PLICNÍ HYPERTENZE U CHRONICKÝCH SRDEČNÍCH CHOROB

Vojtěch Melenovský

Klinika kardiologie IKEM Praha

Sjezd ČKS Brno 2018
Symposium 7.5. 2018
9:45-10:00

Klasifikace PH
a zařazení plicní hypertenze při onemocnění L srdce

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	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	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

aka: „out-of proportion“ PH
„reactive“ PH

PVR: plicní vaskulární rezistence = PA_{mean} - $PAWP_{mean}$/CO

DPG: diastolický tlakový gradient = PA_d - $PAWP_{mean}$

ESC Guidelines on PH, 2015

Co definuje prekapilární komponentu PH 2 typu ?

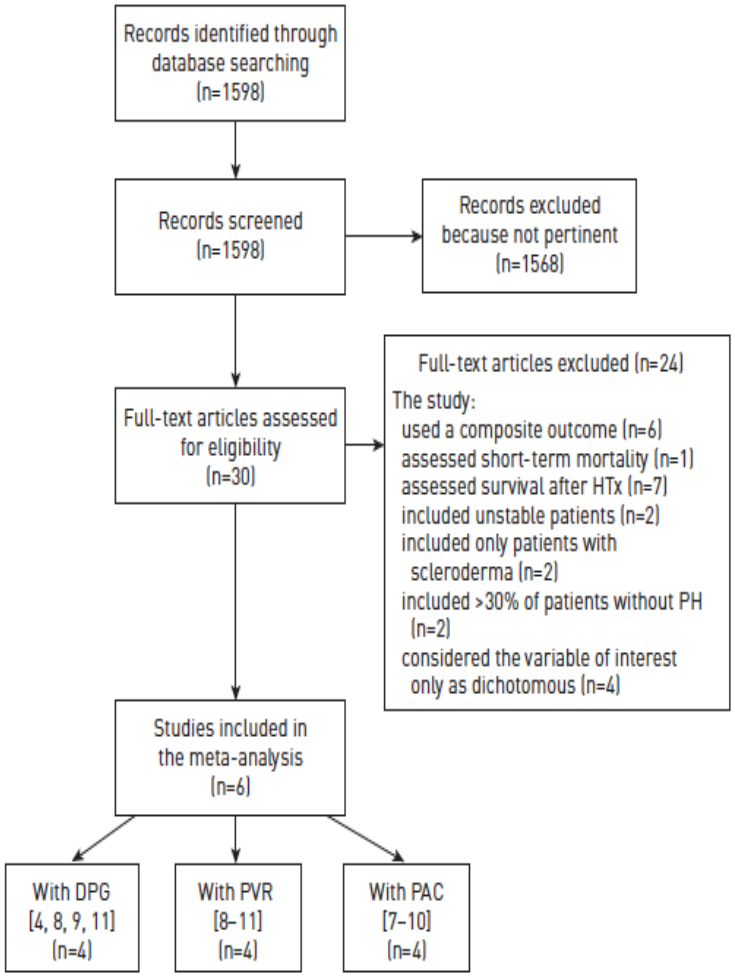
Characteristic	TPG	DPG	PVR	PAC
Physiological background	**-/+**	**+++**	**++(+)**	**++**
Independence from flow and filling pressures	**-**	**+(+)**	**-/+**	**-**
Dependent on quality of PAWP recording	**+**	**++**	**+**	**-**
Specific limitations	- Included in PVR - Limited relevance	- High depency on P quality - Small number	- Interdependent numerator and denominator	- Smallest number - Overestimation
Marker of disease	**+**	**+(+)**	**++**	**-/+**
Marker of prognosis	**-/+**	**+**	**++**	**++**
“Historical” variable	**+++**	**-/+**	**+++**	**-**
Level of comfort for clinical use	**++**	**+**	**+++**	**-**

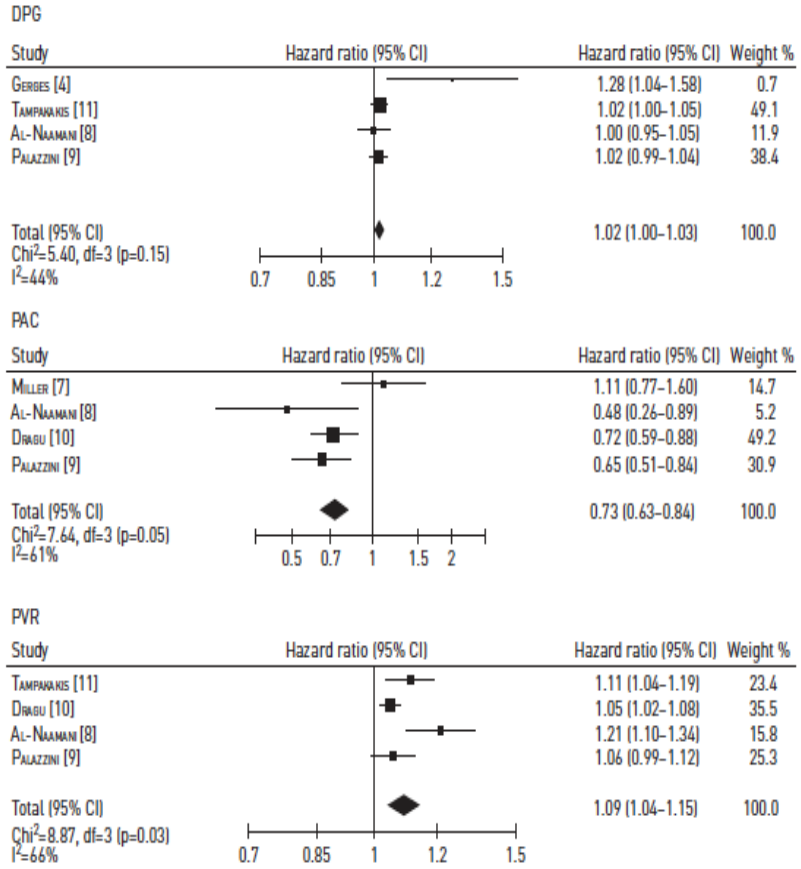
Významná prekapilární komponenta bude definována PVR > 3 w.u.

Co definuje prekapilární komponentu PH 2 typu ?

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

Diastolický tlakový gradient (DPG) nepredikuje mortalitu, na rozdíl od plicní vaskulární rezistence





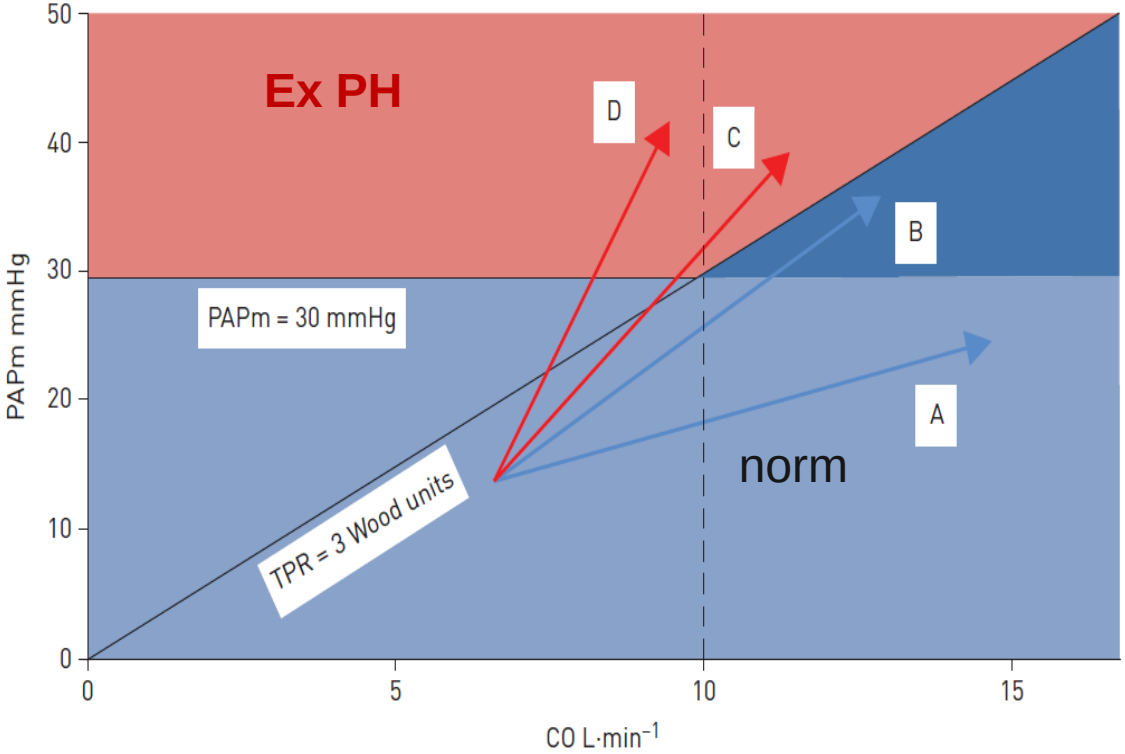
Caravita S et al. Eur Respir J 2018 in press

Zátěžová hemodynamika k detekci plicní vaskulární nemoci

Definice zátěžové plicní hypertenze (Eur Resp Soc 2017)

Definice pomocí vtahu průtok - tlak

Klid mPA < 25, vrcholový mPA > 30 mmHg and totální plicní rezistance (mPA/CO) > 3 w.u.



Herve P, et al. Eur Repir J 2015; 46: 728-737

Kovasc G, Eur Respir J 2017; 50: 1700578

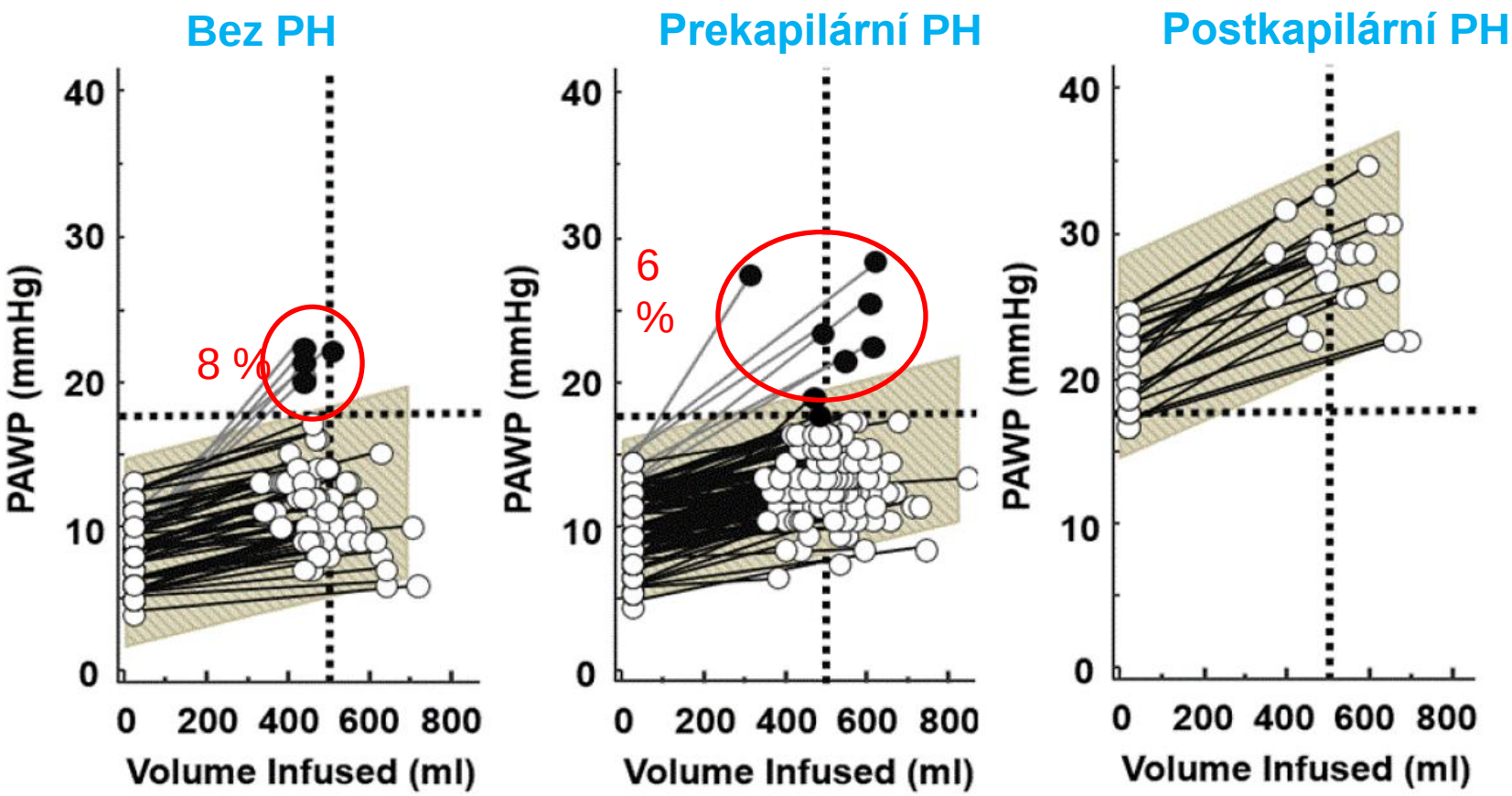
Narůstající zájem o zátěžová vyšetření -

- časná diagnostika PAH asociované s CTD
- dobře diskriminuje mezi PH1 a PH2 typu, lépe než volumexpanze

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

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

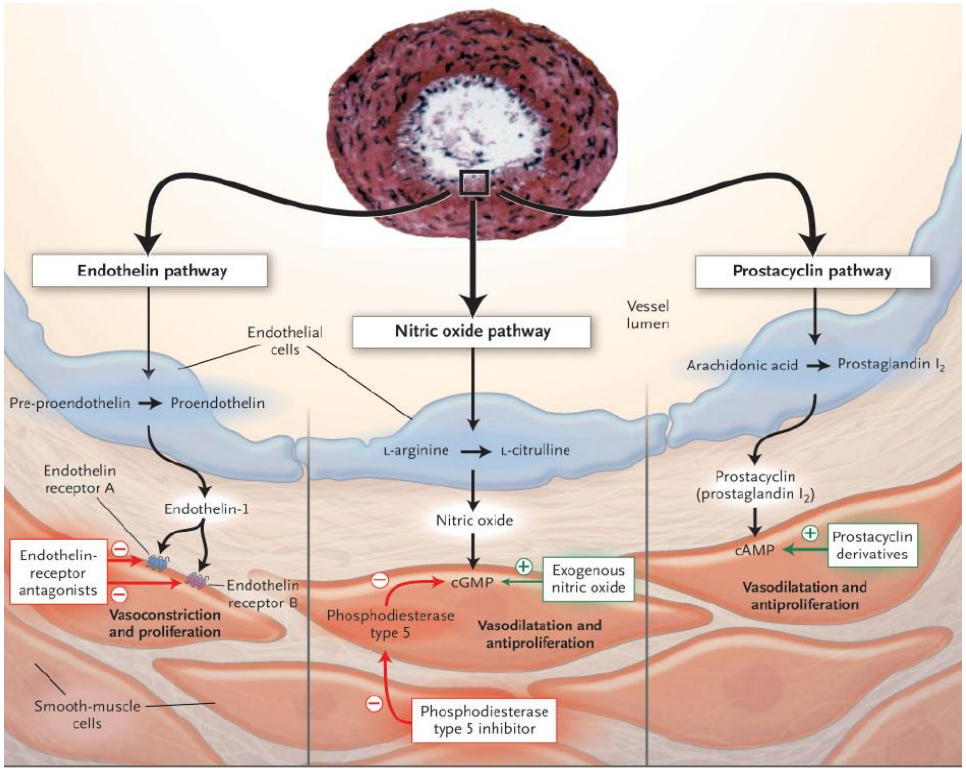


Volumexpanze je bezpečná

D´Alto M, Chest 2017, 151: 119-126

Patofyziologcické mechanismy: proč pacienti s ChSS mají plicní vaskulární nemoc ?

Endotheliální dysfunkce plicního řečiště

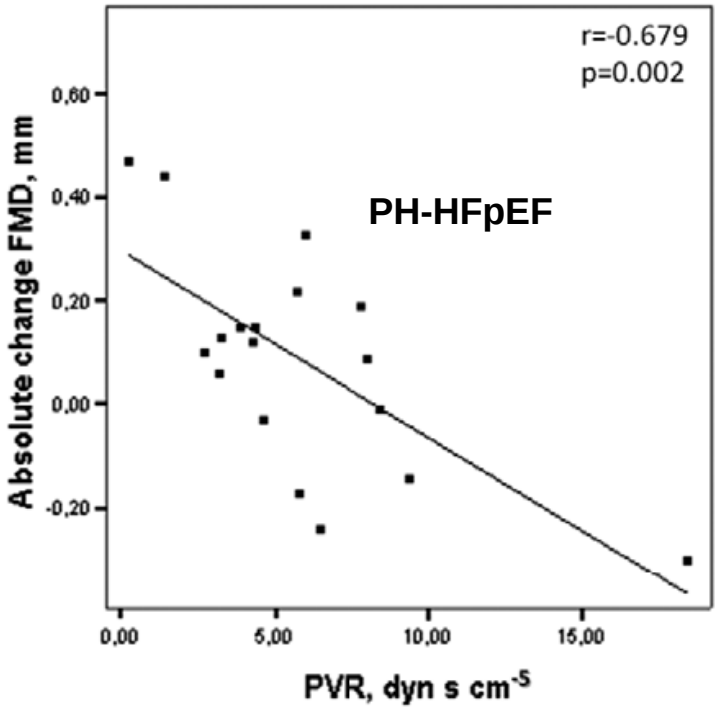


↑ endotheliální vazocontrictory: ET-1

↓ endotheliální vasodilatátory: PGI_2 , NO

Reverzibilní komponenta PVD

je to systémový proces



Plicní vaskulární rezistence (PVR) koreluje s flow-mediated dilatací (FMD) brachiální tepny

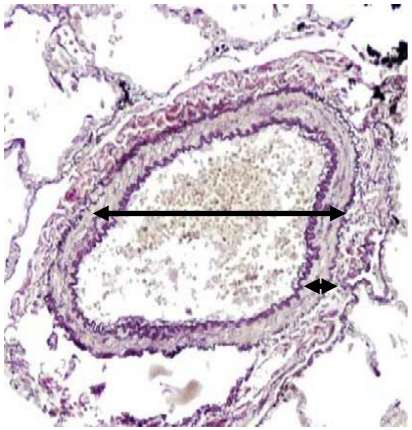
Moraes DL, Circ 2000; 102: 1718-23

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

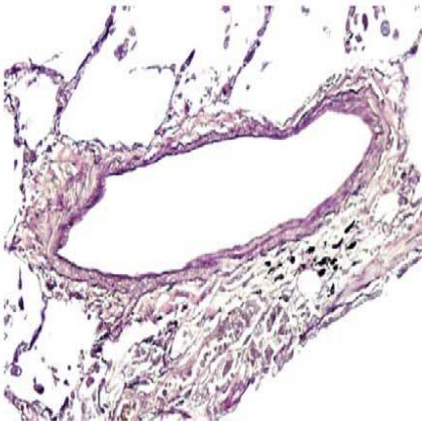
Proč pacienti s ChSS mají plicní vaskulární nemoc ?

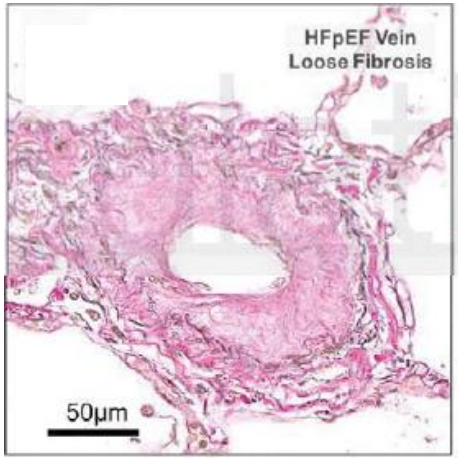
Strukturální změny v plicní cirkulaci

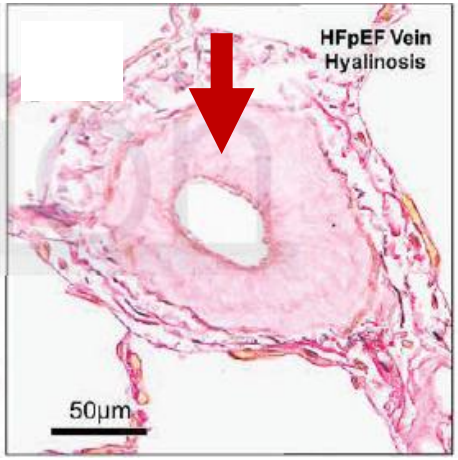
↑ PVR HFrEF



↓PVR HFrEF







Zesílení medie (MT) malých arteriol

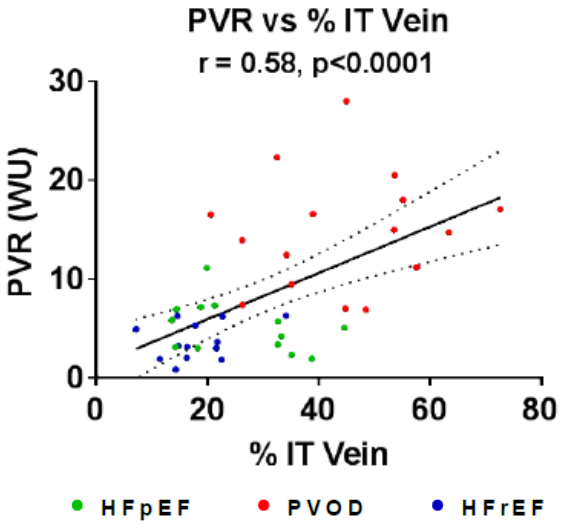
muskularizace medie
proliferace SMC

Delgado JF EJHF 2005 (7) 1011-16

Zesílení intimy (IT) plicních žil

více koreluje s TPG and PVR než arteriální změny
Změny podobné PVOD, ale méně denzní
(loose fibrosis, edematous intima)

„fixovaná“ componenta, která může regredovat při unloadingu LS (LVAD)

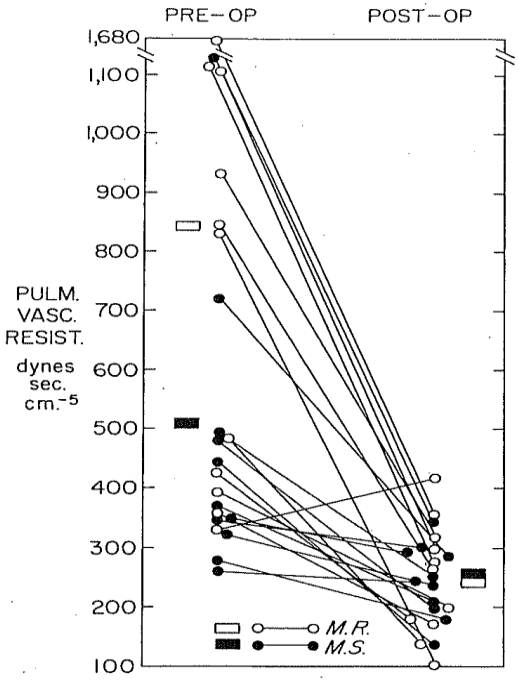


Fayyaz AU, Circulation 2017, in press

Klinické determinanty plicní vaskulární nemoci při PH2 typu

Zvýšený tlak v levé síni

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



Závažnost mitrální regurgitace

Enriques-Sarano M, JACC 1997;29:153-9

Plicní embolie

Stádnutím podmíněné tuhnutí plic. dév

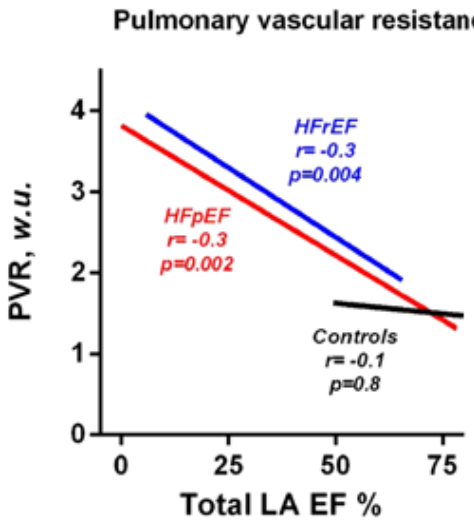
Hereditární dispozice

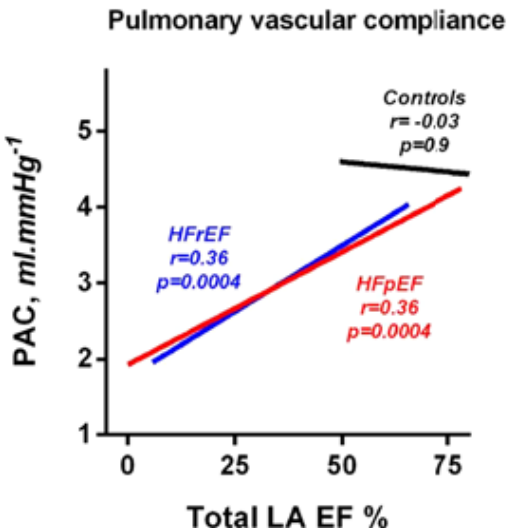
Aassad TR, JACC 2016; 68: 2536

Funkce levé síně

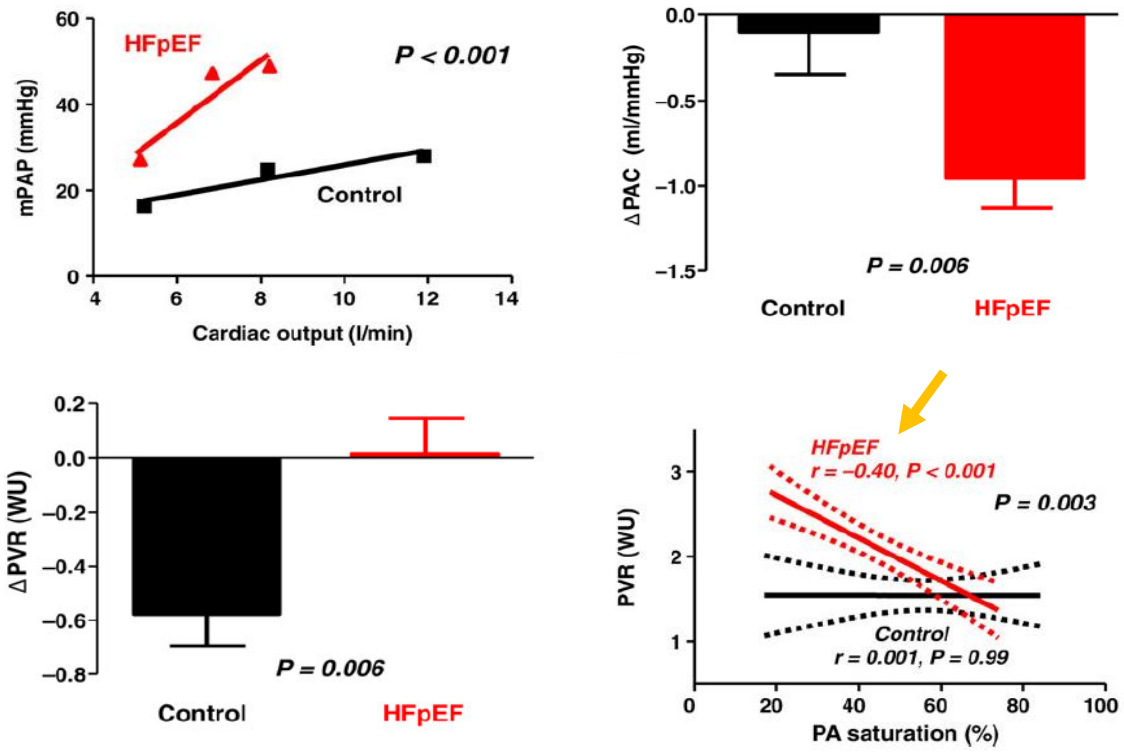
význam LAA ? Stiff LA syndrome..

Melenovsky V., Circ HF 2015; 8: 295-303





Mechanismy zátěží podmíněné PH u ChSS:



Borlaug at al.: EHJ 2016, 43: 3293-3302

Zátěží podmíněná PH 2 typu: přenos tlaku s levé síně

↓ PA compliance

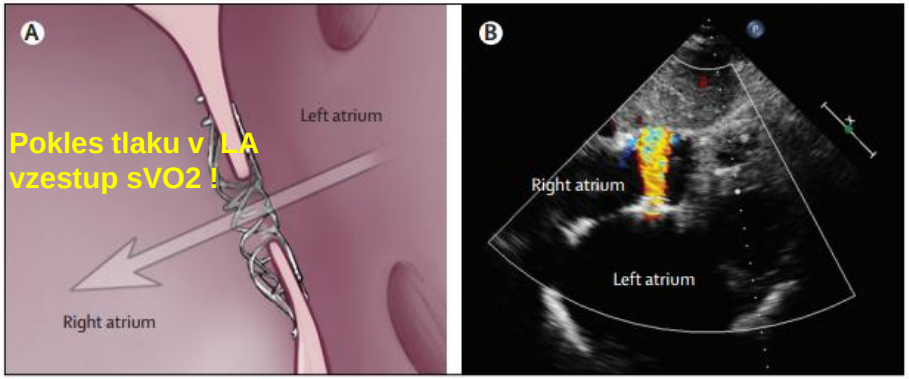
plicní vazokosntrikce

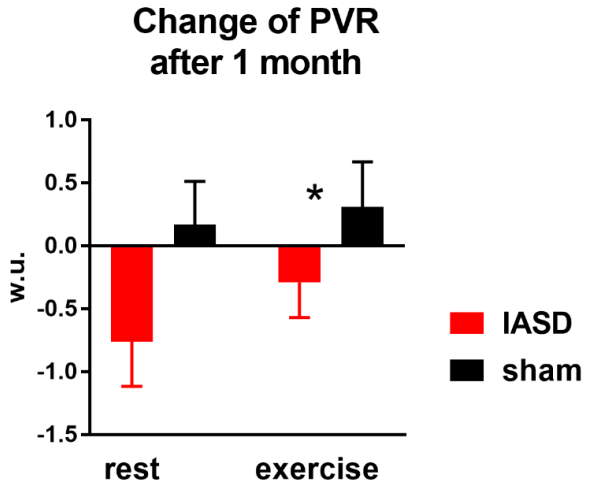
- endoteliální dysfunkce

- plicní venózní hypoxie ?

↓ sVO_2 může podporovat vzestup PVR u ChSS

REDUCE LAP-HF-1 studie





Feldman T, Circulation 2017

Po implantaci interatriálního shuntu (IASD) k redukci tlaku v LS:

↑ **transpulmonálního průtoku, ale** ↓ **PVR**

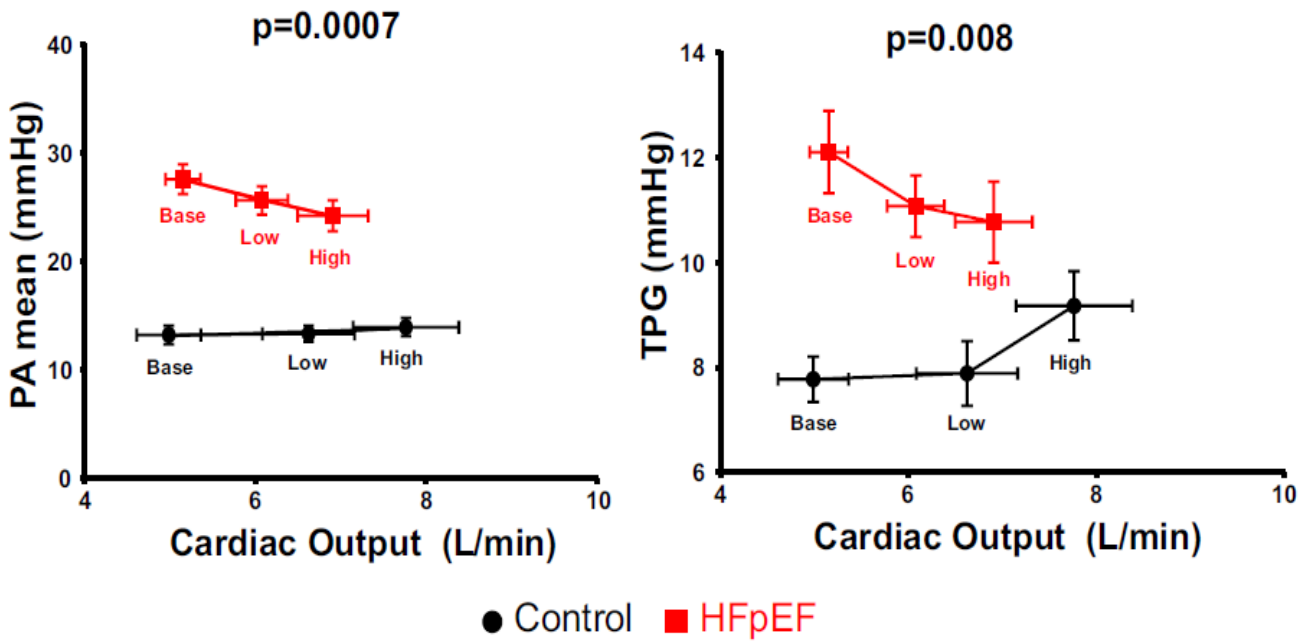
Vasodilatační efekt více oxygenované krve v PA ?

Možná role systémové žilní hypoxie (důsledek nízkého CO) na vzniku prekapilární komponenty PH u ChSS

Taylor BJ J Cardiac Fail 2013: 19: 50-59

Betamimetika vedou k plicní vasodilataci in HFpEF

Akutní efekt infuse dobutaminu na plicní hemodynamiku

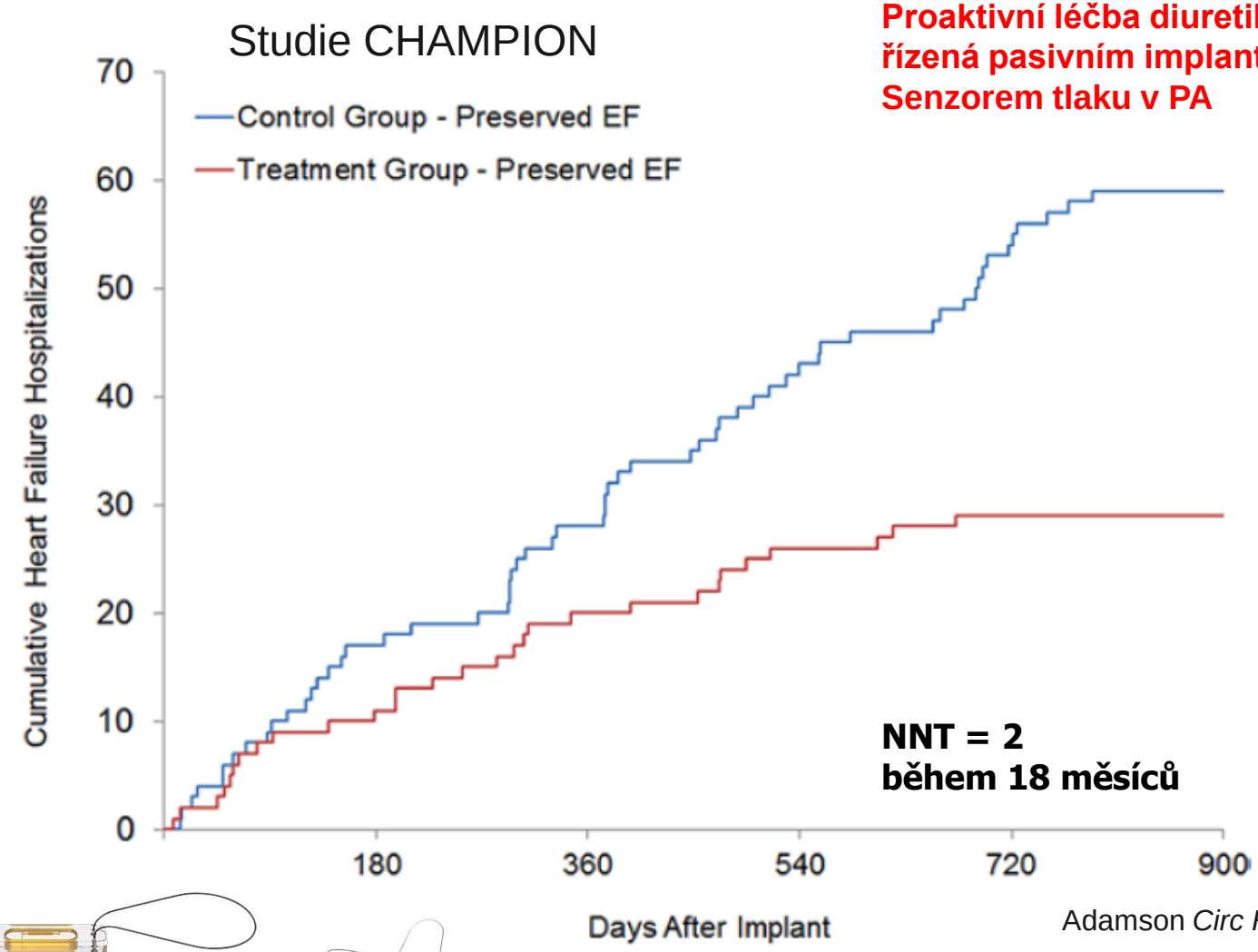


Andersen et al. Cicr Heart Fail 2015; 542-550

Inhaled Beta-adrenergic Agonists to Treat Pulmonary Vascular Disease in Heart Failure With Preserved EF (BEAT HFpEF): A Randomized Controlled Trial (BEAT HFpEF)….. onging

Jak léčit PH 2 typu ? Diuretika.

Proaktivní léčba diuretiky řízená pasivním implantabilním Senzorem tlaku v PA



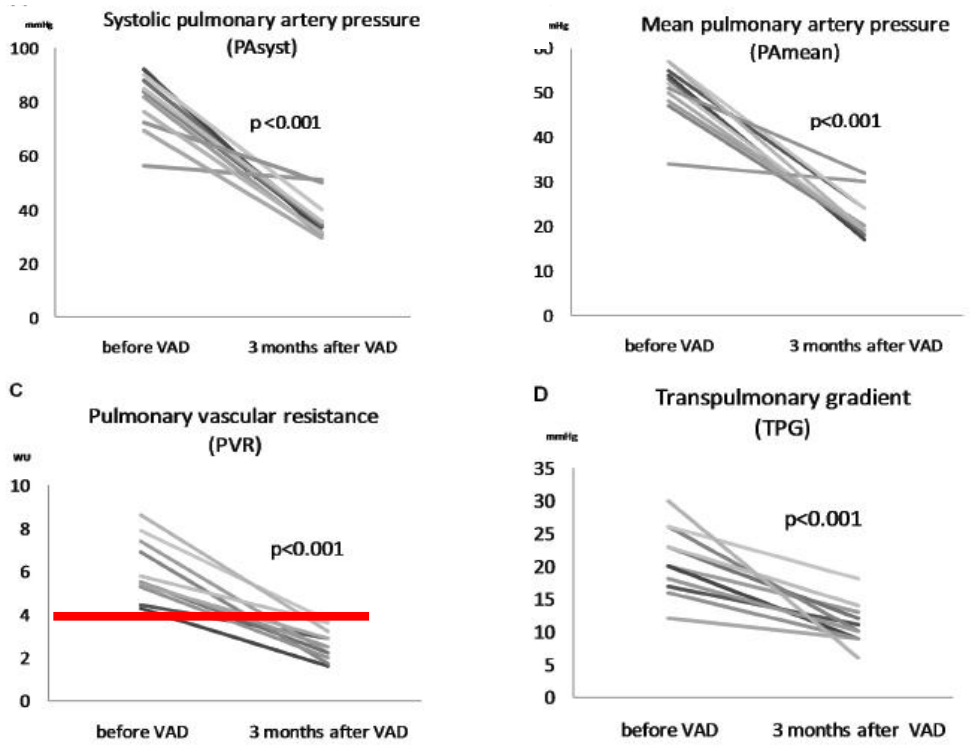
Adamson *Circ Heart Fail* 2014

CardioMEMS, Abbott

Cordella device

Jak (vy)léčit PH 2 typu? LVAD

u HFrEF



KI TX

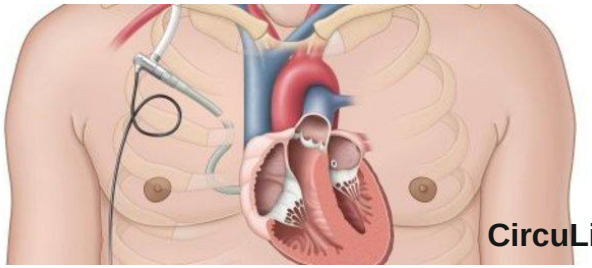
Kettner J, et al., Phys Res. 2011

Regrese histologických změn v plicní cirkulaci po LVAD terapii

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

mini-LVADy k dekompresi levé síně u HFpEF ?

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



CircuLite

Specifické plicní vasodilatátory ? nedávno ukončené studie u PH 2 typu

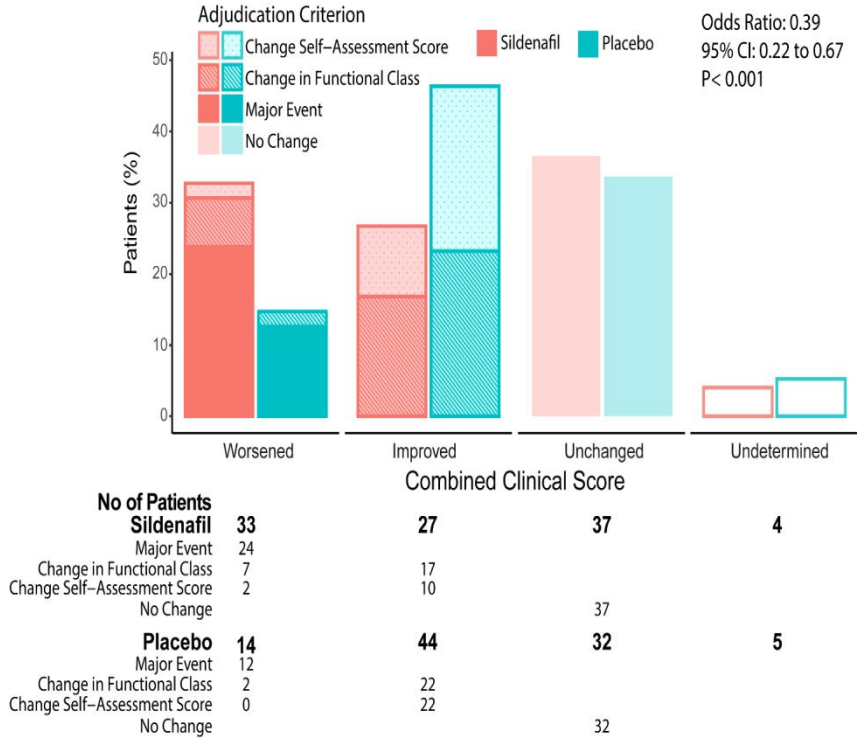
Study	Study Drug	N	Duration	Population	Primary/secondary outcome	Result
Guazzi [1]	Sildenafil	44	12 mo	HFpEF	• HD, RV performance	• **Improvement**
LEPHT [2]	Riociguat	201	16 W	HFrEF	• Change in mPAP vs pbo • PK, PVR, NT-proBNP	• No change in mPAP
Hoendermis[3]	Sildenafil	52	12 W	HFpEF	• Change in mPAP vs pbo • PVR, BNP, Peak VO2	• No change in mPAP • No change 2ary EP
SIOVAC [4]	Sildenafil	231	24 W	Valvular heart disease	Composite clinical score (death, hospitalisation for HF, change in FC, patient GSA)	• **Worse clinical outcomes on sildenafil**
MELODY-1[5]	Macitentan	48	12 W	HF LVEF>30%	• Safety, tolerability • AEs, PK, PVR, NT-proBNP	• +10% of fluid retention in the treated group • No change in PVR

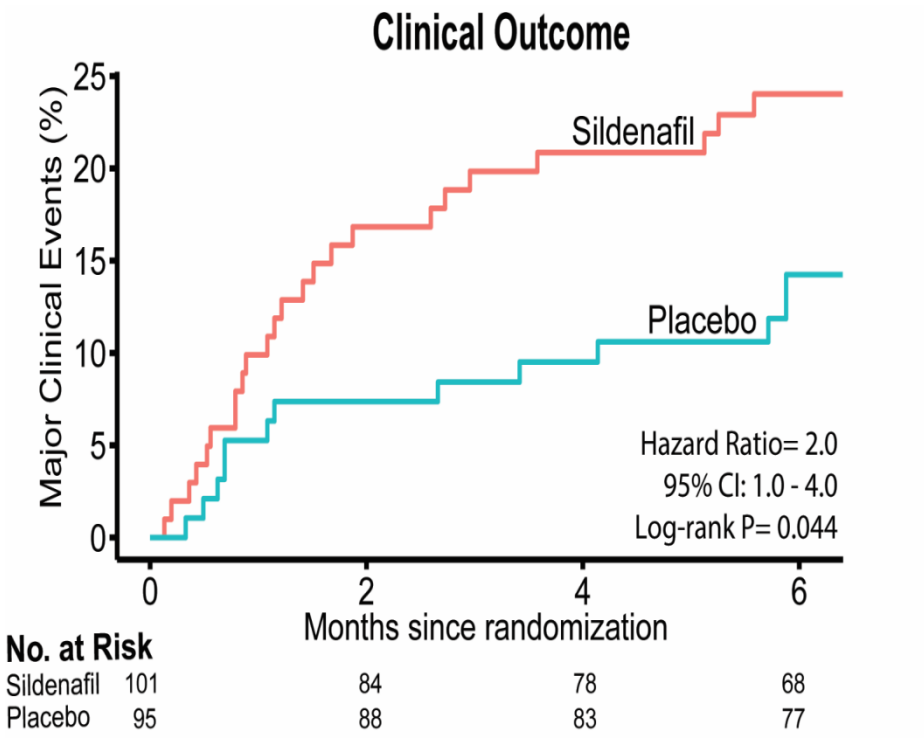
1. Guazzi et al. Circulation 2011. Bonderman et al. Circulation 2013; 128: 502-511. 2. Bonderman D et al. Chest. 2014;146(5):1274-85. 3. Hoendermis E, et al. Eur Heart J 2015; 36:2565-73. 4. Bermejo J et al. Eur Heart J 2017; 38. doi:10.1093/eurheartj/ehx700. 5.Vachiery JL et al. Eur Respir J 2018; 51: 1702589

Studie SIOVAC

Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial

231 pacientů po operaci chlopně (> 1rok, 91% mitrální) s perzistující PH po výkonu (mPA ≥ 30 mmHg)
Sildenafil 3x40 mg/den x placebo, 6 měsíců; kombinovaný end-point





Většinou šlo o starší ženy, NYHA III, s nízkým BNP 50-60 pg/ml
Jen 57% mělo PVR > 3 w.u.

Bermejo J et al. Eur Heart J 2018; 39, 1255-1264

Plánované/probíhající studie se specifickými plicními vasodilatátory u PH 2 typu

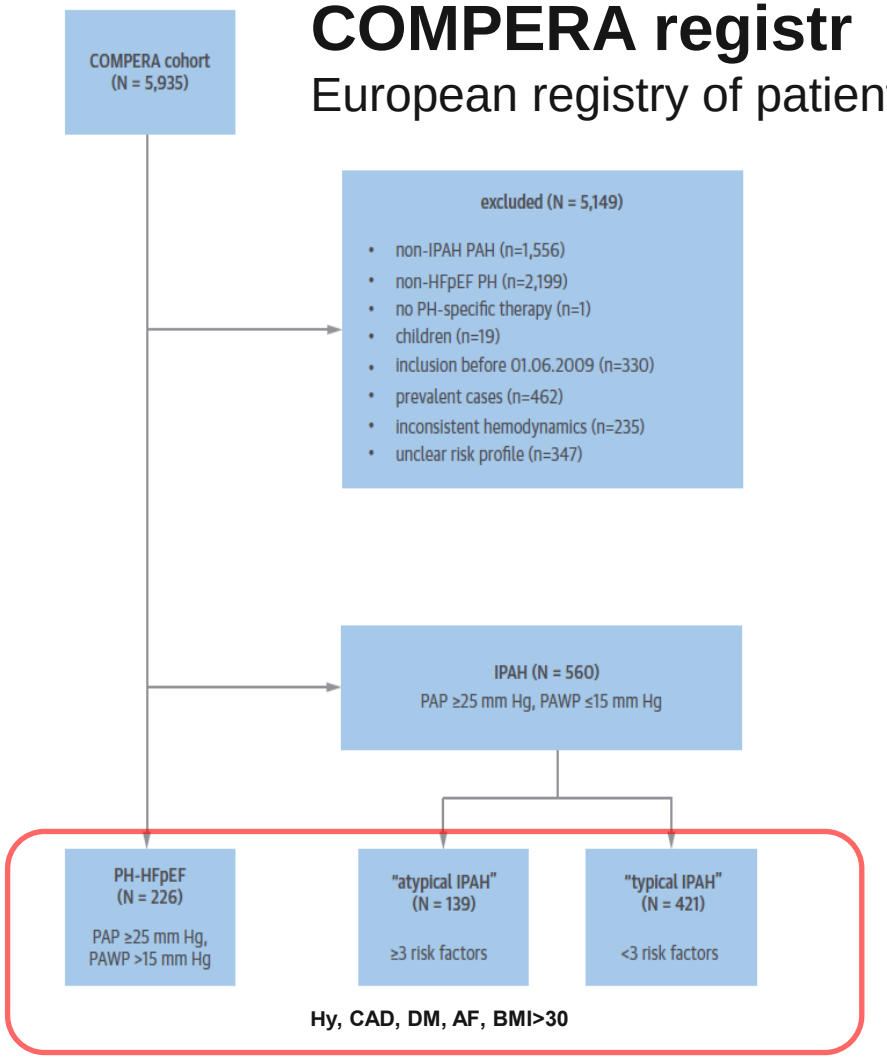
Study	Study Drug	N	Duration	Population	Primary outcome
SPHERE HF NCT02775539	Mirabegron (b3 agonist)	80	16 W	PAWP/LVEDP ≥15, Mean PAP≥25 PVR≥3 UW and/or DPG ≥7 mmHg orTPG ≥12	Change in PVR
SERENADE NCT03153111	Macitentan	300	52 W	LVEF ≥ 40%, ESC defined HFpEF HF hospitalization within 12 months and/orPAWP or LVEDP > 15 mmHg within 6 months, Elevated NT-proBNP	% change from baseline in NT-proBNP @W24
SOPRANO NCT02554903	Macitentan	78	12 W	LVAD within 45 days PH by RHC with PAWP ≤ 18 mmHg and PVR > 3 WU	PVR ratio of Week 12 to Baseline
NCT03015402	Oral $NaNO_2$	26	10 W	PH-HFpEF by RHC AND TPG ≥ 12 mmHg	mPAP during submaximal exercise
NCT03037580	Oral treprostinil	310	24 W	LVEF ≥50%, RHC within 90 days of randomization, 6MWD > 200 meters	Change in 6MWD from Baseline to Week 24
DYNAMIC NCT02744339	Oral riociguat 1.5 mg tid	114	26 W	HFpEF, mPAP $\underline{\geq}$ 25 mmHg and PAWP > 15 mmHg	Change in CO
PASSION	Oral tadalafil	320	NA	HF pEF, PH with PAWP > 15 mmHg AND mPAP $\underline{\geq}$ 25 mmHg AND PVR > 3 WU	Time to first event defined as HF associated hospitalization (independently adjudicated) or death from any cause.

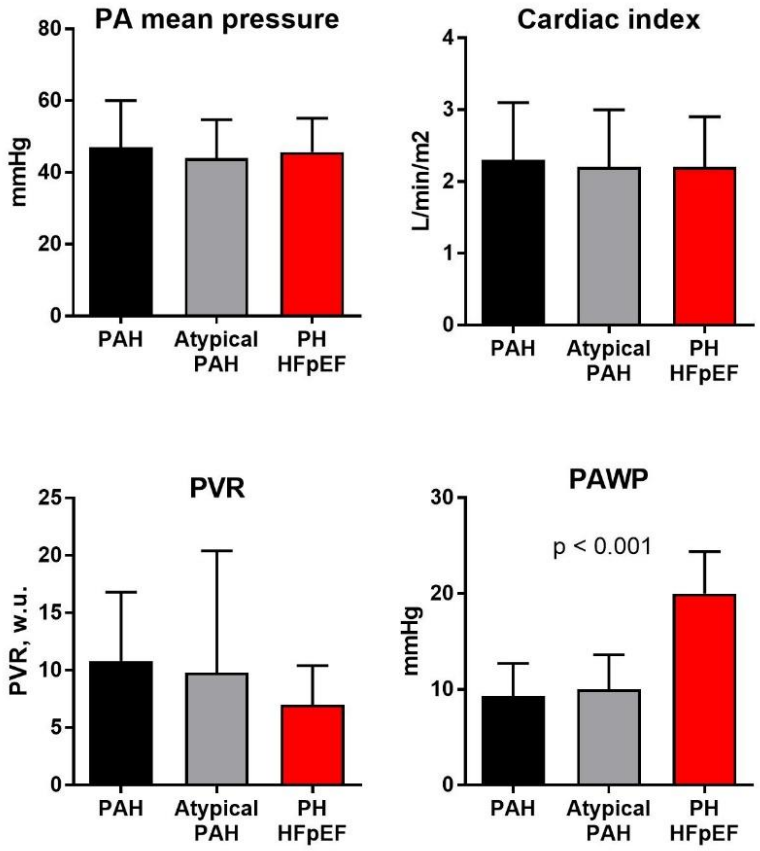
zdroj: JL Vachiery

Specifické plicní vasodilatátory ?

COMPERA registr

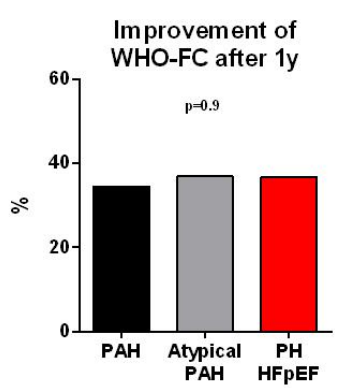
European registry of patients initiated on specific PH vasodilators

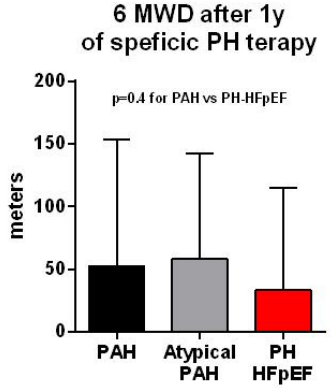


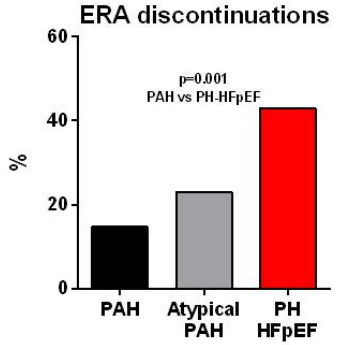


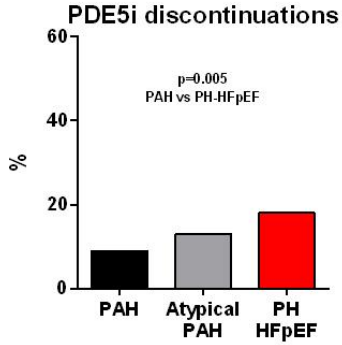
Opitz, C.F. et al. J Am Coll Cardiol. 2016;68(4):368-78.

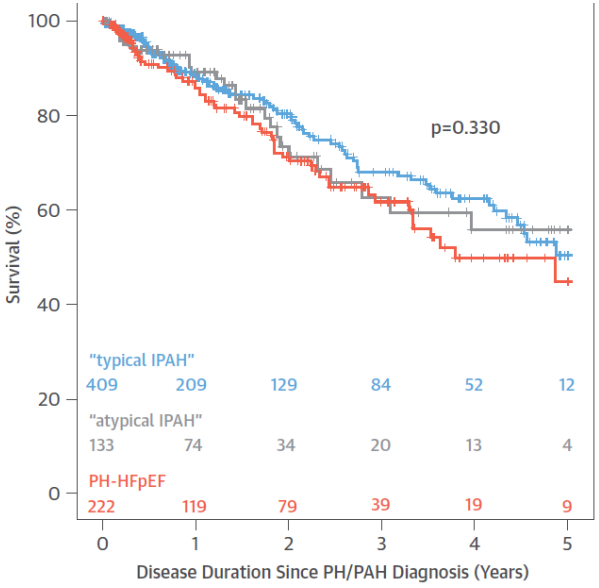
COMPERA registr

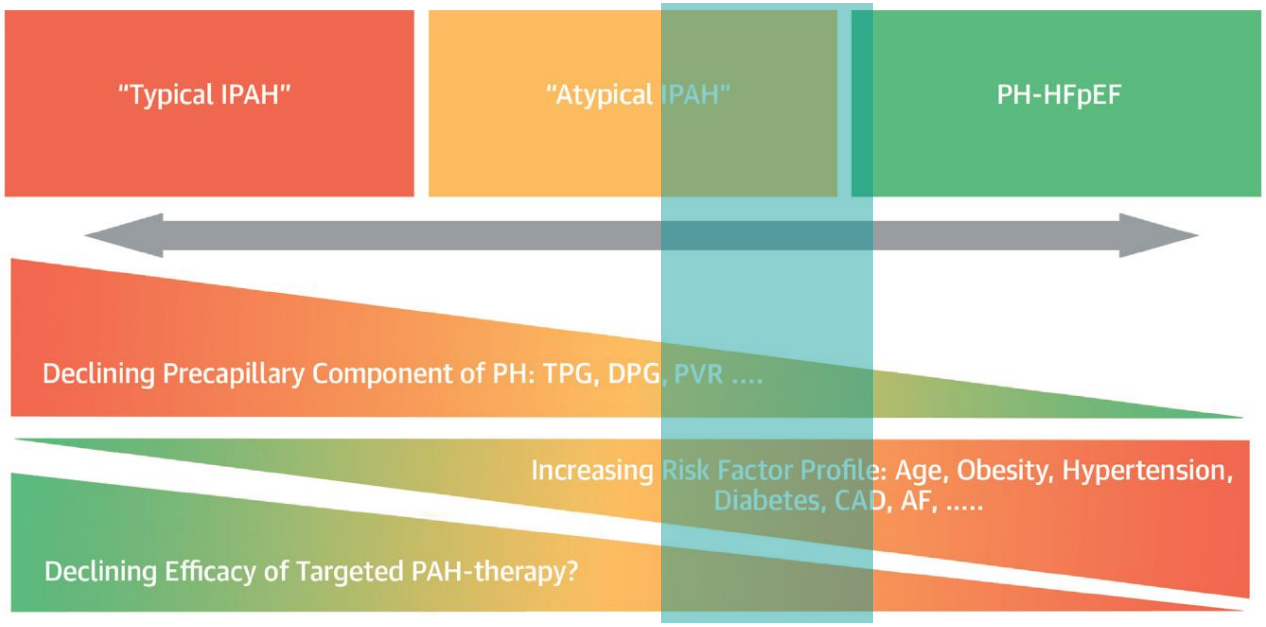












Signál potenciálního efektu – nutnost RCT studí u pacientů s PH-HFpEF (s vysokou PVR)

Opitz, C.F. et al. J Am Coll Cardiol. 2016;68(4):368-78.

Závěry

PH 2 typu je nejčastější plicní hypertenze

Diastolický tlakový gradient se neosvědčil, používat PVR

Provokační testy k upřesnění diagnostiky

Postkapilární PH: PAWP ≥ 18 mmHg při voluexpanzi

Zátěžová PH: klid mPA < 25, vrcholový mPA > 30 mmHg and totální plicní rezistance (mPA/CO) > 3 w.u.

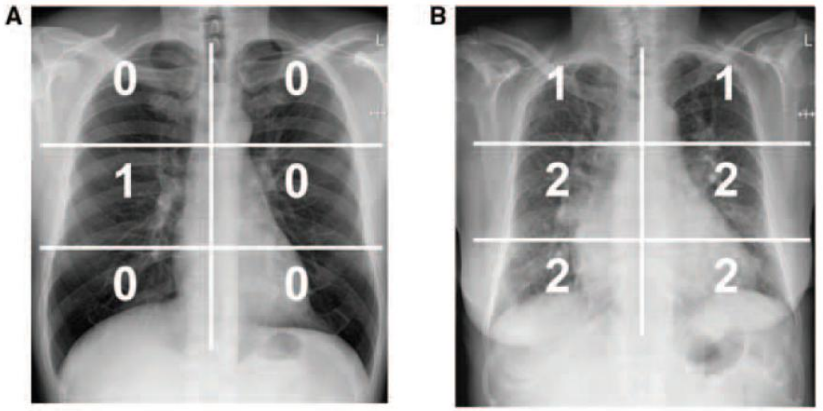
Terapie: redukce tlaku v levé síni = hlavní cíl

- role specifických plicní vasodilatátorů nejasná

Děkuji za pozornost

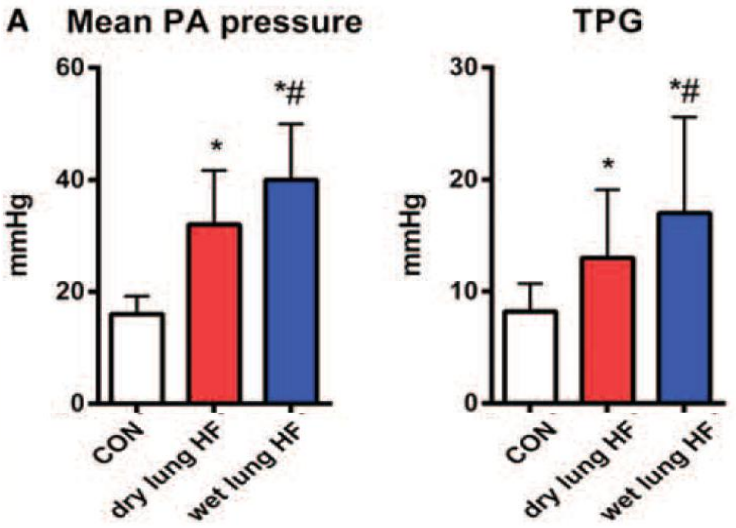
vojtech.melenovsky@ikem.cz

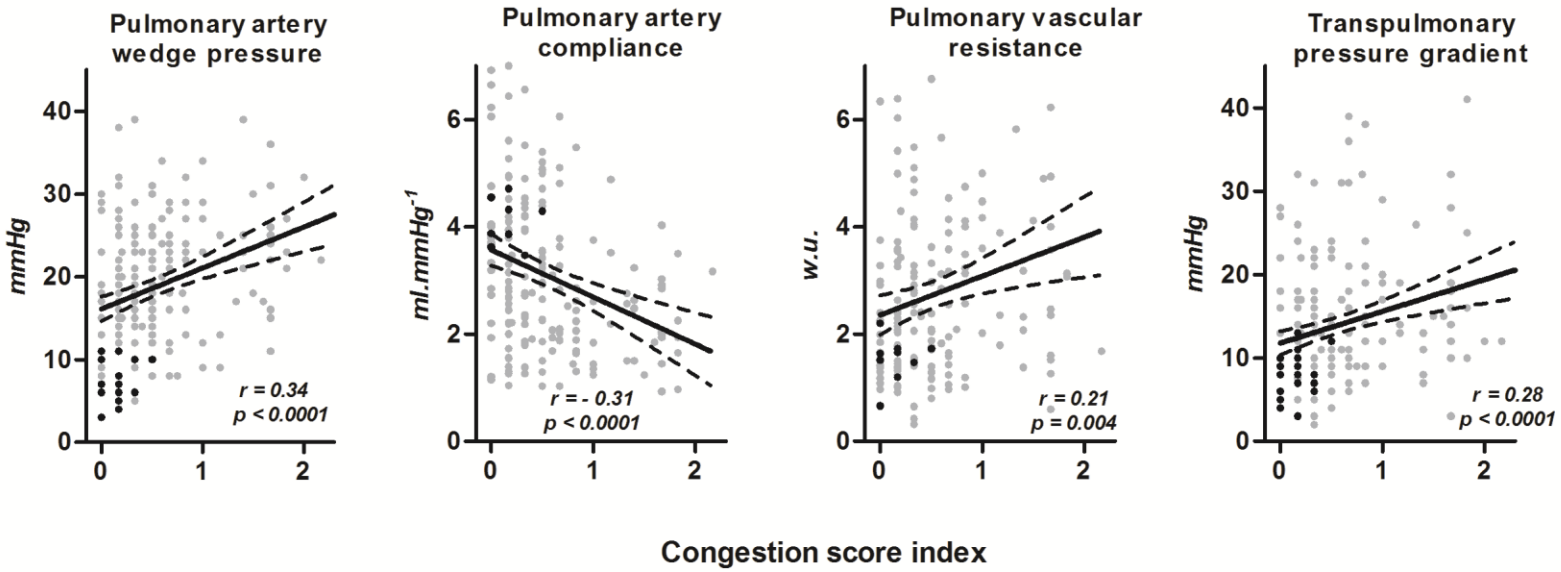
Congestion itself increases pulmonary vascular resistance



„Dry lung“ HF

„Wet lung“ HF





Melenovsky V. EJHF 2015, 17, 1161-71

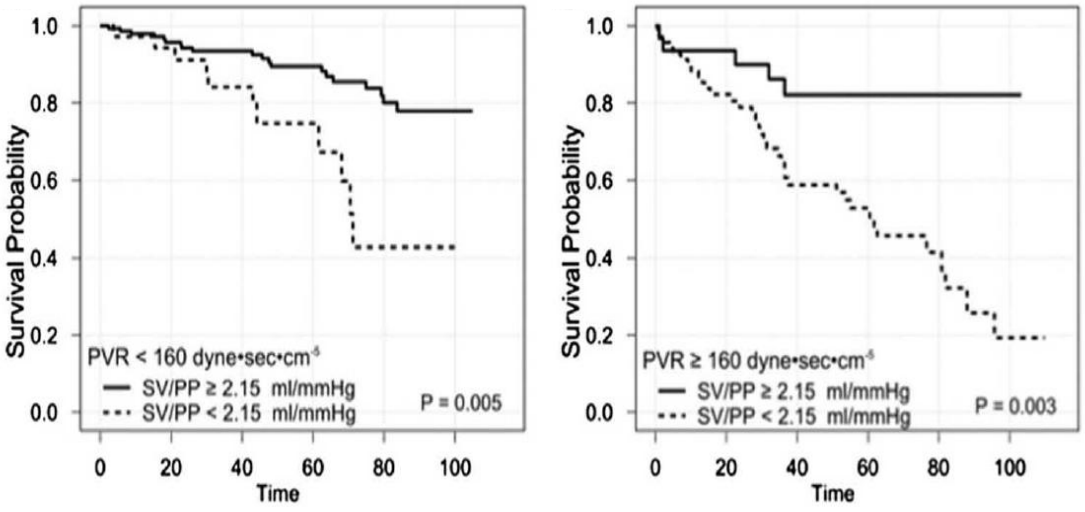
Pulmonary arterial compliance contributes to RV loading

RV load: steady component (PA pressure, PVR)
oscillatory component – PA compliance (PAC) ~ SV / PA PP

↑ LA pressure negatively affects PA compliance

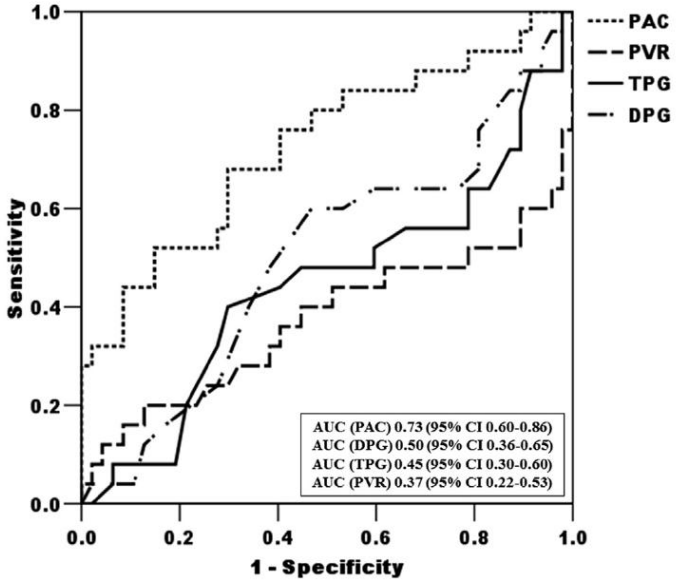
Tedford RJ, Circ 2012;125: 289-97

HFrEF



PAC predicts mortality even in patients with low PVR

HFpEF



PAC outperforms PVR, TPG, DPG
In predicting survival in HFpEF

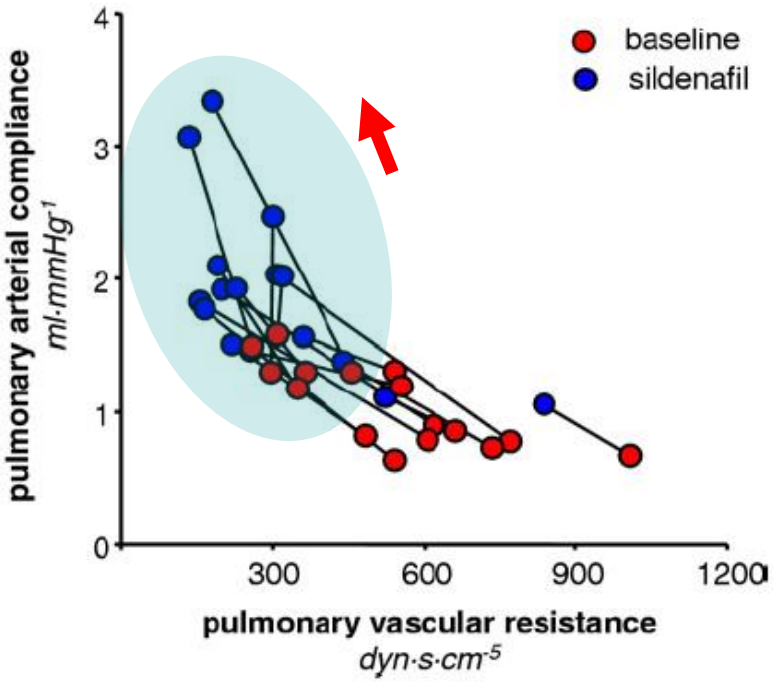
Pellegrini P, Chest 2014; 143 (5) 1064-1070

Al-Naamani JACC HF 2015; 3: 467-74

By reducing PAC, some interventions reduce RV load, even if PVR or PAm does not change so much

PDE5 inhibitor

24 high PVR HFrEF patients (before and after 40 mg of sildenafil)



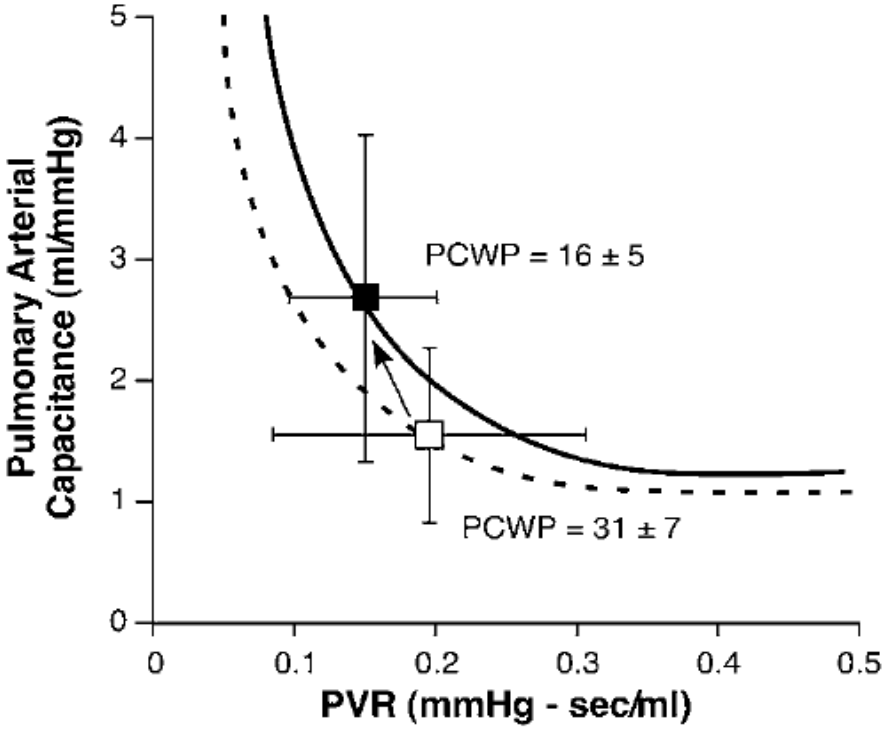
↓ PVR but ↑↑↑ PAC

apparent mostly in borderline-elevated PVR

coupled with ↑ transpulmonary cGMP release

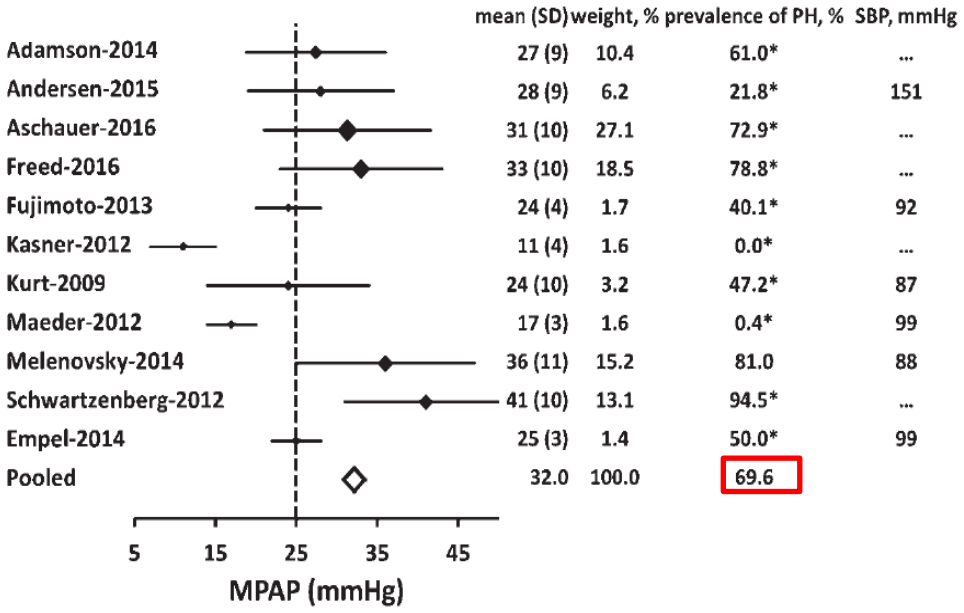
Melenovsky V, JACC 2009; 54: 595-600

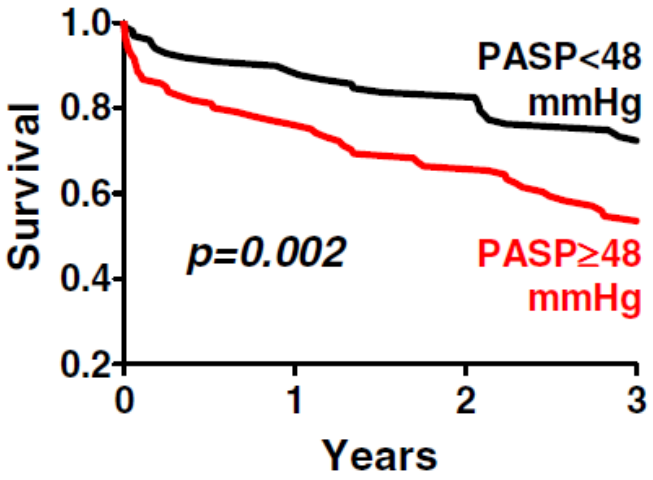
Decongestion



Dupont M, Circ HF 2012; 5: 78-85

PH is common in HFpEF and affects prognosis





~ 70% of HFpEF patients have PH

10 mm Hg ↑ PASP:
~ 30 % ↑ in mortality

PH due to Left heart diesease (group II PH)
mean PA ≥ 25 mmHg, PAWP ≥ 15 mmHg

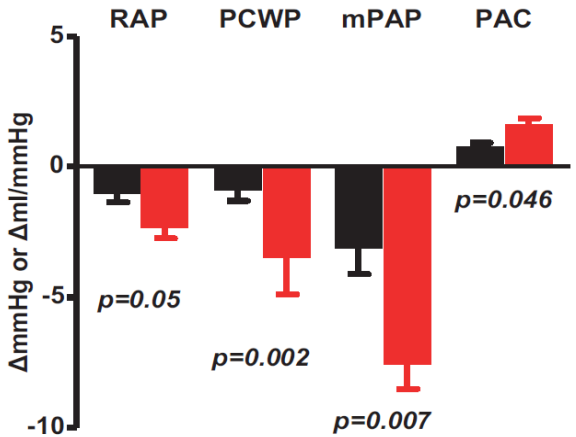
Gorter et al. *Eur J Heart Fail 2016*

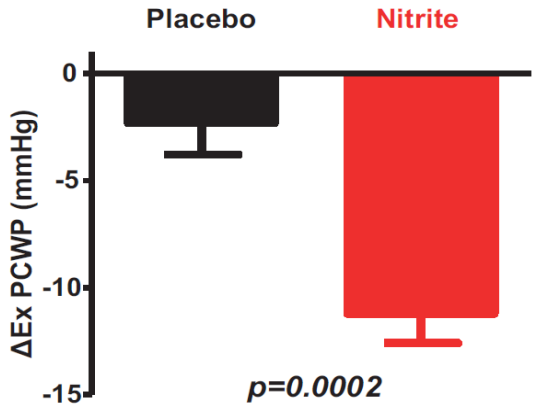
Lam CS, JACC, 2009
Gerges M, AJRCCM 2015, 1492:1234-46
Bursi F, JACC 59: 222-31

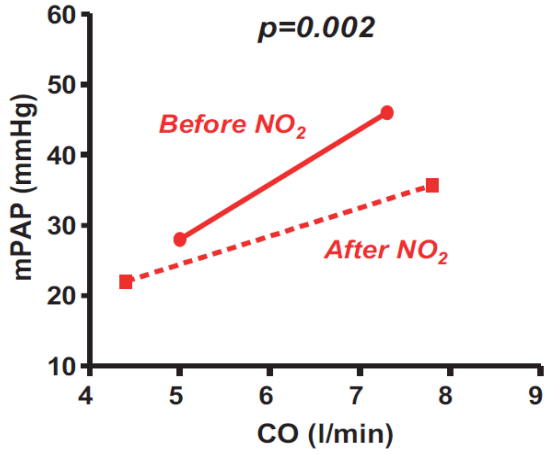
Novel approach- selective targeting of pulmonary vasculature – anorganic nitrites

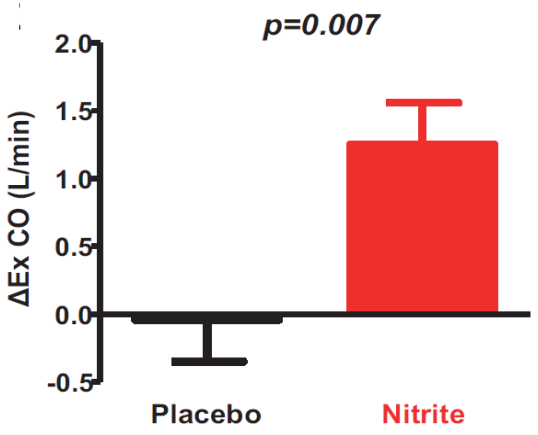
In hypoxic conditions, Nitrite (NO_2^-) is converted into NO by deoxy-hemoglobin

Intravenous or <u>inhaled</u> micronebulised $NaNO_2$ - effect on ex hemodynamics in HFpEF









Borlaug BA et al.
JACC 2015;66(15):1672-82.

Borlaug, Melenovsky et al.
Circ Res. 2016;119(7):880-6

Reddy Y, Circ HF 2017; 10:e003862

Inhaled miconebulised nitrite:

ad-hoc relieve of SOB ?
selective
no hypotension

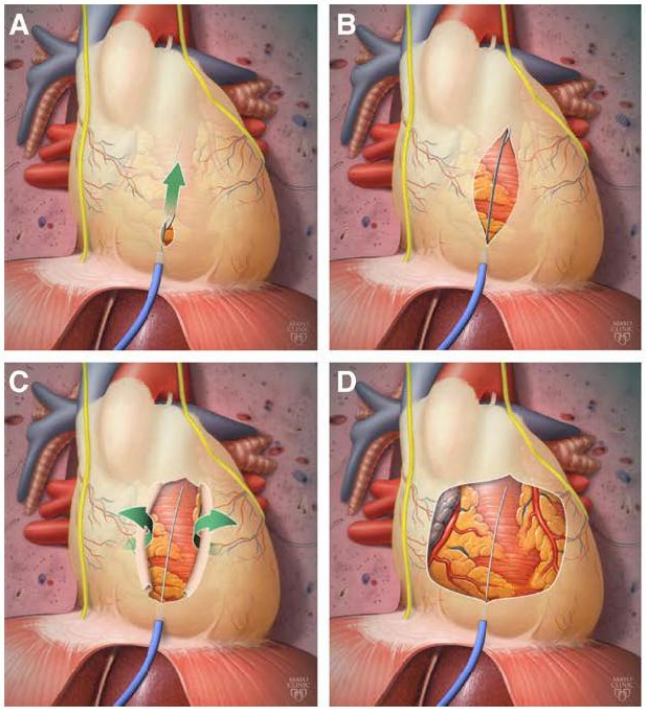
INDIE-HFpEF Trial

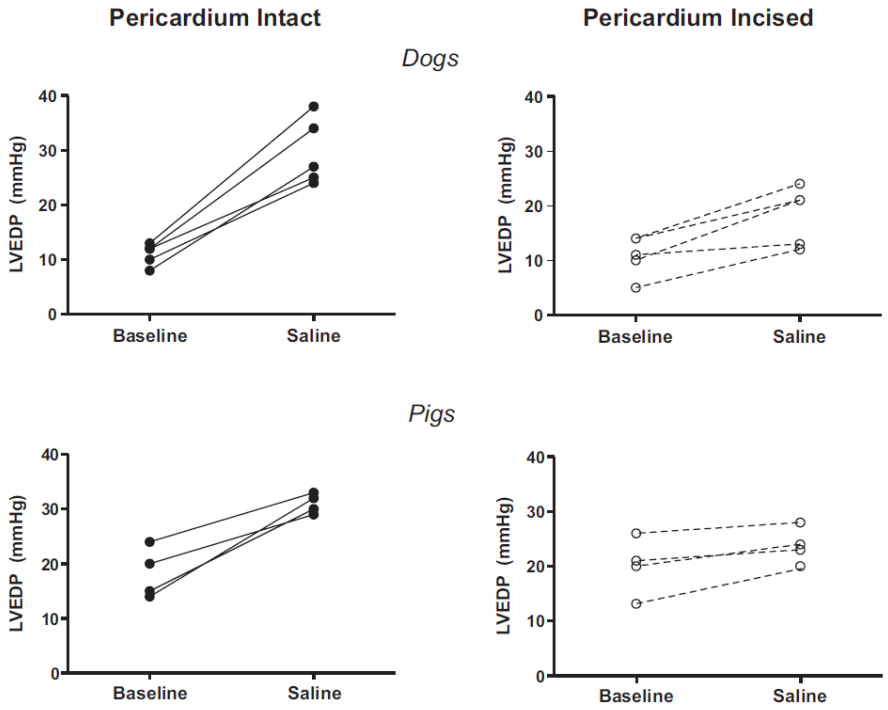
NCT02742129

aer. NO_2/placebo on VO2max

How to alleviate enhanced interventricular dependence ?

Intervention ? – minimally invasive parcial pericaridectomy





Borlaug et al. Cicr Heart Fail 2017; 10: e003612

Pharmacotherapy ?

SGLT2 inhibitor dapagliflozine reduces epicardial fat thickness

Shiina K et al. Circulation. 2017;136: A14832 – presented at AHA 2017

Symptomy a PVR u pacientů před Tx srdce

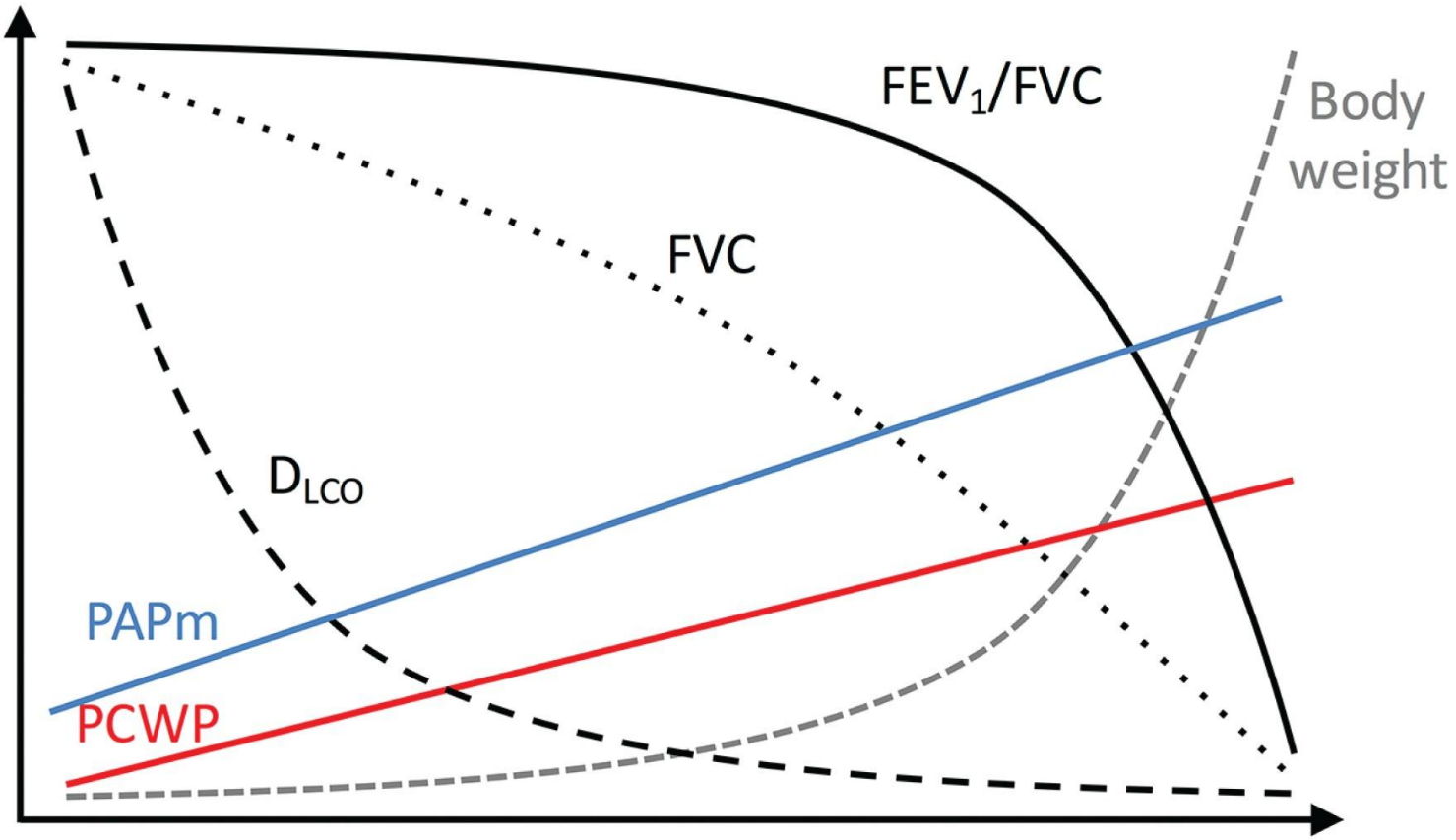
N = 320 pacientů s ChSS (Vanderbilt U.), RHC před indikací k Tx srdce

		28%	26%	17%	19%	
	Overall	PVR (WU) <1.5	PVR (WU) 1.5–2.49	PVR (WU) 2.5–3.49	PVR (WU)	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 J, JACC 1999; 34: 1802-6

- **normální PVR (< 1.5 w.u.) u 28% patientů**
- **vysoká PVR byla stejně často u pacientů s NYHA II tak i NYHA IV**
- **i málo symptomatičtí pacienti můžou mít vysokou PVR ! (mladé ženy)**



LUNG CONGESTION

Dry lung

Pulmonary oedema

European Journal of Heart Failure (2017) **19**, 1222–1229

Definice klinické skupiny PH
největší výzva PH-HFpEF vs PAH

	Riziko záměny s iPAH	Obtížná diferenciální diagnostika	Přímé terapeutické konsekvence
Srdeční selhání se sníženou EF	Ne	Ne	Malé *
Srdeční selhání se zachovanou EF	Ano	Ano	Větší **
Chlopenní vady	Ne	Ne	Významné ***