u onemocnění levého srdce



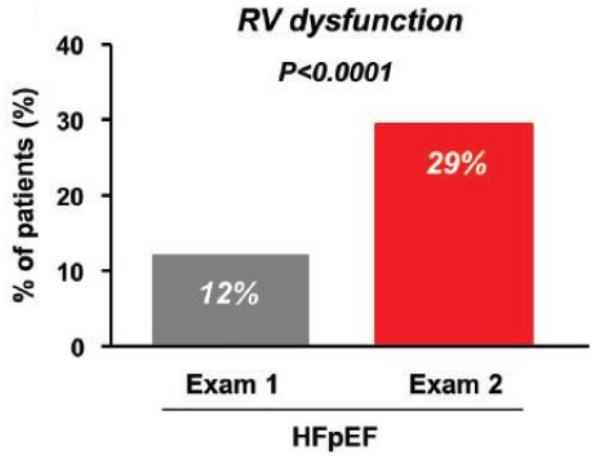
Plicní hypertenze vede k selhání pravé komory (s jistou variabilitou průběhu)

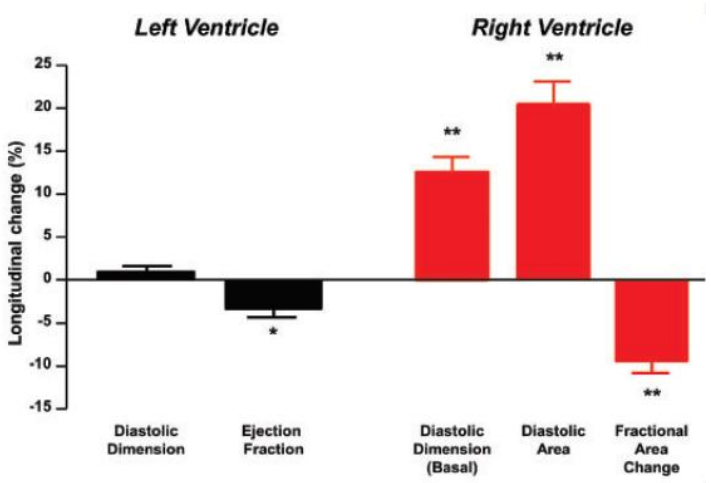
Rozvoj biventrikulární dysfunkce je společnou finální cestou progrese všech typů srdečního selhání

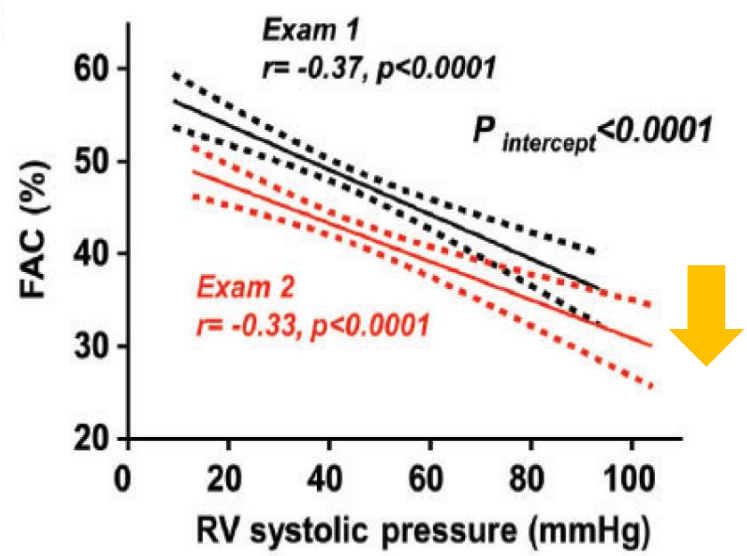
Rosenkrantz S, EHJ 2016, 37: 942-54

Dysfukce PK může progredovat nezávisle na PH
Longitudinální studie PA-RV coupling u HFpEF

271 HFpEF patientů vyšetřených 2x během 4 let







Deterioration of RV function (2.5x increase if RVD)
No change of RV systolic pressure !

Predictors of development of de novo RVD

- **Atrial fibrillation, prev. or inc. (OR 2.8, p < 0.001)**
- **CAD (OR: 2.0, p=0.03)**
- **DM (OR: 1.9, p=0.04)**
- **RV systolic pressure (OR per 1SD: 1.5, p=0.006)**

Obokata M et al. Eur Heart J 2019

World PH summit Nice 2018:
Co je nového u PH2 typu ?

Cut-off pro PH snížen na mPA: > 20 mmHg

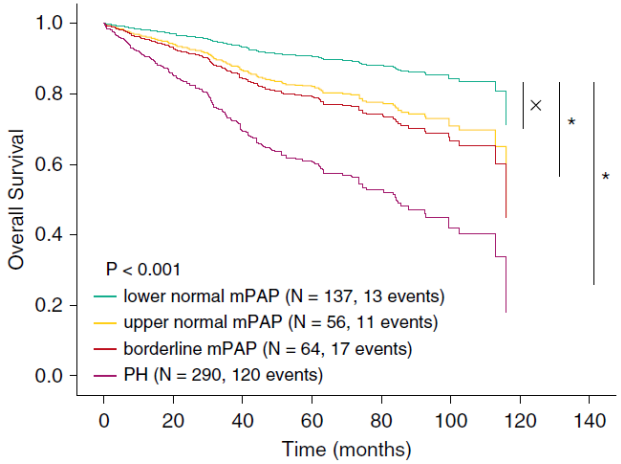
Racionale

1) **Metaanalýza dat ukázala, že „normální“ hodnota u zdravých mPA je 14 ± 3.3 mmHg**

Kovacs et al. Eur Respir J 2009; 34: 888-975

mean + 2* SD = 20.6 mmHg - upper limit of normal (97,5% upper limit of normal)

2) **mPA 20-25 mmHg je již spojen nezávisle zvýšeným rizikem mortality a symptomy**



Douschan et al. Am J Respir Crit Care Med 2018; 197(4):509-516

Prekapilární komponenta PH je definována pouze PVR > 3 w.u.

diastolic pressure gradient (DPG) je mrtev

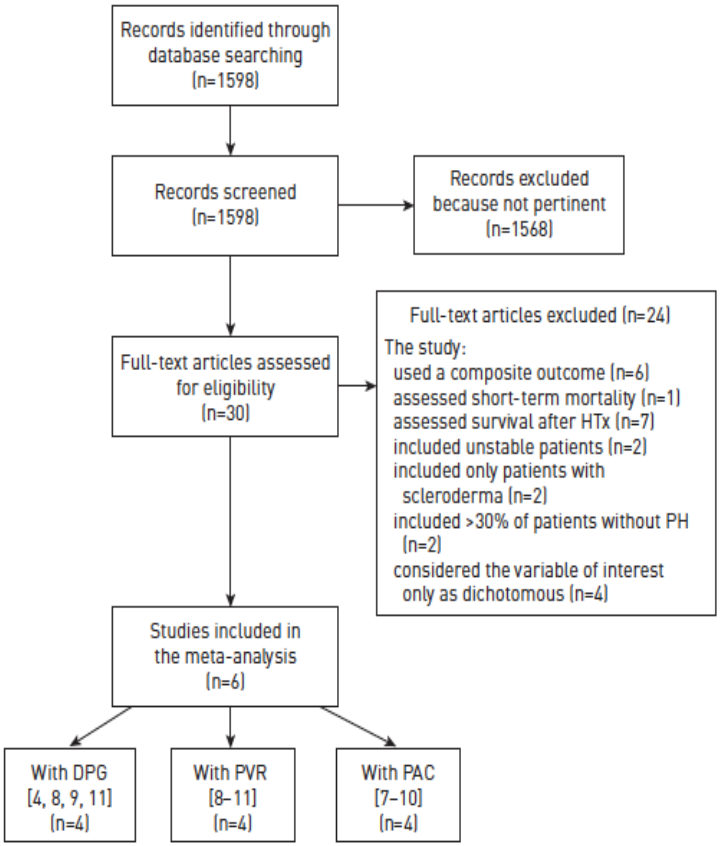
Vachiery JL et al. Eur Respir J 2019

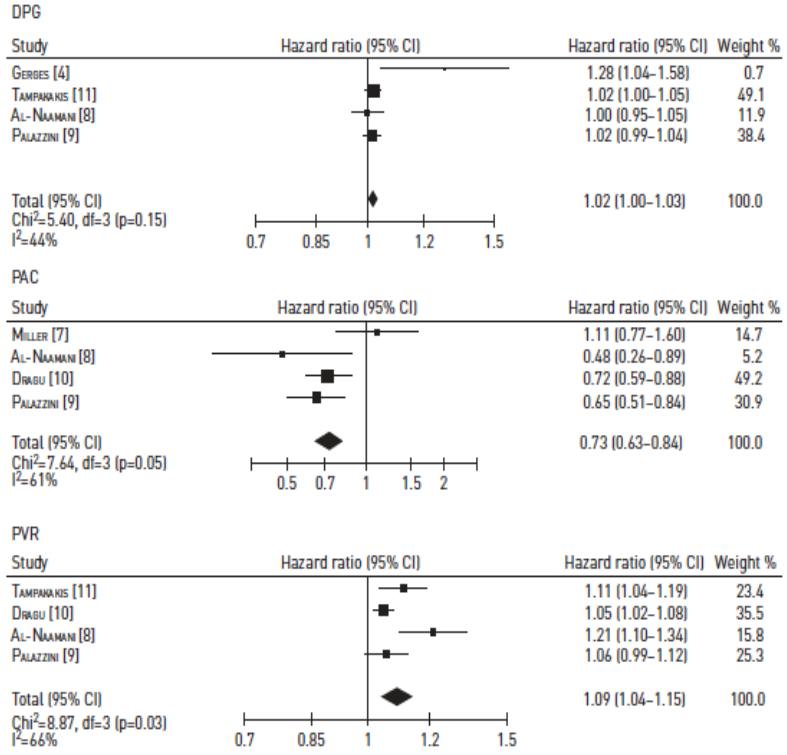
Definice prekapilární kompenty u PH 2 typu

Haemodynamics to predict outcome in pulmonary hypertension due to left heart disease: a meta-analysis

Caravita S et al. Eur Respir J 2018

PVR, but not DPG, predicts mortality





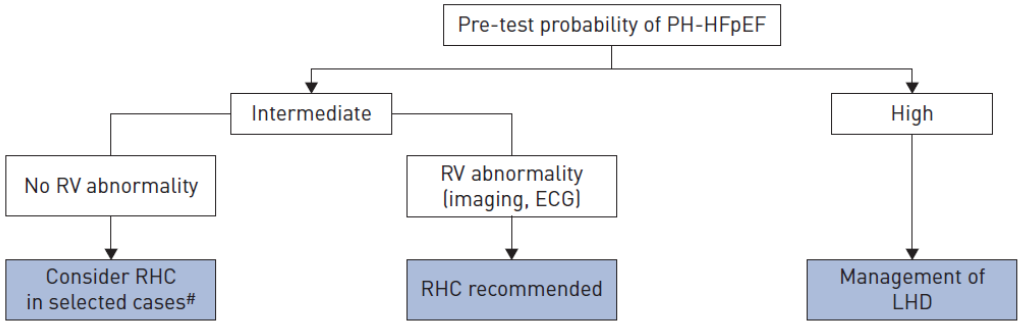
PAH world summit, Nice 2018:
PVR (but not DPG) will be used for future definition of precapillary component of PH

Co nového v doporučeních z Nice 2018 u PH 2 typu ?

Hlavní diagnostický problém: rozlišení PH-HFpEF vs PAH

Pre-test probability fenotypu levostranného srdečního onemocnění

Feature	High probability	Intermediate probability	Low probability
Age	>70 years	60–70 years	<60 years
Obesity, systemic hypertension, dyslipidaemia, glucose intolerance/diabetes	>2 factors	1–2 factors	None
Previous cardiac intervention#	Yes	No	No
Atrial fibrillation	Current	Paroxysmal	No
Structural LHD	Present	No	No
ECG	LBBB or LVH	Mild LVH	Normal or signs of RV strain
Echocardiography	LA dilation; grade >2 mitral flow	No LA dilation; grade <2 mitral flow	No LA dilation; *E/e′* <13
CPET	Mildly elevated V'_E/V'_{CO_2} slope; EOV	Elevated V'_E/V'_{CO_2} slope *or* EOV	High V'_E/V'_{CO_2} slope; no EOV
Cardiac MRI	LA strain or LA/RA >1		No left heart abnormalities



Pravostranná katetrizace doporučena při:

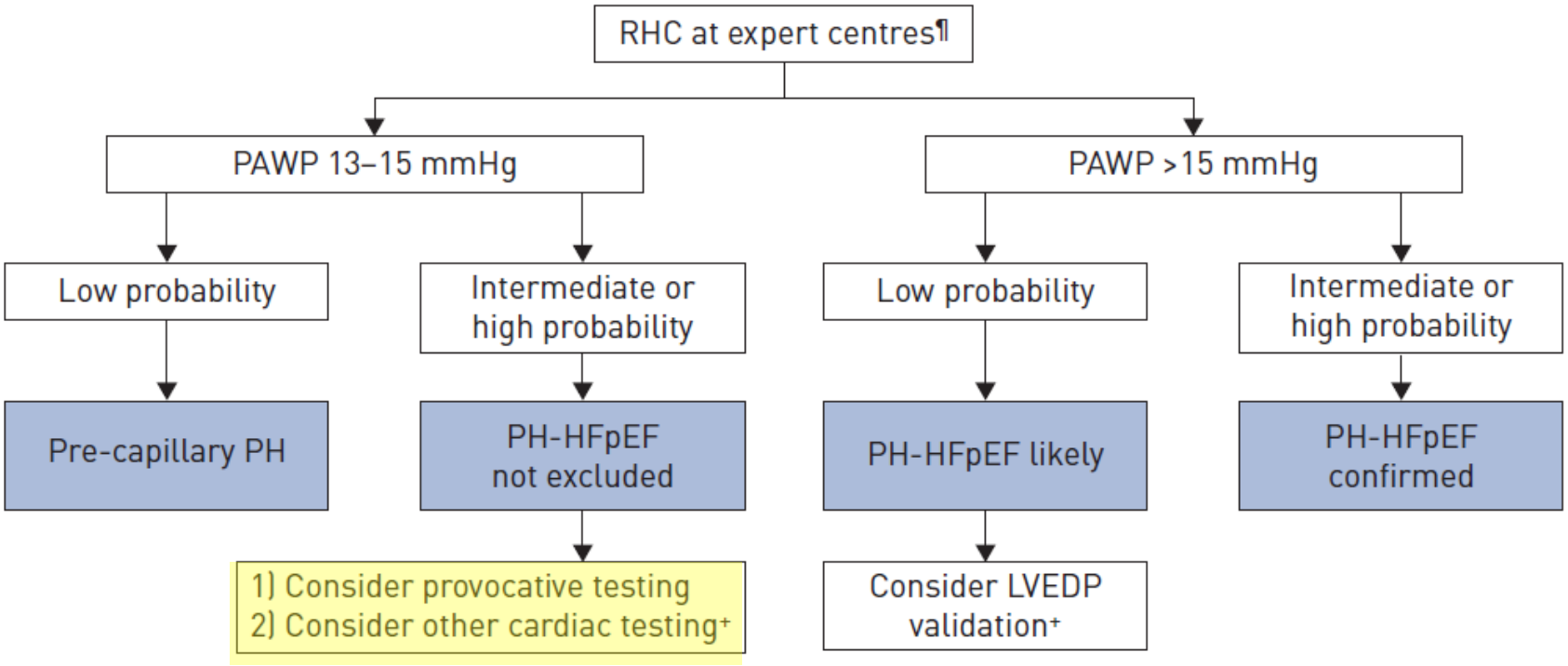
dysfunkci pravé komory a intermediální pravděpodobnosti PH

podezření na CTEPH; při systémové sklerodermii

dušnost nejasné etiologie

Vachiery JL et al. Eur Respir J 2019

Pravostranná katetrizace a zátěžové testy



Volumexpanze: infuze FR 500 ml nebo ml/kg (37^0 C) během 5-10 min
vzestup PAWP ≥ 18 mmHg po infusi = postkapilární PH

D´Alto M, Chest 2017, 151: 119-126

Horizontální ergometr: 20W začátek, dál 10W inkrementy po 3 min
PAWP ≥ 25 mmHg při zátěži je jasně abnormální

Andersen MJ, Circ Heart Fail. 2015;8(1):41-8

PAWP/CO slope > 2 mmHg/L/min

Eisman AS, Circ HF 2018

Terapie prekapilární komponenty PH 2 typu: nedávno ukončené studie

TABLE 4 Recently completed randomised controlled trials targeting the phosphodiesterase type 5 inhibitor/nitric oxide and endothelin pathways in pulmonary hypertension due to left heart disease

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

Ale: mPA není relevantní endpoint (↑CO vede k ↑ mPA)

netestované populace:

- HF(p)EF s významně zvýšenou PVR (atypická PAH)
- HFrEF před Tx

Vachiery JL et al. Eur Respir J 2019

Terapie prekapilární komponenty PH 2 typu: probíhající či připravované studie

Study[#]	Study drug	Dose	Subjects n	Duration	Population	Primary outcome
SERENADE (NCT03153111)	Macitentan	10 mg once daily	300	52 weeks	LVEF ⩾40% and ESC-defined HFpEF; HF hospitalisation within 12 months and/or PAWP or LVEDP >15 mmHg within 6 months; elevated NT-proBNP; PVD or RVD	% change from baseline in NT-proBNP at week 24
SOPRANO (NCT02554903)	Macitentan	10 mg once daily	78	12 weeks	LVAD within 45 days; PH by RHC with PAWP ⩽18 mmHg and PVR >3 WU	PVR ratio of week 12 to baseline
DYNAMIC (NCT02744339)	Oral riociguat	1.5 mg 3 times a day	114	26 weeks	HFpEF; mPAP >25 mmHg and PAWP >15 mmHg	Change in CO
Oral treprostinil (NCT03037580)	Oral treprostinil		310	24 weeks	LVEF ⩾50%; RHC within 90 days of randomisation; 6MWD >200 m	Change in 6MWD from baseline to week 24
PASSION (not registered)	Oral tadalafil	40 mg once daily	320	NA	HFpEF; PH with PAWP >15 mmHg and mPAP >25 mmHg and PVR >3 WU	Time to first event defined as HF-associated hospitalisation (independently adjudicated) or death from any cause

Vachiery JL et al. Eur Respir J 2019

Klinické determinanty plicní vaskulární nemoci při PH2 typu

Zvýšený tlak v levé síni

Braunwald E, Circ. 1965:10: 509-1

Závažnost mitrální regurgitace

Enriques-Sarano M, JACC 1997;

Plicní embolie

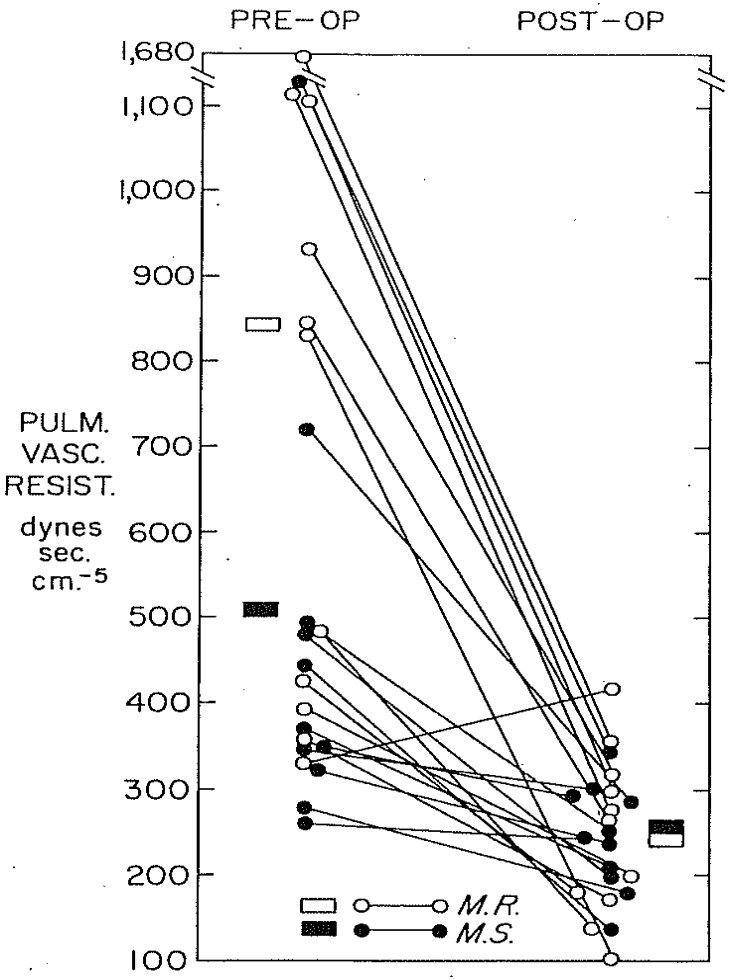
Stádnutím podmíněné tuhnutí plic. dév

Hereditární dispozice

Aassad TR, JACC 2016; 68: 2536

Funkce levé síně

Melenovsky V., Circ HF 2015; 8: 295-3

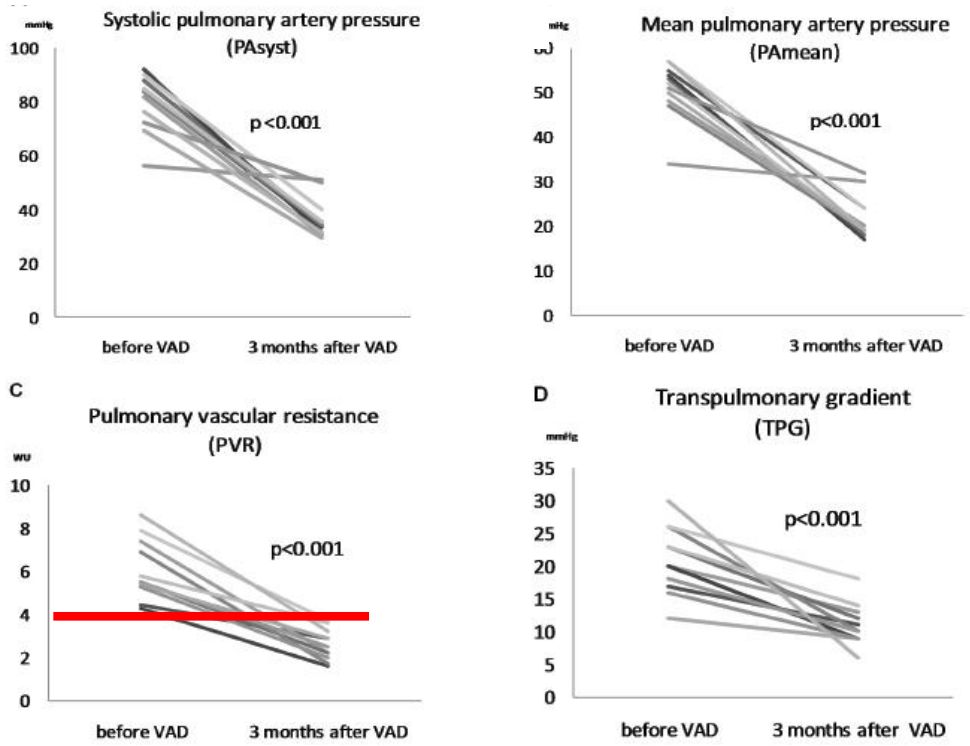


Braunwald E, Circ. 1965:10: 509-14

Snížení tlaku v levé síni: hlavní cíl léčby PH 2 typu

Left atrial unloading by LVAD lowers PVR

in HFrEF



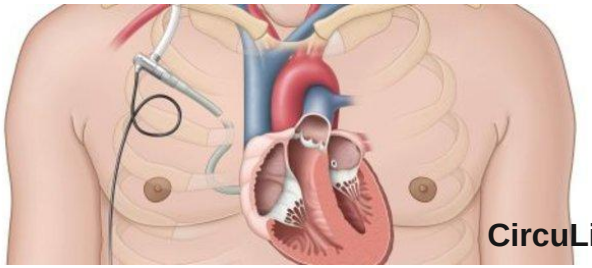
Heart Tx
Contractindication

Kettner J, et al., Phys Res. 2011

Regression of changes on pulmonary histology

Hunt JM Am J Physiol 305, L725-36, 2013

mini-LVAD for LA decopression for HFpEF ?

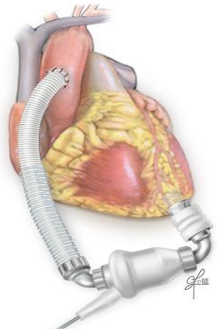


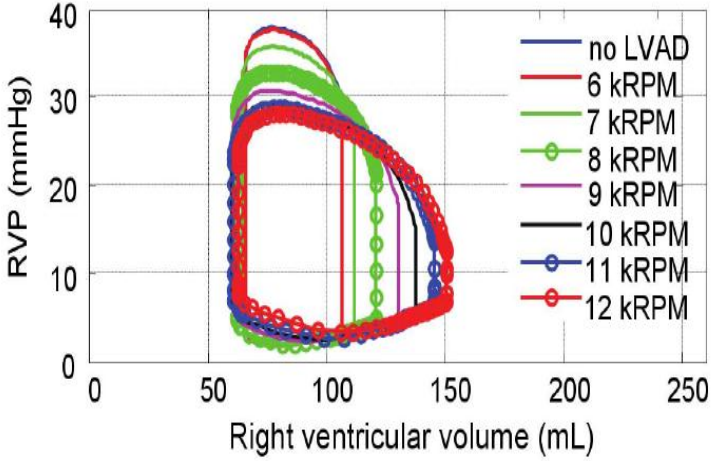
Burkhoff D, J Am Coll Cardiol HF 2015;3:275–82

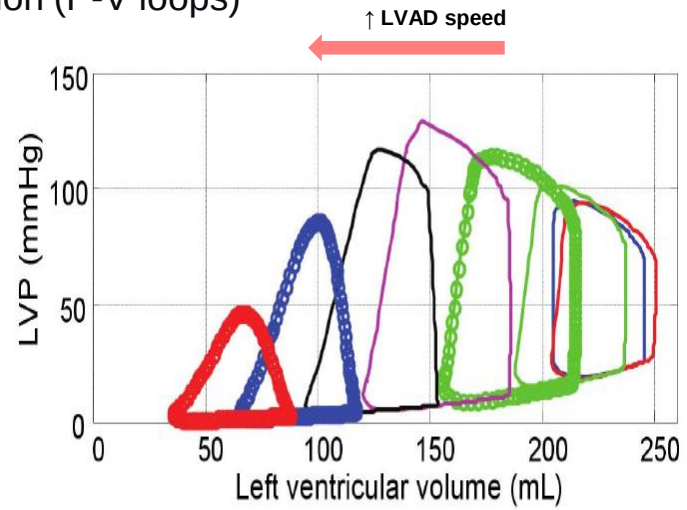
CircuLite

LVAD – redukuje RV afterload, ale zvyšuje RV preload

Effect of LVAD speed increase LV and RV function (P-V loops)







LVAD zvyšuje práci pravé komory

Wang Y, PLOS One 2014, 9 (1): e85234

RV pressure load ↓
RV volume load ↑

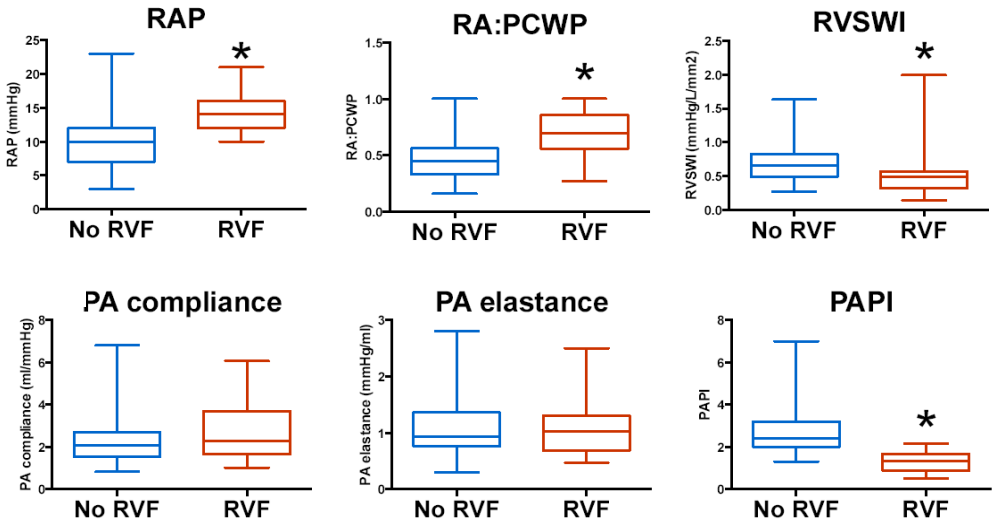
Méně efektivní pohyb septa
RV dilatace, ↑ Tri R

Riziko selhání PK po LVAD
je dána dysfunkcí PK, nikoliv PH

Houston BA, JHLT 2017

Těžká dysfunkce PK (+TR) bez PH je nejrizikovější
Z hlediska selhání PK po LVAD

Riziko selhání PK po implantaci LVAD: hemodynamické prediktory



	AUC (95% CI)	SE	Sensitivity	Specificity	PPV	NPV
PAPi <1.85	0.942 (0.904, 0.980)	0.0195	0.938	0.810	0.832	0.928
RA (mmHg) >11.5	0.846 (0.781, 0.911)	0.0326	0.968	0.650	0.735	0.954
RA:PCWP >0.59	0.837 (0.749, 0.925)	0.0195	0.719	0.870	0.847	0.756
PA pulse pressure (mmHg) <22.5	0.742 (0.613, 0.817)	0.0520	0.718	0.640	0.663	0.695
RVSWI (mmHg/L/m2) <0.57	0.692 (0.576, 0.809)	0.0595	0.786	0.631	0.680	0.747
Mod-sev TR	0.678 (0.571, 0.783)	0.0542	0.743	0.446	0.603	0.680

132 konskutivních pacientů s konitn. Flow LVAD, Tufts, Boston

24% vyvinulo selhání PK po LVAD (inotropes ≥ 14d or RVAD)

Nejlepší prediktor selhání PK:

PA pulsatility index (PAPi)
(PA sysolic-PA diastolic)/ RA

PASP, PVR, TPG:
nepredikují RVF po LVAD !

Morine KJ, J Card Fail 2016

Významnou část end-stage HF nelze řešit izolovaným LVAD
nutnost vývoje biventrikulárních systémů podpor !

Závěry

PH 2 typu je nejčastější typ PH a je spojen se zvýšenou mortalitou

Přítomnost plicní vaskulární nemoci (PVR> 3 WU) dále zhoršuje prognózu

Odlišení PAH a PH 2 typu je složité zvláště u pacientů se zachovanou EF LK
definuj pravděpodobnost onemocnění levého srdce
u šedé zóny indikuj P-katetrizaci

Specifická terapie PAH není zatím u PH2 typu indikována
(s výjimkou speciálních situací – PH-HFrEF před Tx)

LVAD snižuje tlak v levé síni i PVR, ale může přetížit selhávající PK

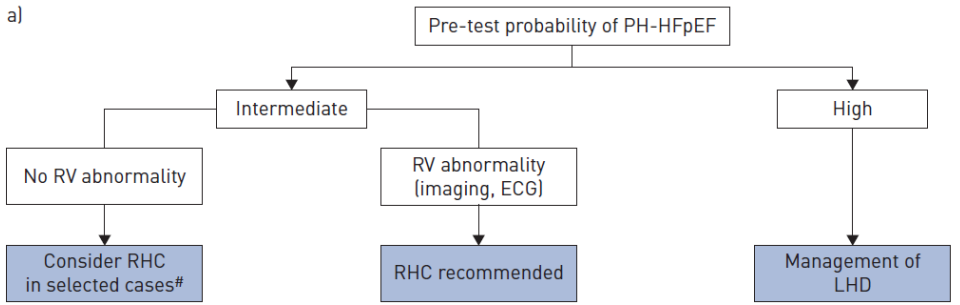
K LVAD nutné indikovat před rozvojem těžké biventrikulární dysfunkce

Děkuji za pozornost

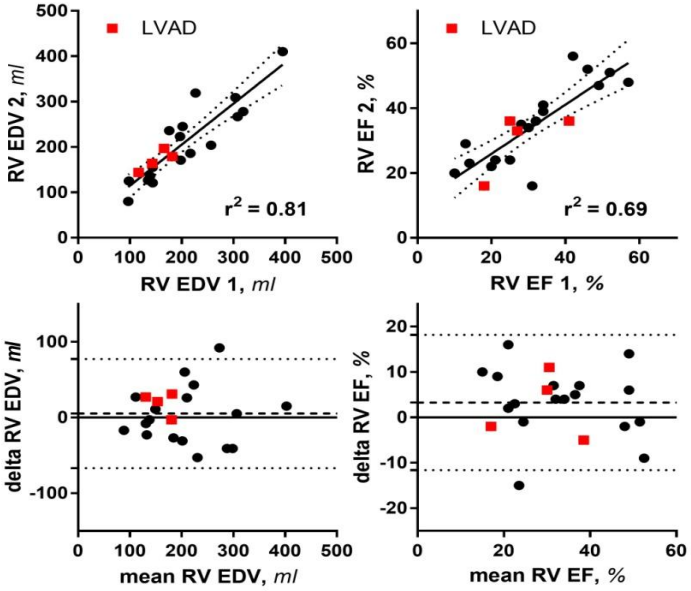
vojtech.melenovsky@ikem.cz

Zvyšuje podávání léků s hypotenzním účinkem mortalitu ?

Indikace pravostranné katetrizace závisí na pre-test probalitě PH-HFpEF

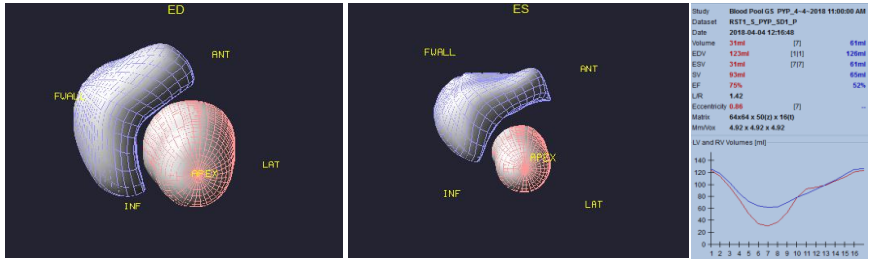


RV function assesment using 3D gated blood-pool SPECT using new, faster camera

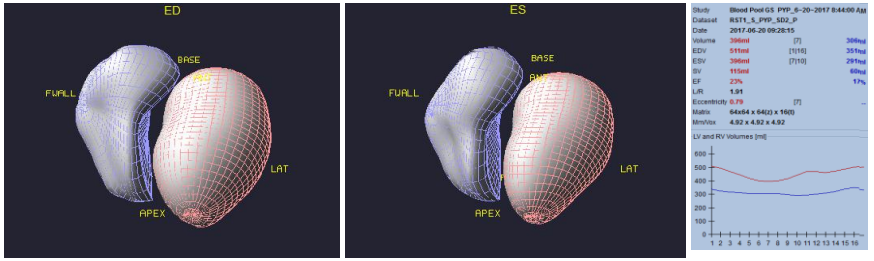


precise
fast
works with LVADs

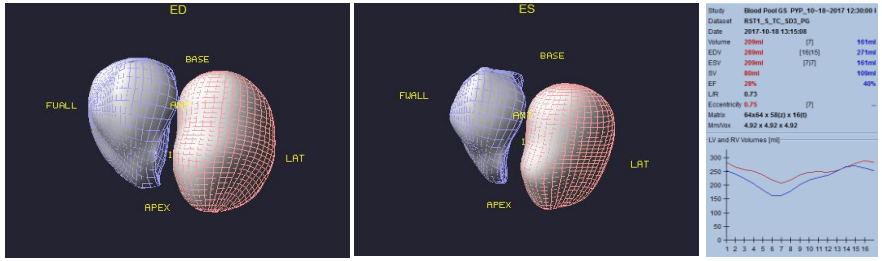
End-diastolic frame **End-systolic frame**



Control subject, 40y female, non-cardiac SOB



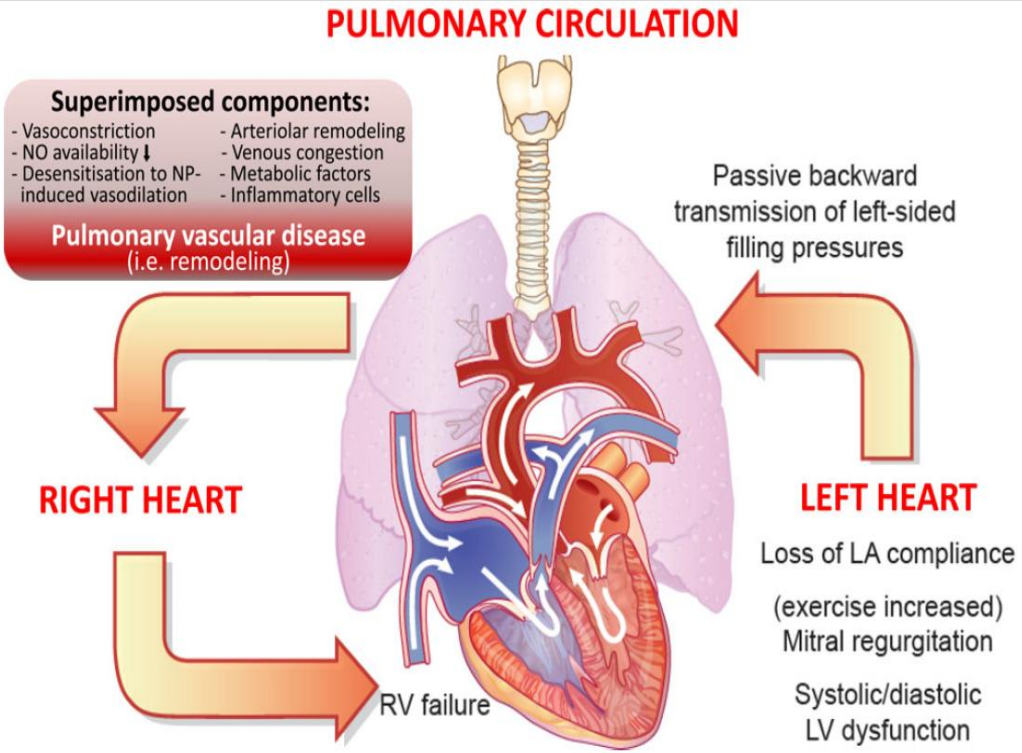
End-stage DCM, 51-years old male, AoI 2/4, PAm=44 mmHg, INTERMACS 3, prior LVAD implantation

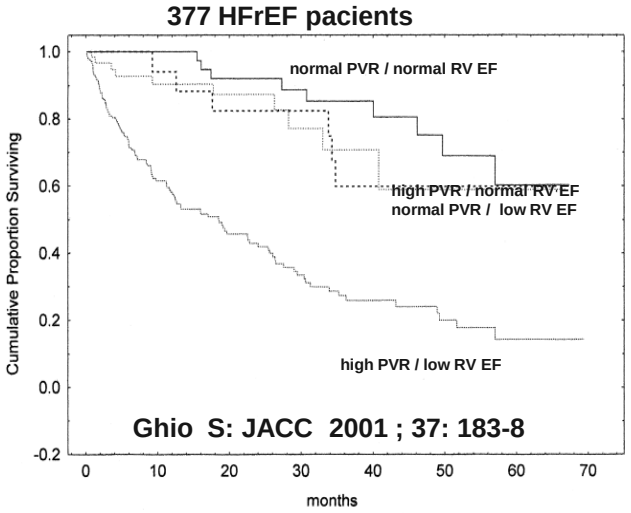


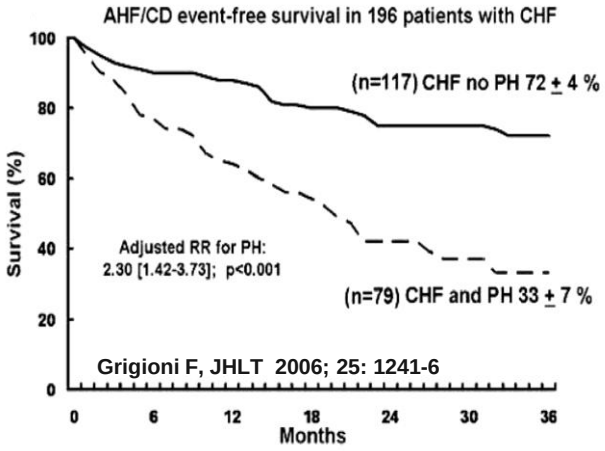
The same subject as above, 4 months after AVR + **HM3 implantation**

ISHLT 2018, poster 1215

Konsekvence PH u ChSS: biventrikulární selhání





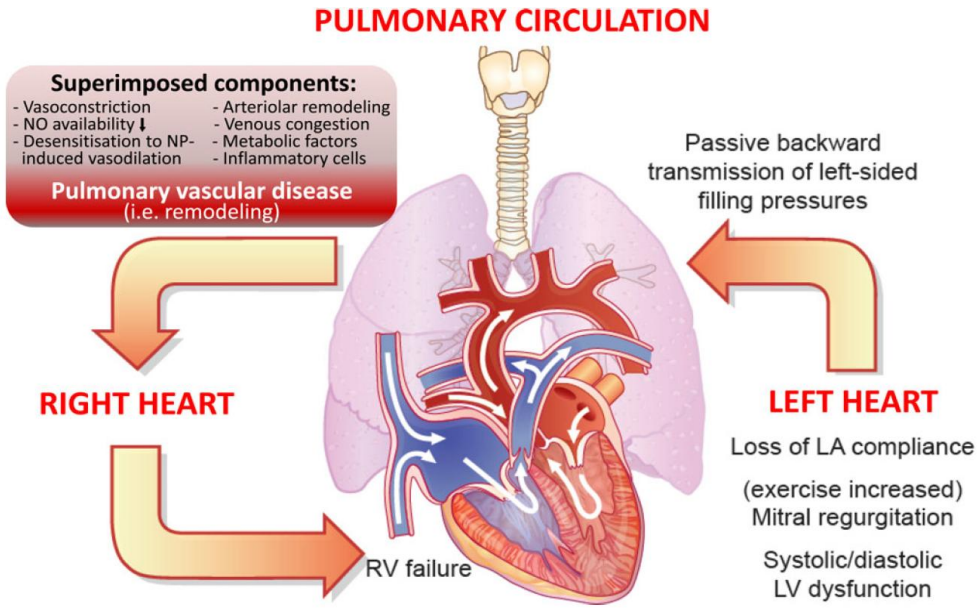


- **pacienti s PH+HF mají 2-3x vyšší riziko úmrtí než ti bez PH**

- **rozvoj dysfunkce pravé komory a pravostranného selhání souvisí s PH**

Pulmonary Hypertension in Heart Failure

50-70 % of HF (rEF or pEF) patients have pulmonary hypertension (mPA ≥ 25 mmHg)



Passive pressure transmission from left heart

"isolated postcapillary PH"
Ipc-PH

Superimposed pulmonary vascular disease (PVD)

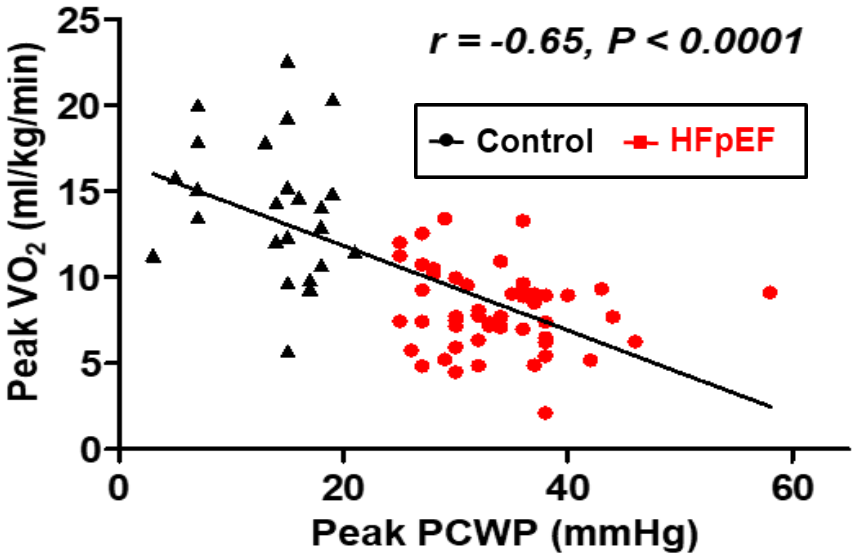
"combined pre- and post-capilary PH", **Cpc-PH**
Pulmonary vascular resistance ≥ 3 w.u. at rest

15% of general HF population
less severe PVD far more common in HF

Hoeper MM, EHJ 2016: 0: 1-5
Rosenkrantz S, EHJ 2016, 37: 942-54
Gerges M, AJRCCM 2015, 192: 1234-46.

Exercise LA pressure correlates with symptoms and prognosis

LA pressure (PAWP) during exercise: **- reflects multiple pathophysiologic pathways of HFpEF**



Reddy M, submitted

- eads to ex. limiting dyspnoea

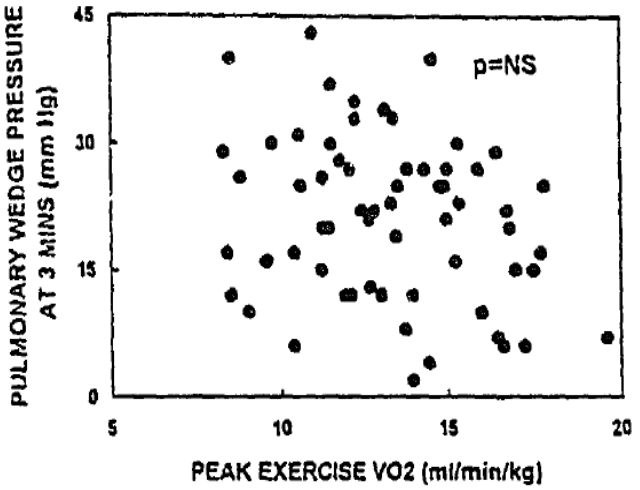
- correlates with 6MWD in HFpEF

Wolsk E, EJHF 2017, in press

- predicts survival

Dorfs S, EHJ 2014; 35: 3103-12

HFrEF

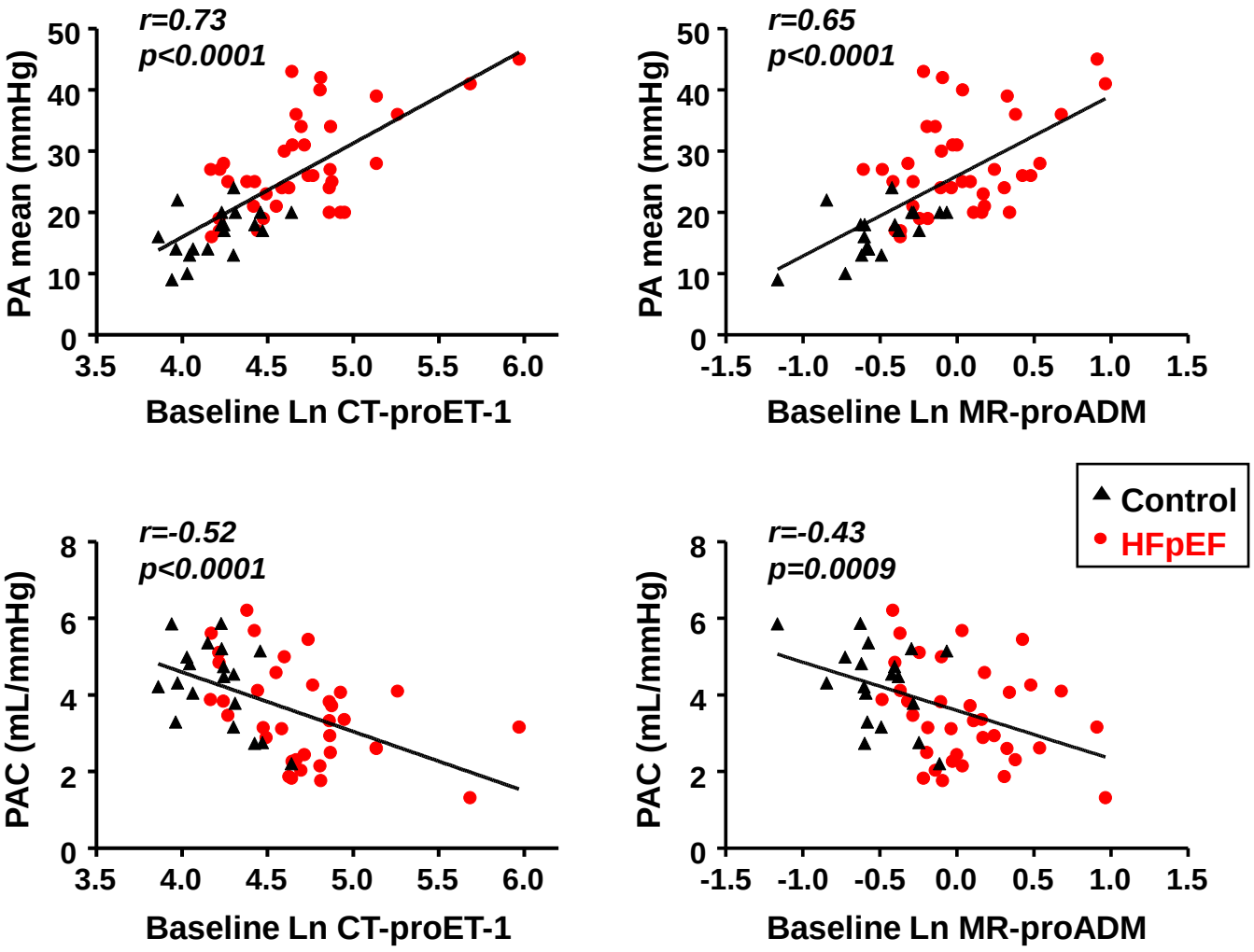


no relation of ex PAWP to peak VO_2 in HFrEF

*Franciosa, JA, Am J Cardiol. 1984;**53**(1):127-34*
*Wilson JR, Circ. 1995;**92**(1):47-53*
*Wilson JR, JACC 1995;**26**(2):429-35*

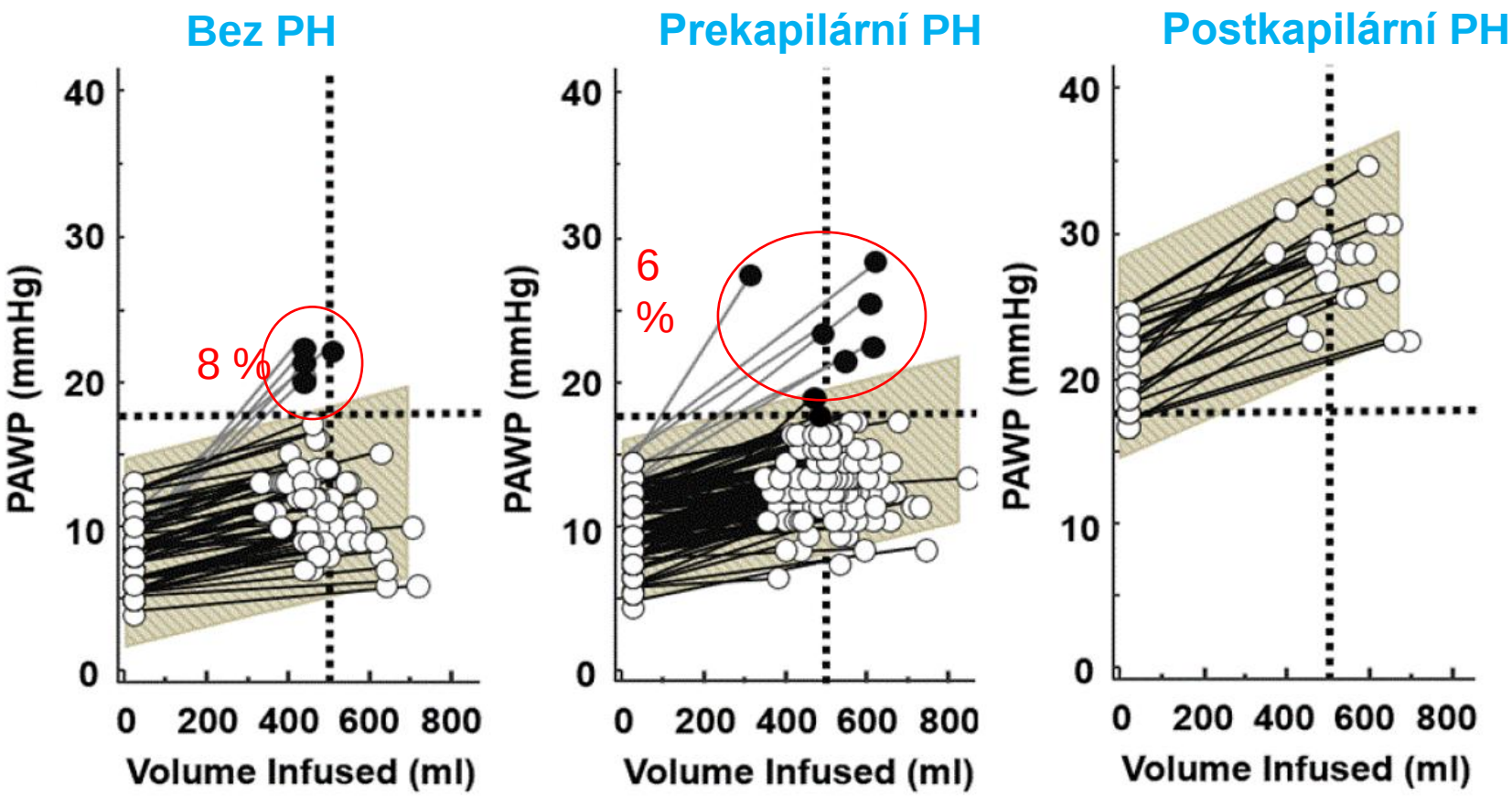
Elevated exercise PAWP in HFpEF - not only marker, but treatment target

Endothelial dysfunction of pulmonary circulation



PH 1 nebo 2 typu? Dynamické testy akutní volumexpanze

222 pacientů s RHC, **zátěžový test: infuze 7 ml/kg FR během 5-10 min.**
Vzestup PAWP ≥ 18 mmHg po infusi = postkapilární PH



Volumexpanze je bezpečná

D´Alto M, Chest 2017, 151: 119-126

World PH summit Nice 2018: Co je nového u PH2 typu ?

Hlavní současný diagnostický problém: rozlišení PH-HFpEF vs PAH

Doporučený přístup:

Určit pre-test probability fenotypu levostranného srdečního onemocnění

Feature	High probability	Intermediate probability	Low probability
Age	>70 years	60–70 years	<60 years
Obesity, systemic hypertension, dyslipidaemia, glucose intolerance/diabetes	>2 factors	1–2 factors	None
Previous cardiac intervention#	Yes	No	No
Atrial fibrillation	Current	Paroxysmal	No
Structural LHD	Present	No	No
ECG	LBBB or LVH	Mild LVH	Normal or signs of RV strain
Echocardiography	LA dilation; grade >2 mitral flow	No LA dilation; grade <2 mitral flow	No LA dilation; *E*/*e*′ <13
CPET	Mildly elevated V'_E/V'_{CO_2} slope; EOV	Elevated V'_E/V'_{CO_2} slope *or* EOV	High V'_E/V'_{CO_2} slope; no EOV
Cardiac MRI	LA strain or LA/RA >1		No left heart abnormalities

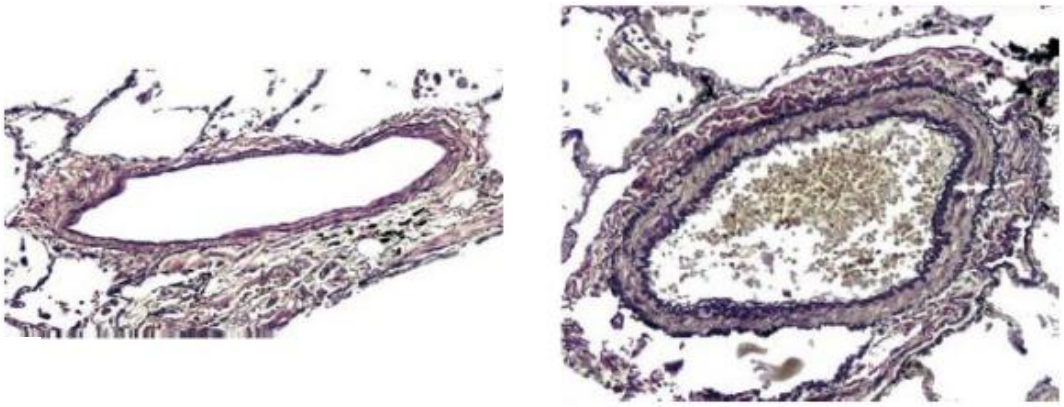
Invazivní hemodynamické vyšetření pouze u intermediate probability

First author [ref.]	Subjects n	Age (sex)	Protocol	Average PAWP: rest to peak mmHg	Comment
Exercise					
Wright [62]	28 healthy	55 years (12 female)	Semi-upright	11±3–22±5 early to 17 ±6 late	Time-variant changes, early increase and late decrease
Wolsk [63]	62 healthy	20–80 years (50% female)	Supine	8–10 rest; 16 leg raising; 19 at 25% peak $V'O_2$; 23 at 75% peak $V'O_2$	35% elderly had PAWP >25 mmHg
Andersen [52]	26 (14 HFpEF, 12 controls)	70 years HFpEF (57% female); 63 years controls (58% female)	Supine exercise *versus* fluid loading	Control: 7±3–13±5; HFpEF: 14±3–32±6	Similar increase in healthy subjects; 2-fold increase in all filling pressures during exercise *versus* fluid loading in HFpEF
Fluid loading					
Fujimoto [53]	60 healthy; 11 HFpEF	Young: <50 years; older: ⩾50 years	100–200 mL·min^{-1}	Young: 10±2–16±2; older: 9±2–17±2; HFpEF: 14±4–20±4	Normals reach PAWP 18–19 mmHg
Andersen [52]	26 (14 HFpEF, 12 controls)	70 years HFpEF (57% female); 63 years controls (58% female)	10 mL·kg^{-1}·min^{-1} saline (150 mL·min^{-1})	Control: 7±3–13±5; HFpEF: 14±3–21±4	Similar increase of PAWP in healthy subjects
Fox [55]	107 SSc with PH suspicion	59 years PAH (94% female); 66 years OPVH (64% female)	500 mL saline (5–10 min)	PAH: 8±3–12±2 (LVEPD 9–12); OPVH: 12±3–17±5 (LVEDP 15–21)	Retrospective analysis; OPVH defined by increase in PAWP >15 mmHg
Robbins [57]	207 PAH	51 years PAH (82% female); 57 years OPVH (74% female)	500 mL saline (5–10 min)	PAH: 9±3–11±4; OPVH: 12±2–19±3	Retrospective analysis; 30% had increase in PAWP >15 mmHg, predominantly female, mostly in normal range
D'Alto [65]	212 PH evaluation	58 years pre-capillary (68% female); 65 years post-capillary	7 mL·kg^{-1} rapid infusion	PAH: 9±2–12±2; HPH: 11±2–22±3	Overlap between groups; cut-off for PAWP abnormal response at 18 mmHg

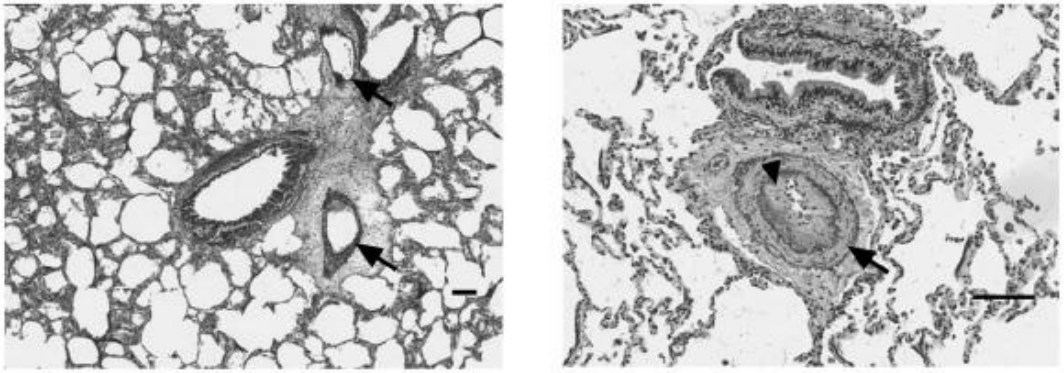
How HF patients develop pulmonary vascular disease ?

Structural changes in pulmonary arterioles

Low PVR HFrEF | **High PVR HFrEF**

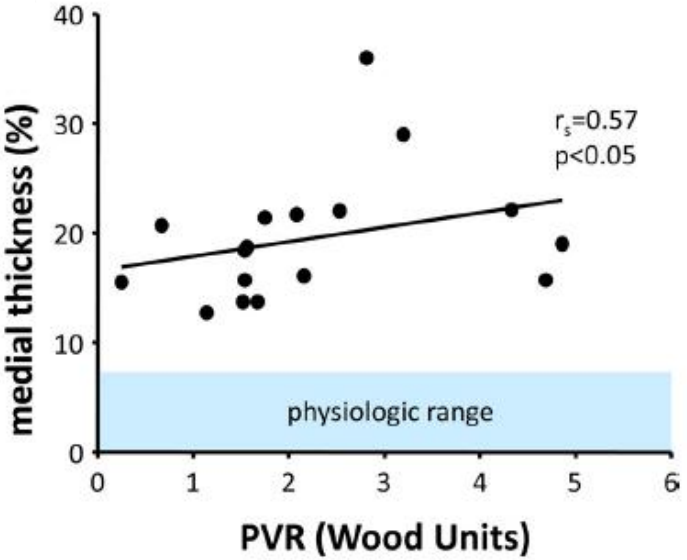


Delgado JF. Eur J HF 2005 (7) 1011-16



Hunt JM Am J Physiol 305, L725-36, 2013

No plexiform lesions (typical for group 1 PH)

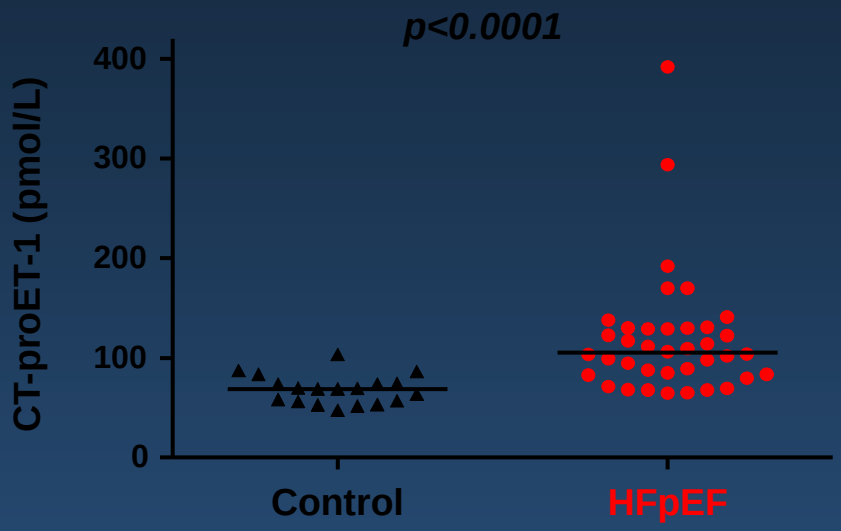


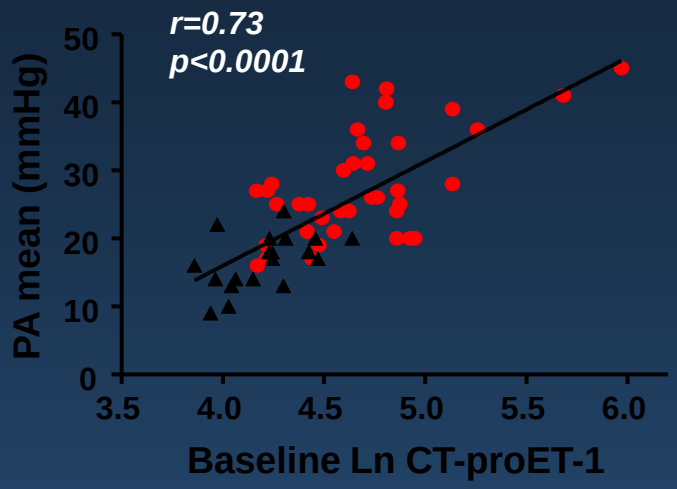
Medial thickening (MT) of small PA arterioles

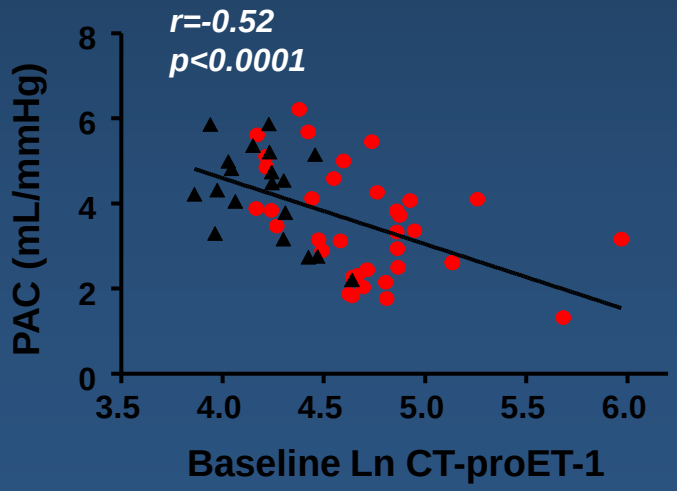
muscularisation of media, proliferation of SMC

adaptation against pulmonary edema ?

Aktivace endotelinového systému u PH-HFpEF







Endotelin-1 je zvýšený u HFpEF, proporcionálně se stupněm PH

Studie testující efekt ET-1 inhibitorů jsou zatím negativní

- **vedlejší účinky ?**
- **ET-1 je jen surogát ?**

Obokata M, Melenovsky V, Jarolim P, Borlaug BA, submitted