

Hypoxická plicní vazokonstrikce

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<http://fyziologie.lf2.cuni.cz>

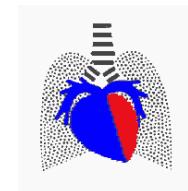
<http://vh.cuni.cz>



prof. MUDr. Jan Herget, DrSc
(1945-2019)



UNIVERZITA KARLOVA
2. lékařská fakulta



von Euler U. S. & Liljestrand G.:
Observations on the pulmonary arterial
blood pressure in the cat.
Acta Physiol. Scand. 12: 301-320, 1946



Ulf Svante von Euler (1905-1983)



Göran Liljestrand (1886-1968)



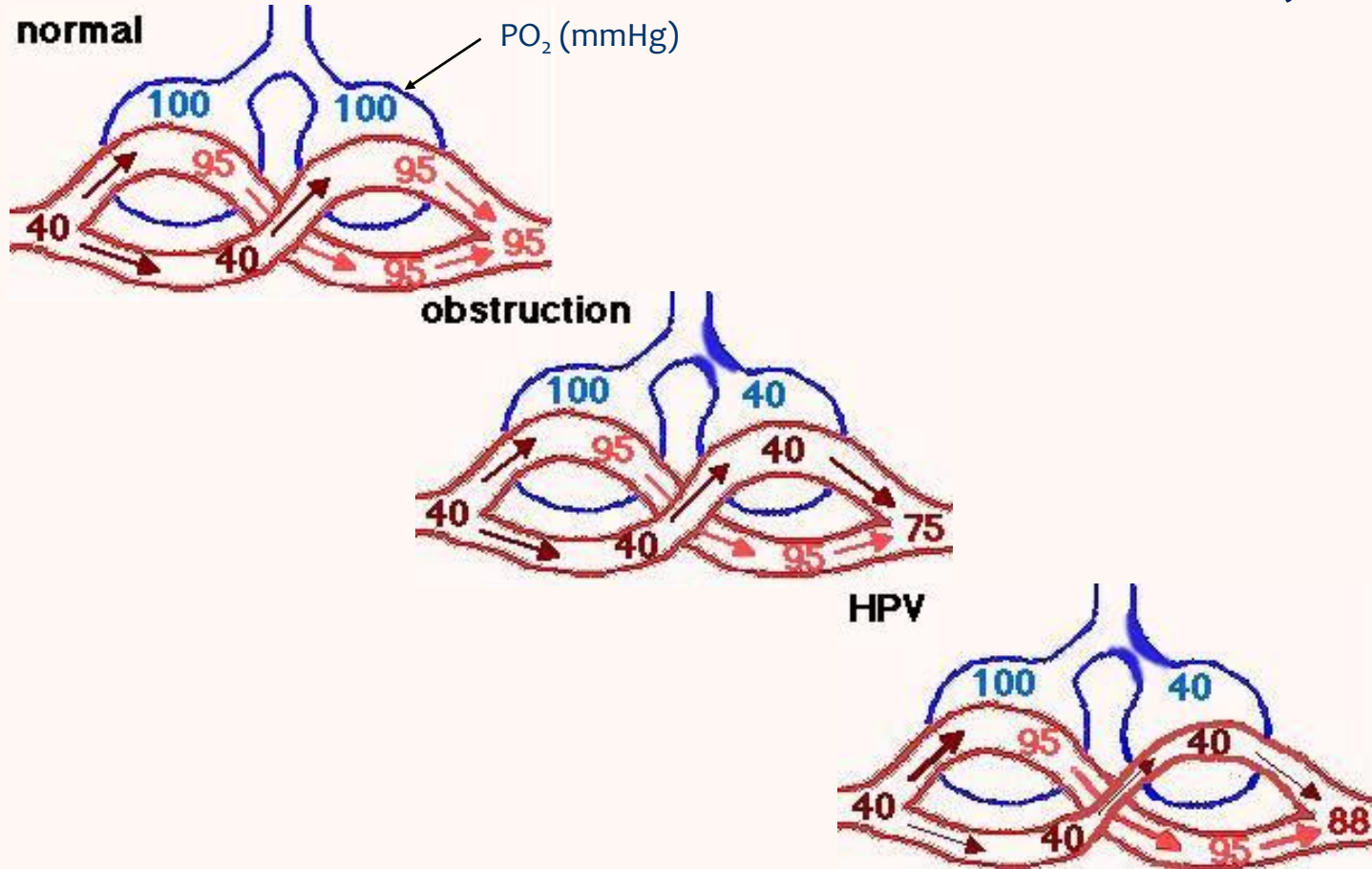
Bradford & Dean:
The pulmonary circulation.
J Physiol 16: 34-96, 1894.

plícnice

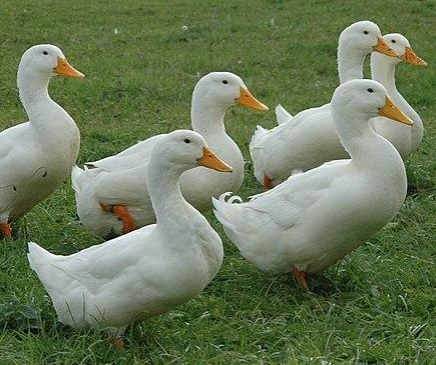
karotida



Hypoxická plicní vazokonstrikce (HPV) udržuje \dot{V}/Q



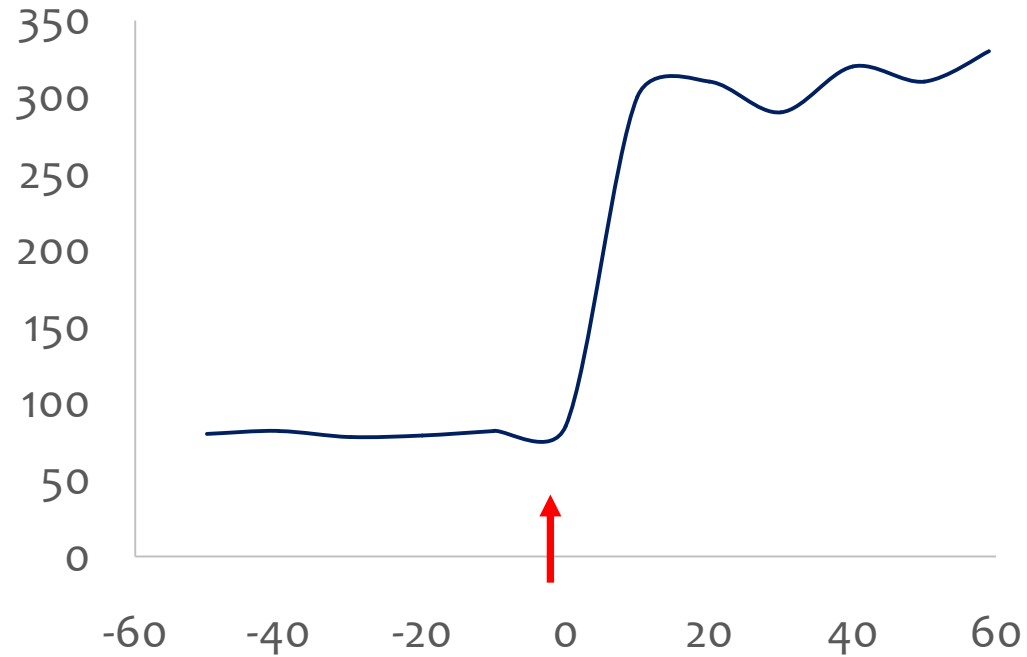
HPV u všech obratlovců





Průtok krve plícemi při narození

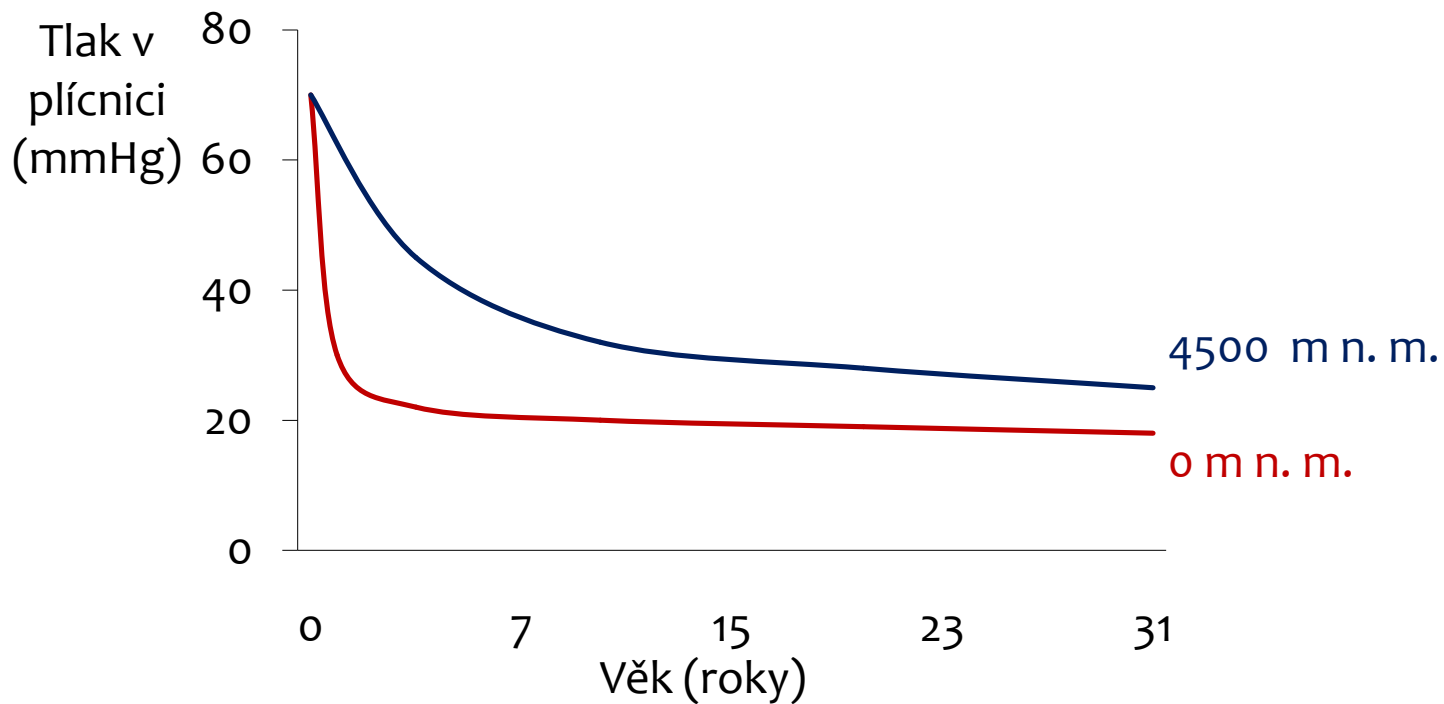
Průtok
krve
plícemi
(ml/min)



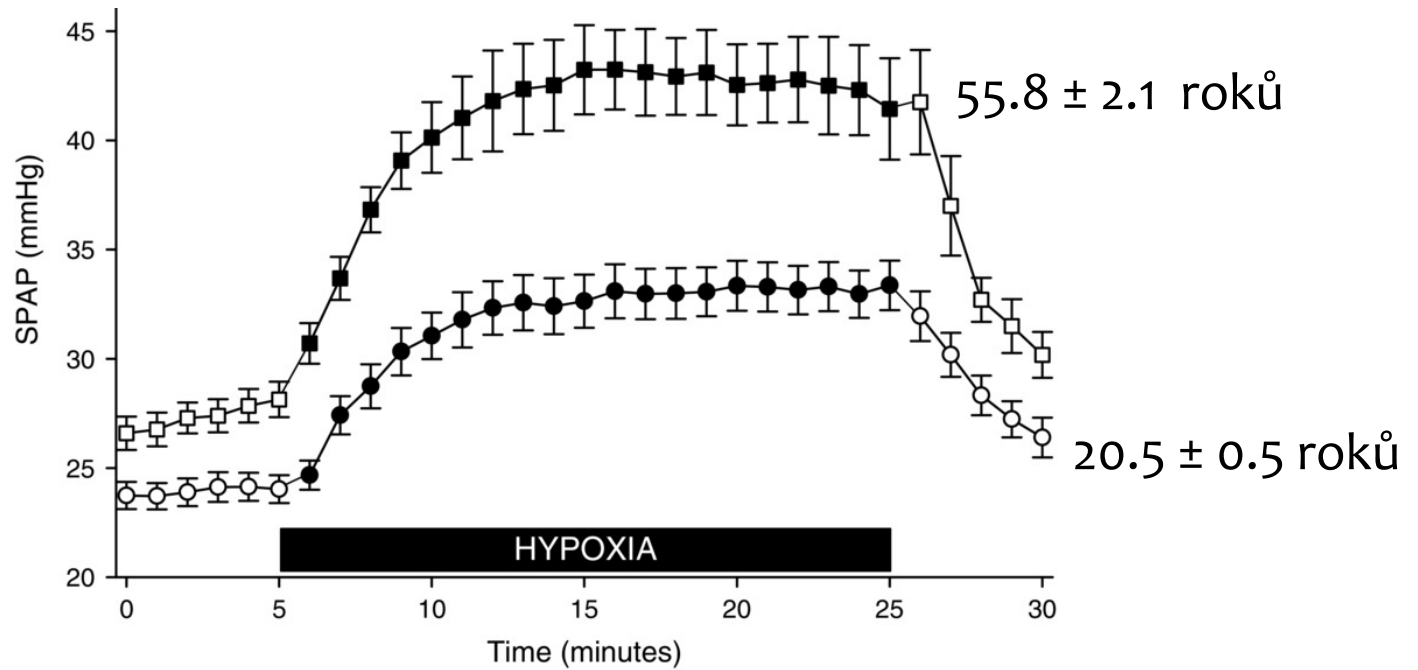
minuty od narození

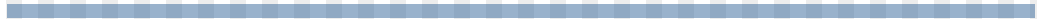


Hypoxie brzdí pokles tlaku v plicnici po narození



HPV roste s věkem





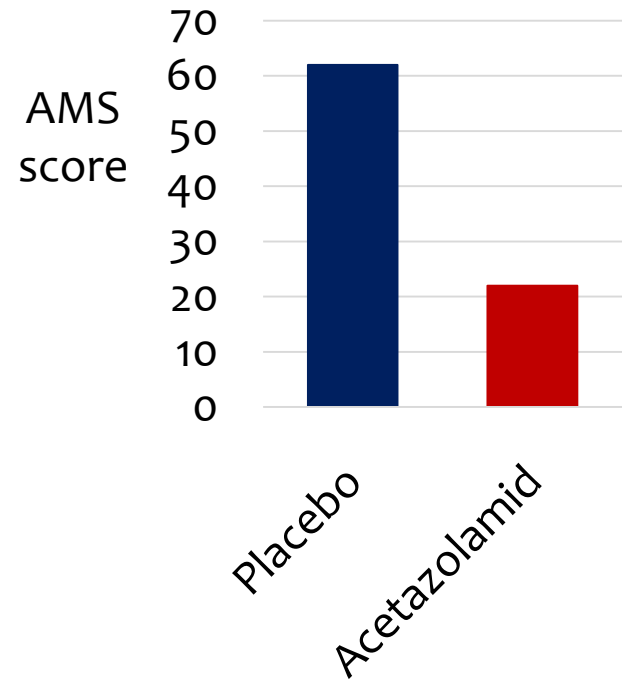
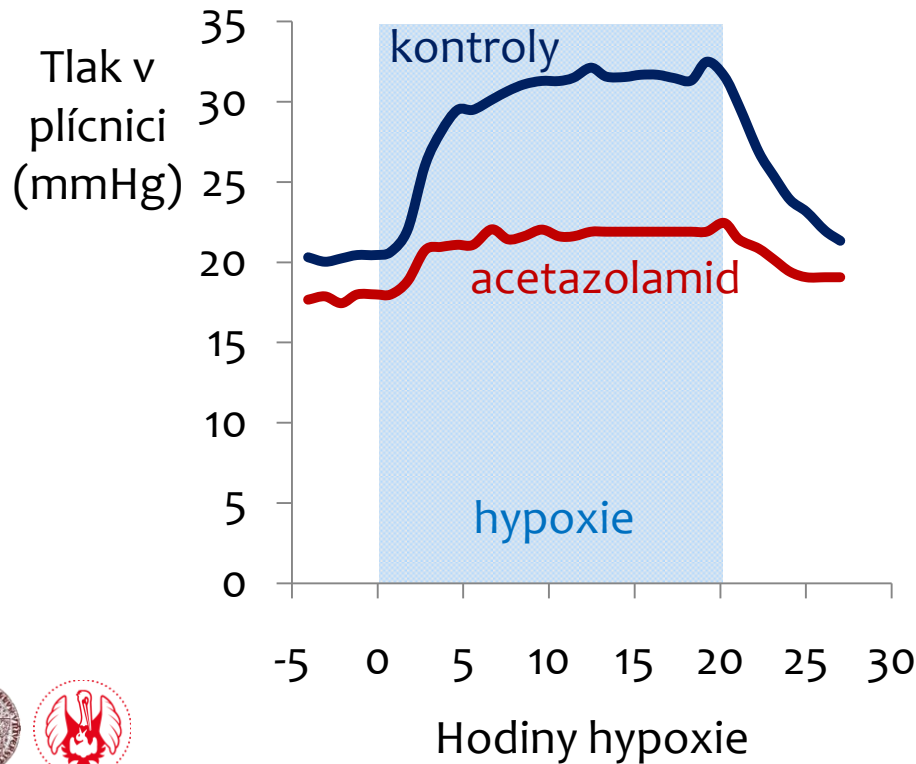


Denisované (*Homo denisova*)

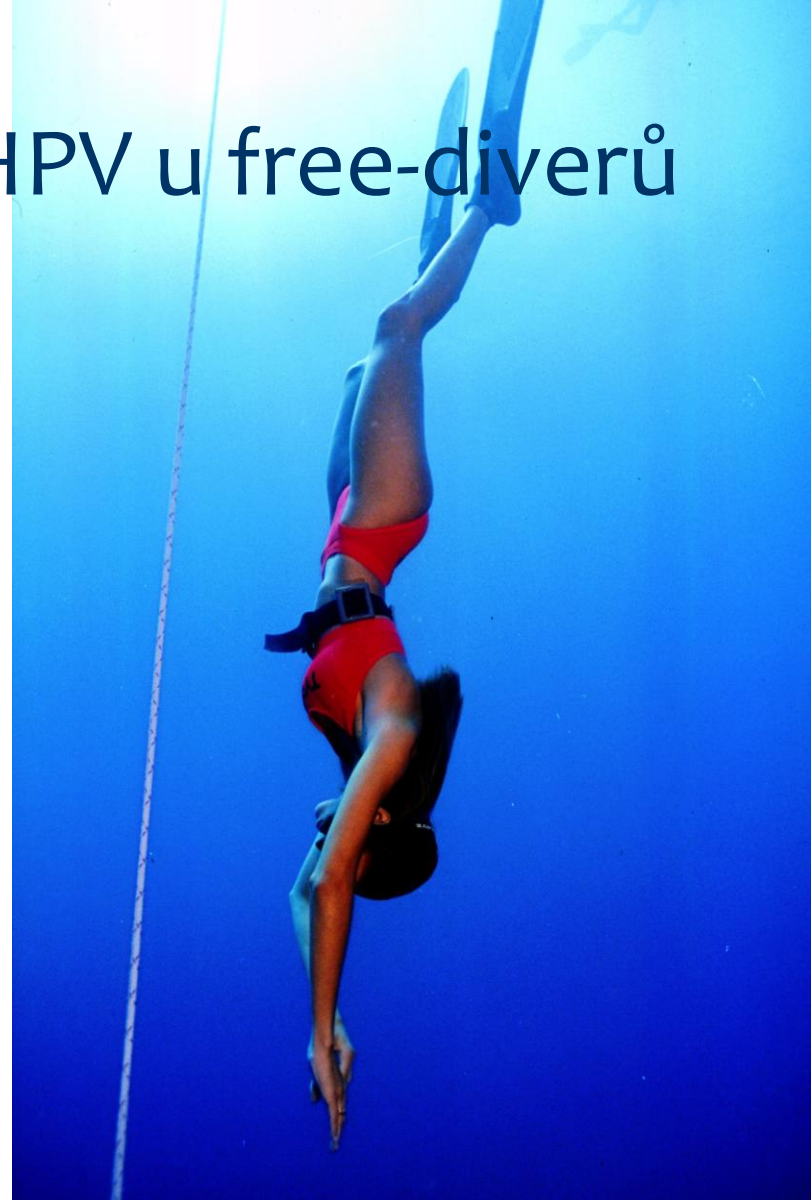
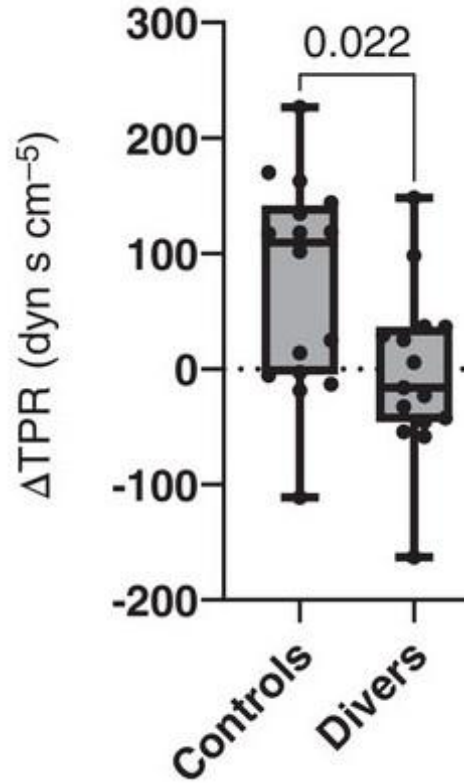
- objeveni 2008-2010 Altaj
- druh žijící paralelně s *Homo sapiens* a *Homo neanderthalensis*
- 2019 nález v Tibetu (3280 m)
- Tibet'ané ~4% jejich genomu



Acetazolamid pomáhá s výškovou nemocí a inhibuje HPV



Oslabená HPV u free-diverů

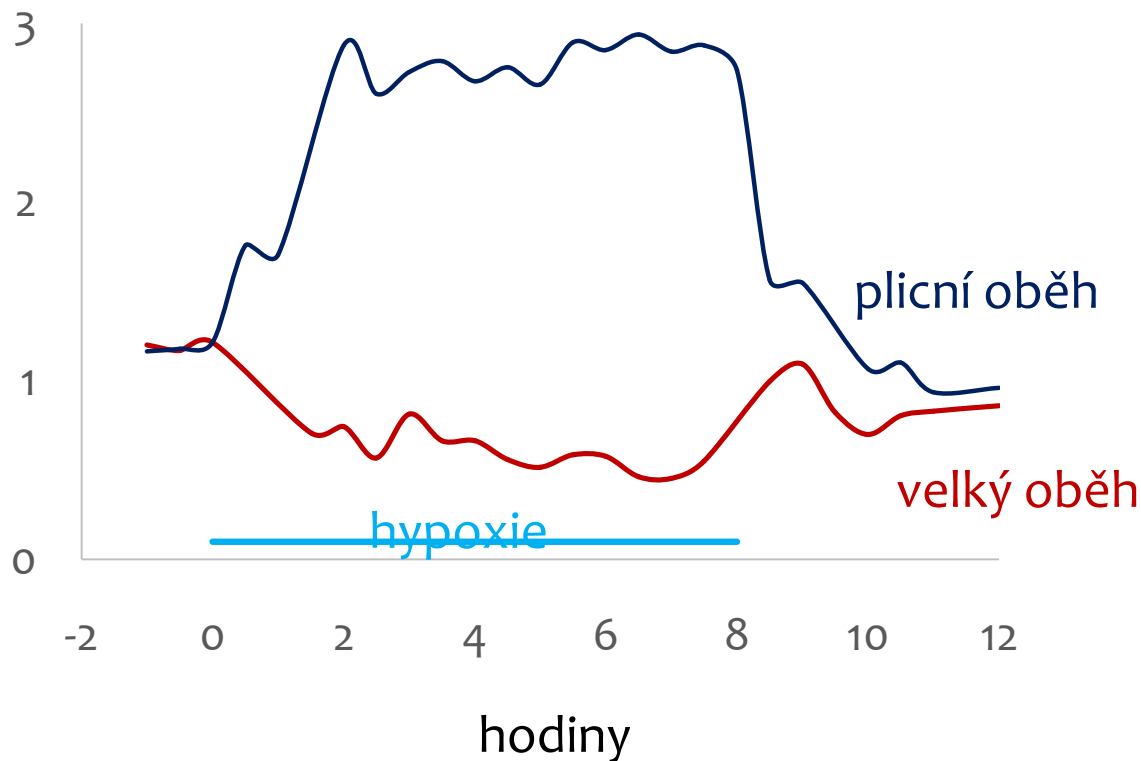


Kelly et al 2022

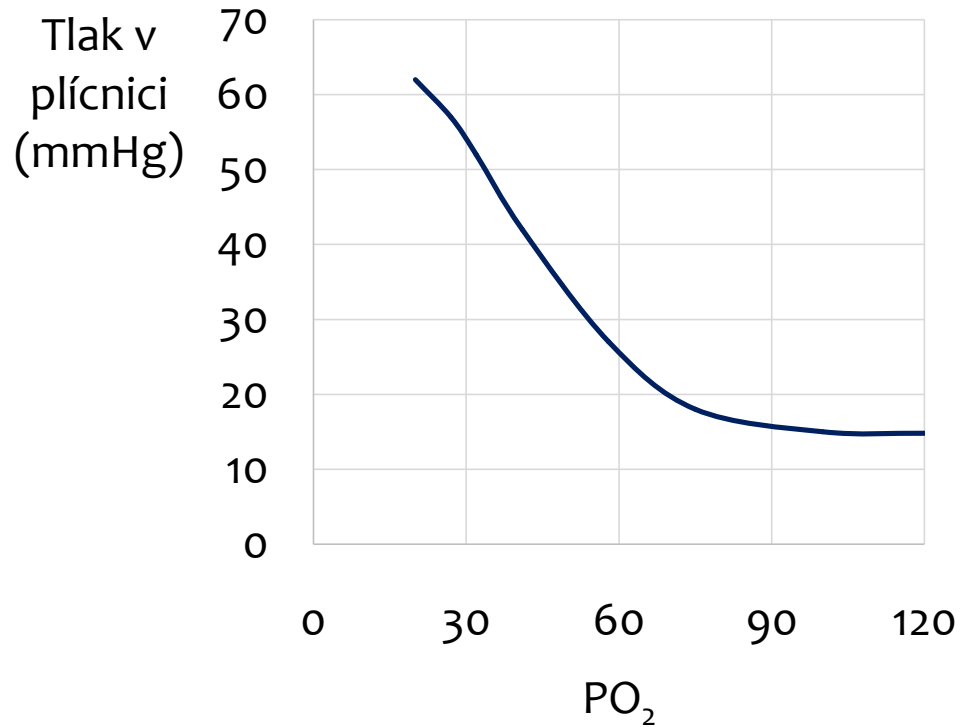


HPV: rychlá, setrvalá, rychle reverzibilní

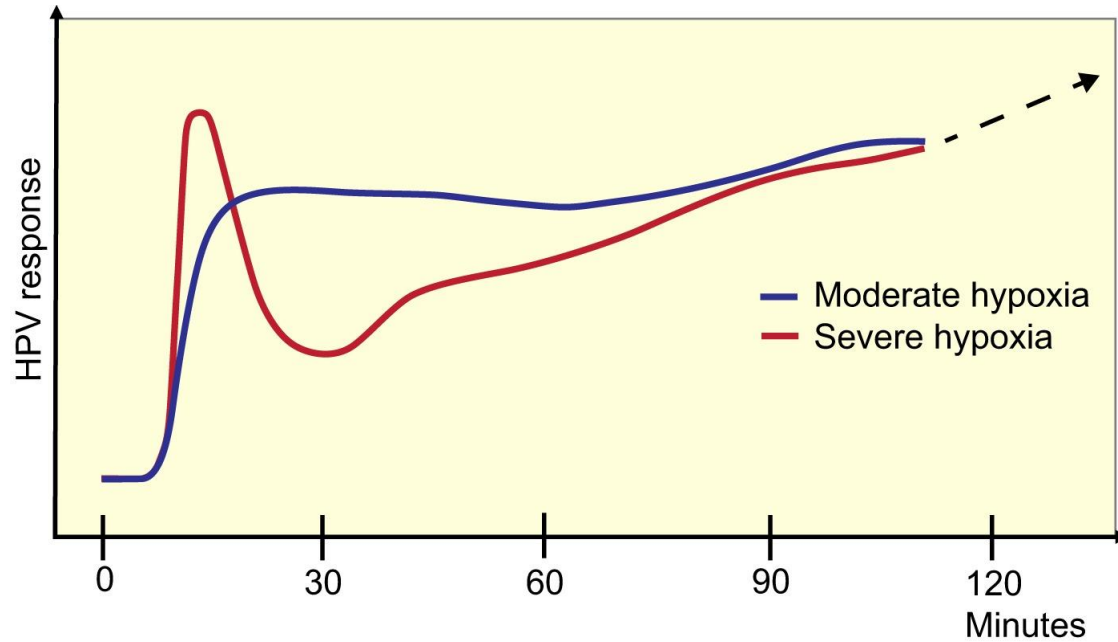
Cévní odpor
(násobky normálu)



HPV: závislá na stupni hypoxie



Průběh HPV v čase – různé mechanismy?



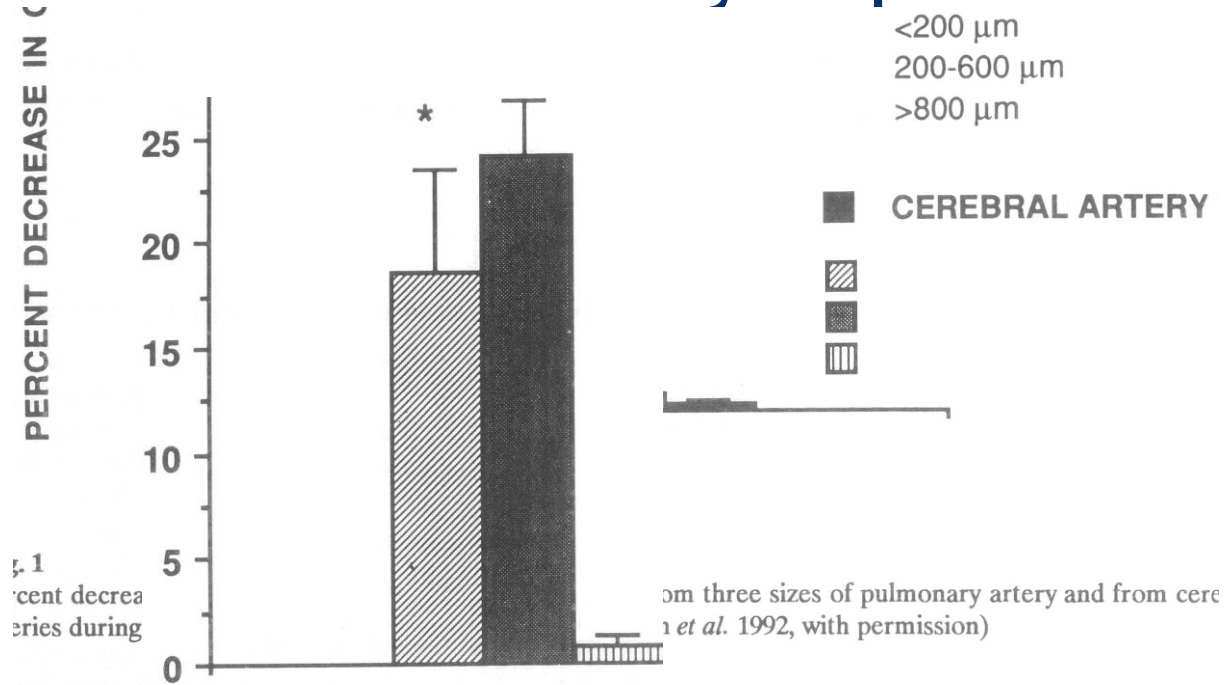
Acute
phase

Sustained
phase

?



HPV je ve svalech malých plicních tepen



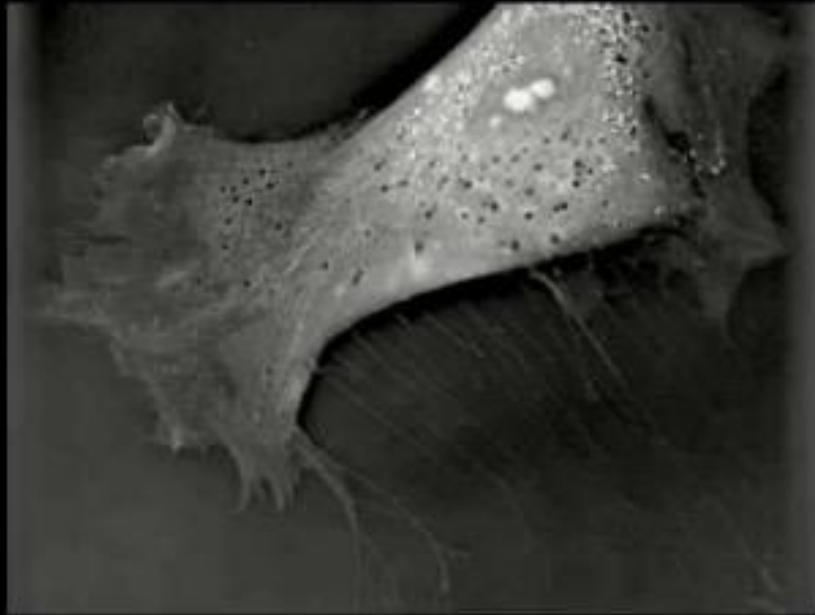
Requirement for extracellular Ca^{++} : HPV is (Michelakis et al. 1989). Attention is now focused on the direct e

Žíly také, ale o hodně méně

Michelakis et al 1995



Hladký sval sval malých plicních tepen (PASMC) = sensor, převaděč signálu i efektor



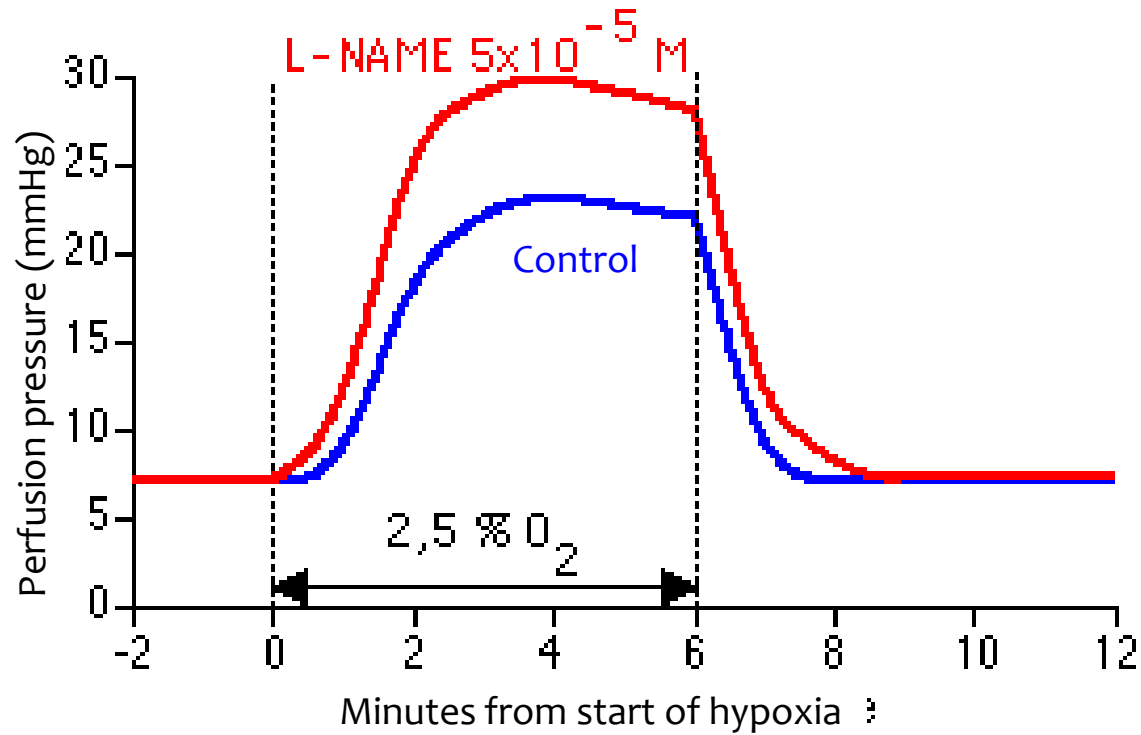
Endotel mírní HPV v izolovaných lidských plicních tepnách (2 mm)

* $P < 0.01$.

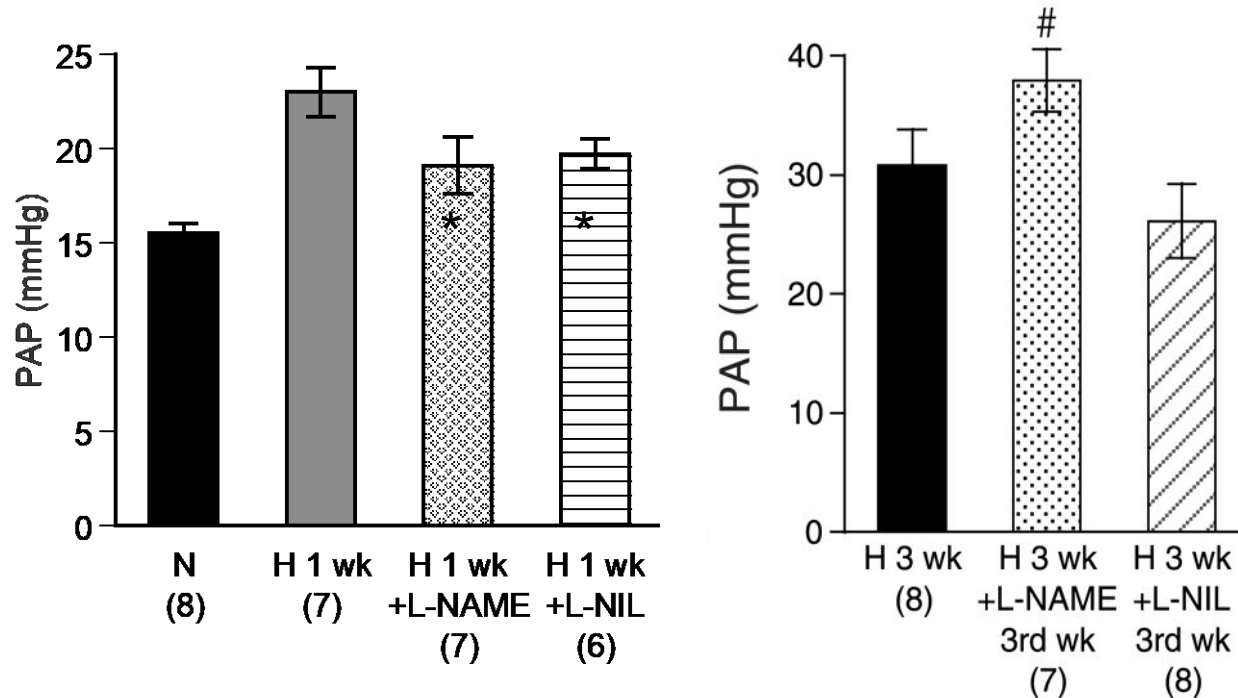
ooth muscle frequently requires an ini
staglandin or histamine, before hyp
is blocked with a specific receptor bloc
contractile response produced in this
alone and required no pre-constricti
ed contraction'. In the present study,
y, even in the case of an outer diam



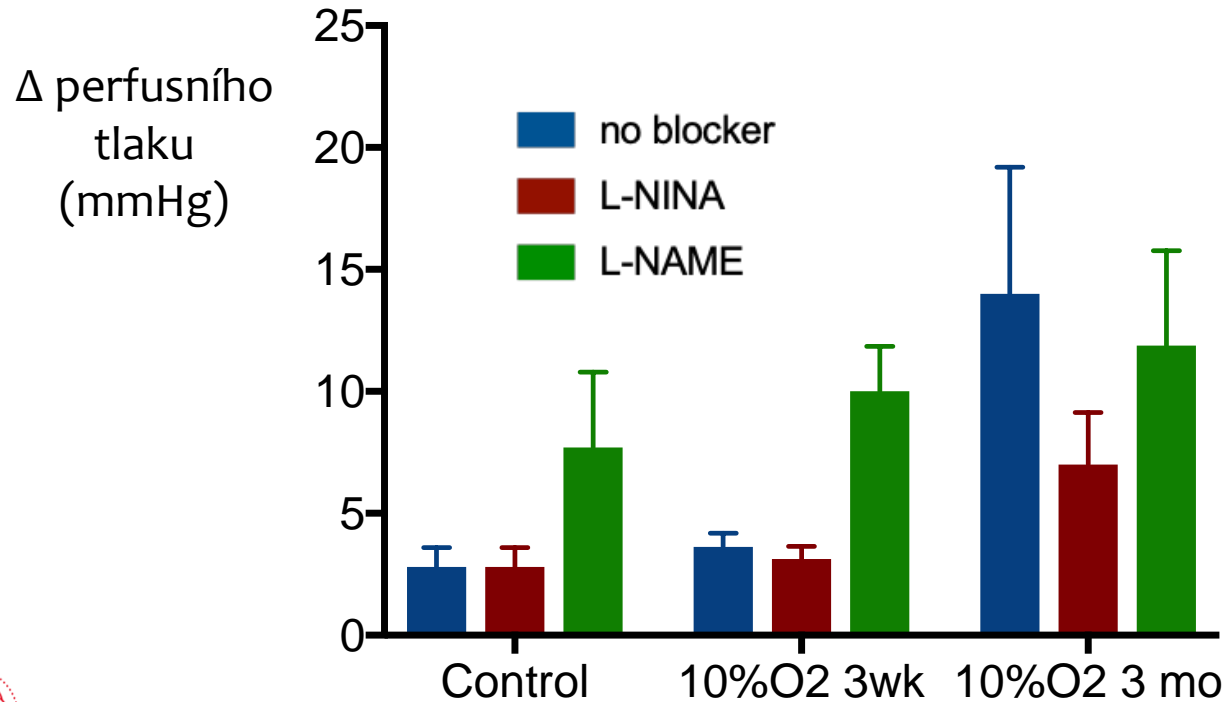
Role NO



iNOS na začátku chronické hypoxie přispívá k rozvoji plicní hypertenze

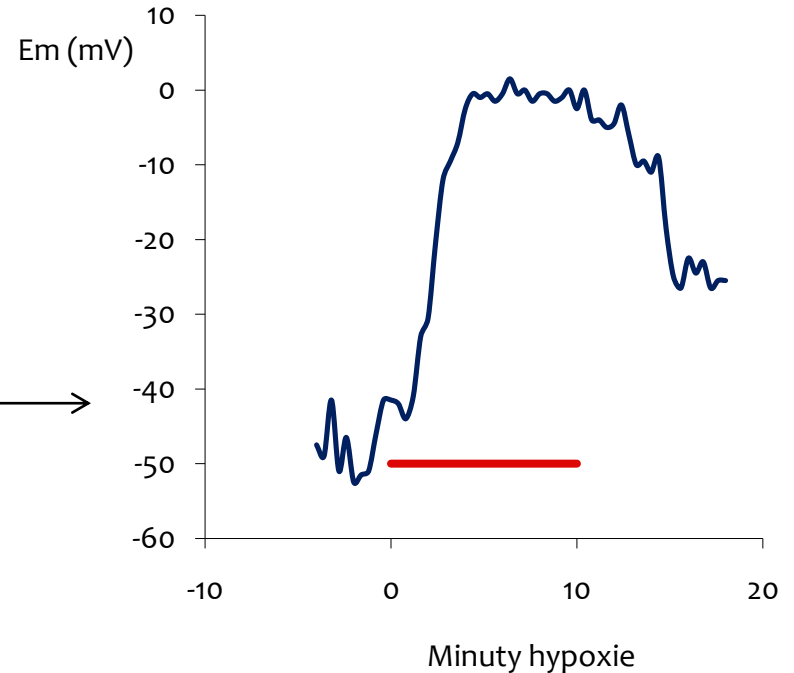


L-NINA snižuje HPV zvýšenou velmi dlouhou hypoxií

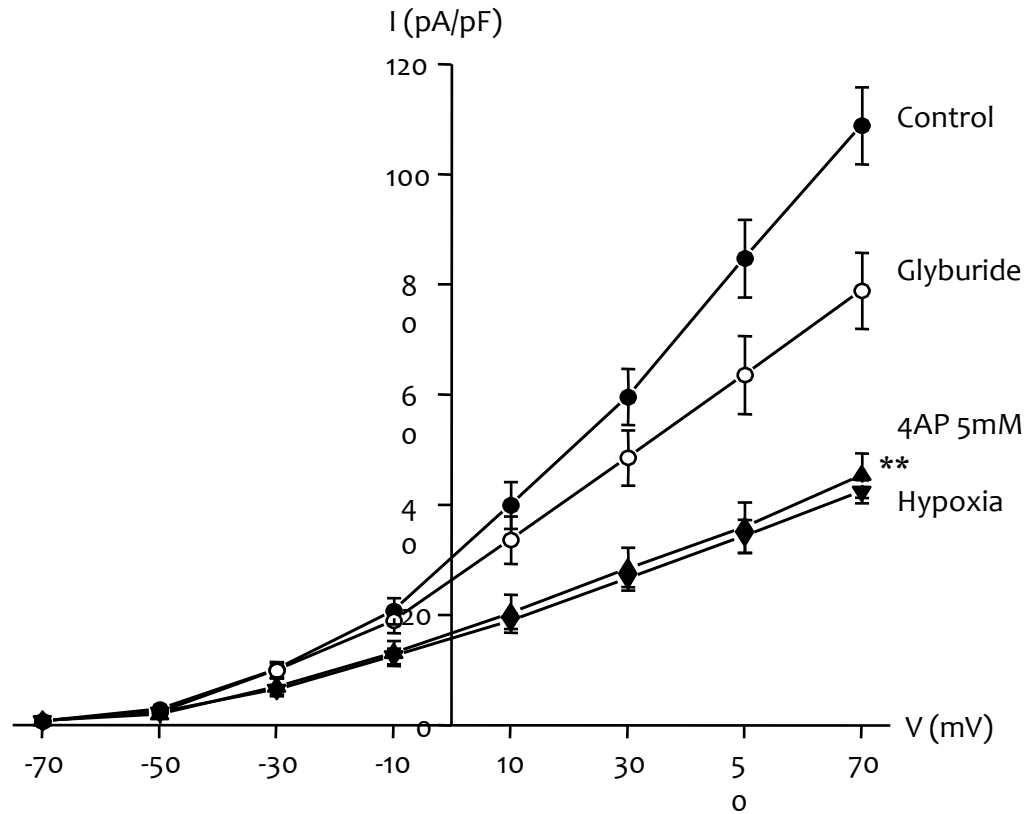


Mechanismus HPV

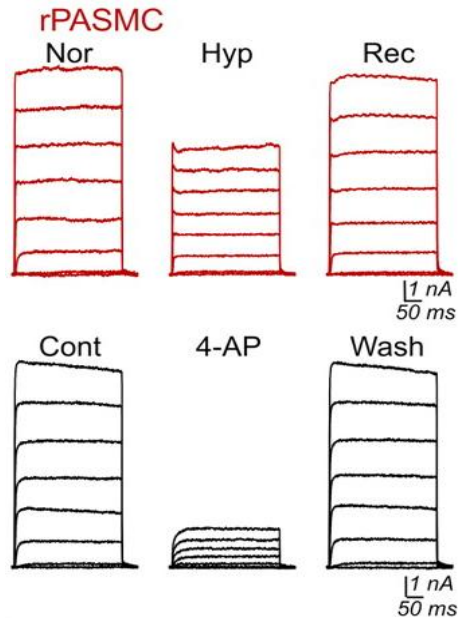
- Redoxní změny???
- Inhibice K^+ kanálů
- Depolarizace →
- Aktivace Ca^{2+} kanálů (L)
- Influx Ca^{2+} (CICR)
- Uvolnění Ca^{2+} z intracelulárních zásob
- Aktivace kontraktilního aparátu



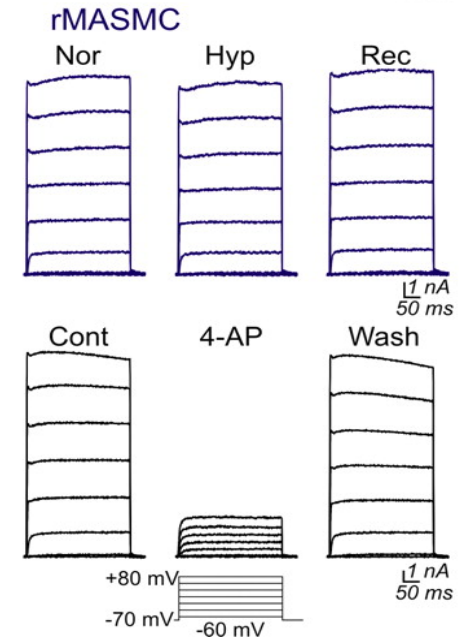
Hypoxie inhibuje K_V kanály v PASMC



K kanály

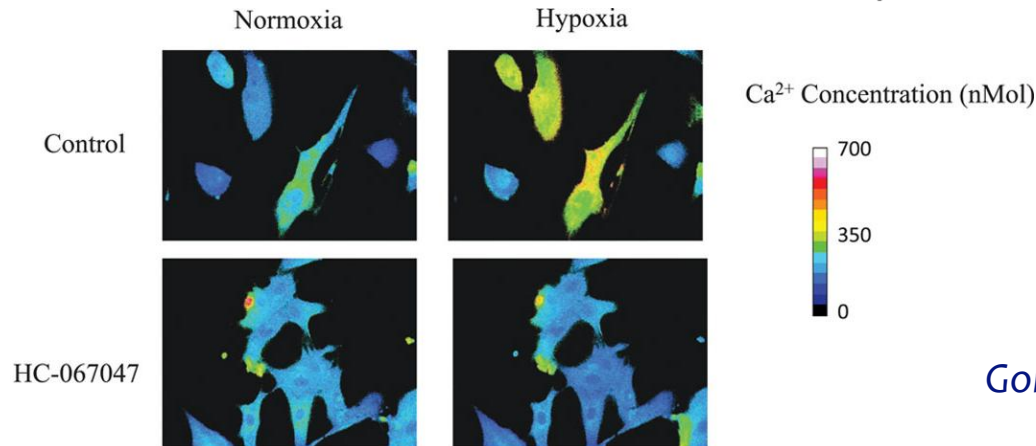
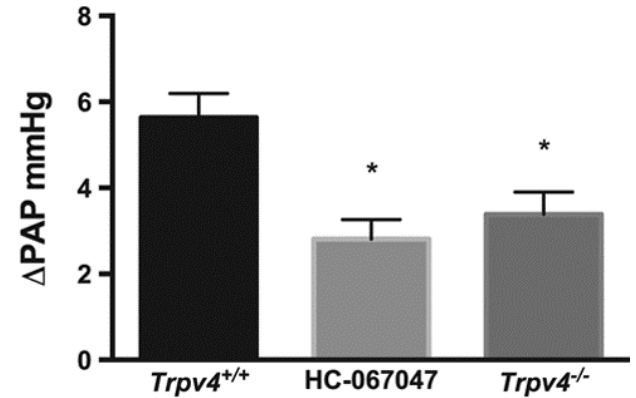
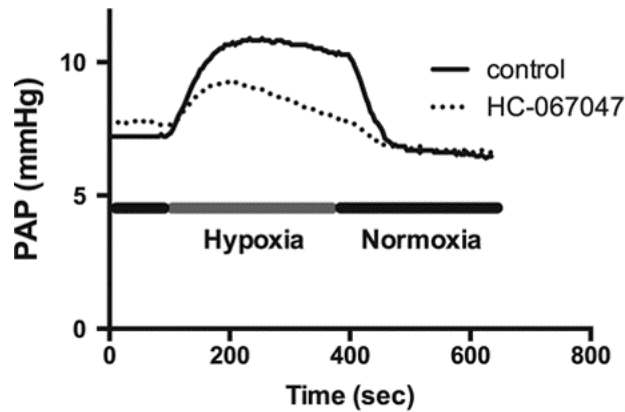


- KCNA5 = Kv α podjednotka
- Krysí PASM po transfekci lidského KCNA5 odpovídají na hypoxii
- Systémové SMC ne

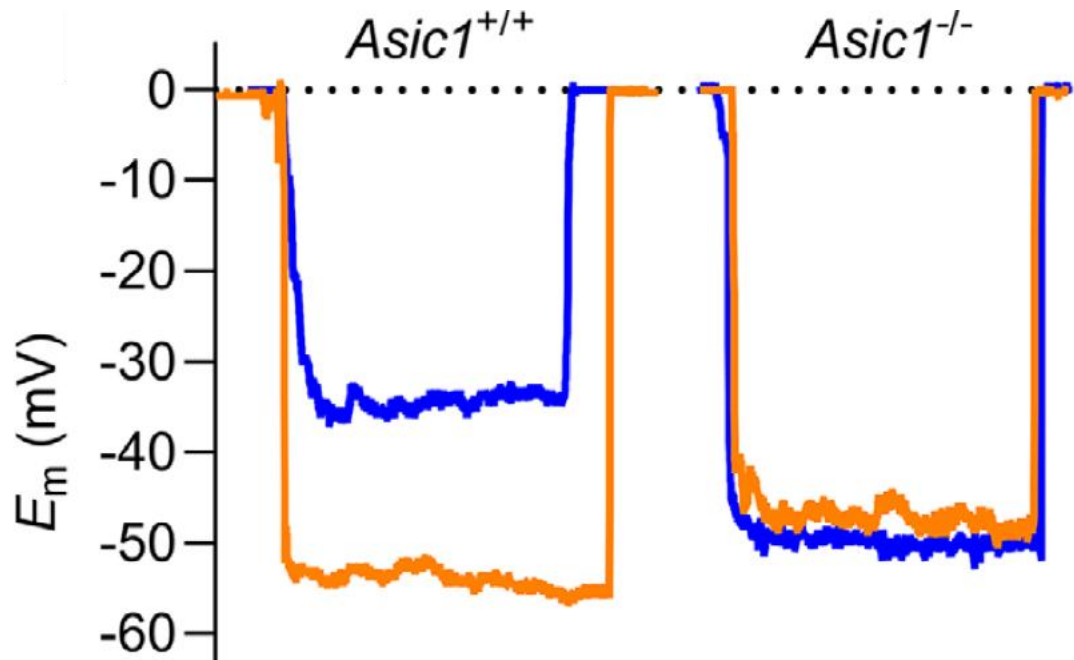


TRPV4 je nezbytný pro HPV

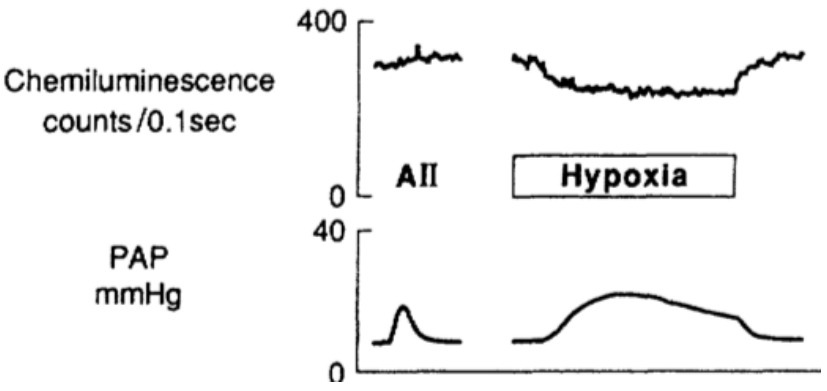
Transient receptor potential cation channel subfamily V member 4
Ca²⁺-permeable, nonselective cation channel



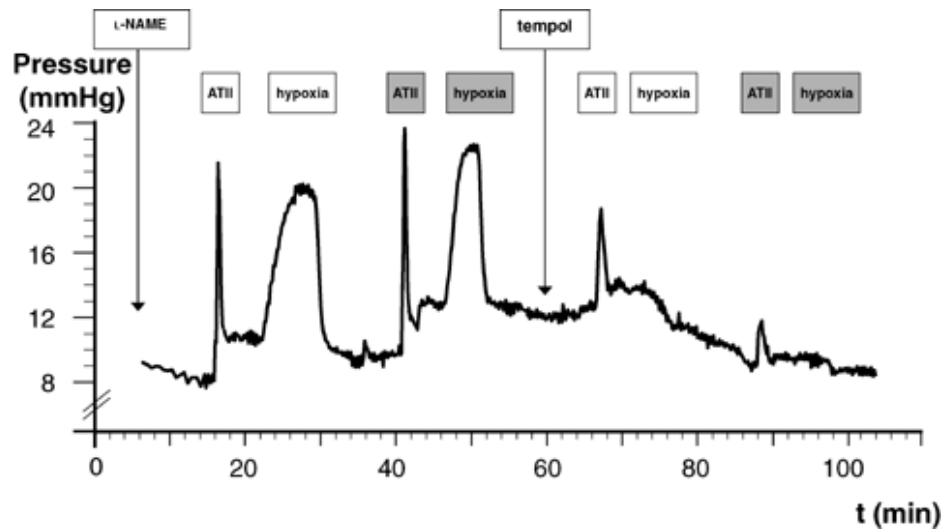
Acid-sensing ion channel 1 přispívá k depolarizaci PASMC při chronické hypoxii



ROS ↓ nebo ↑?



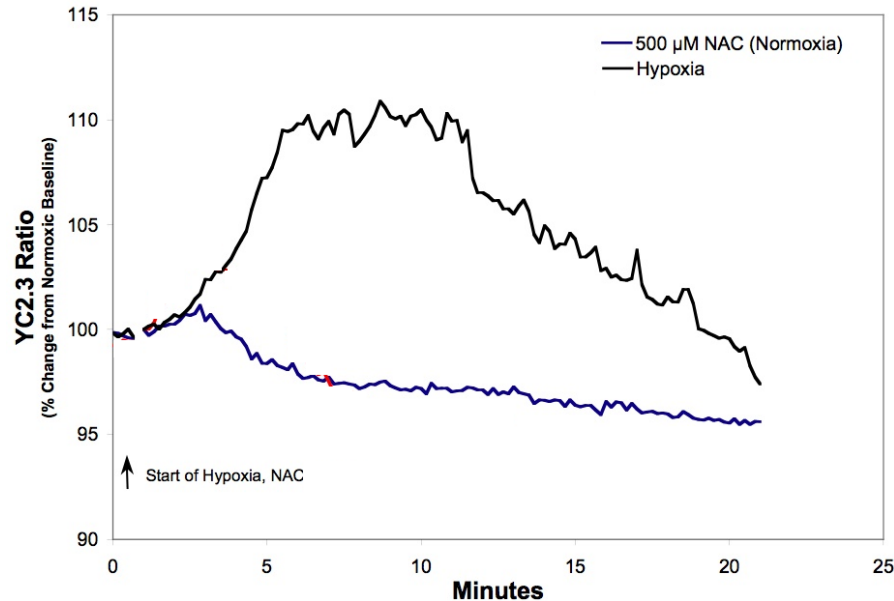
Archer et al 1993



Hodyc et al 2007



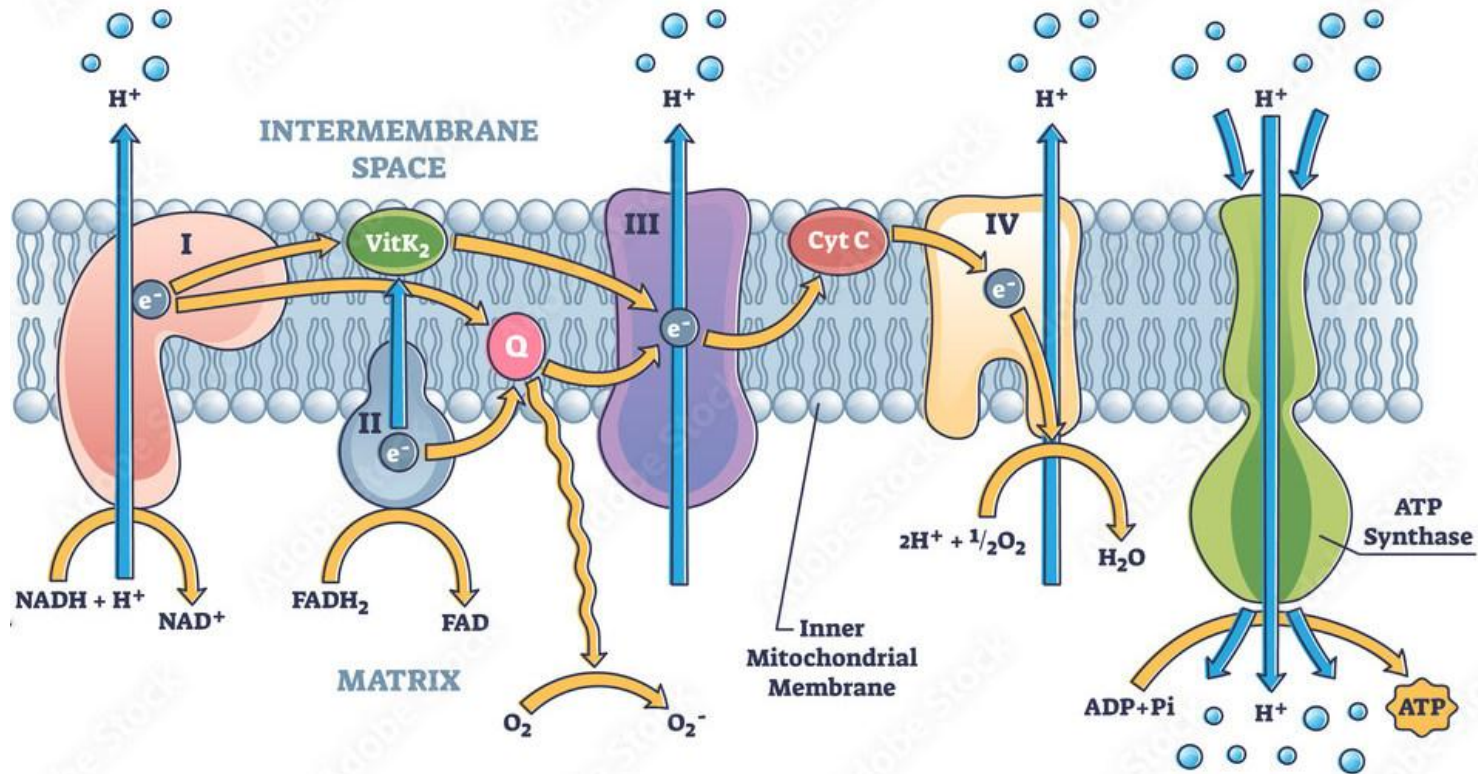
Hypoxie stimuluje tvorbu ROS (v mitochondriách)



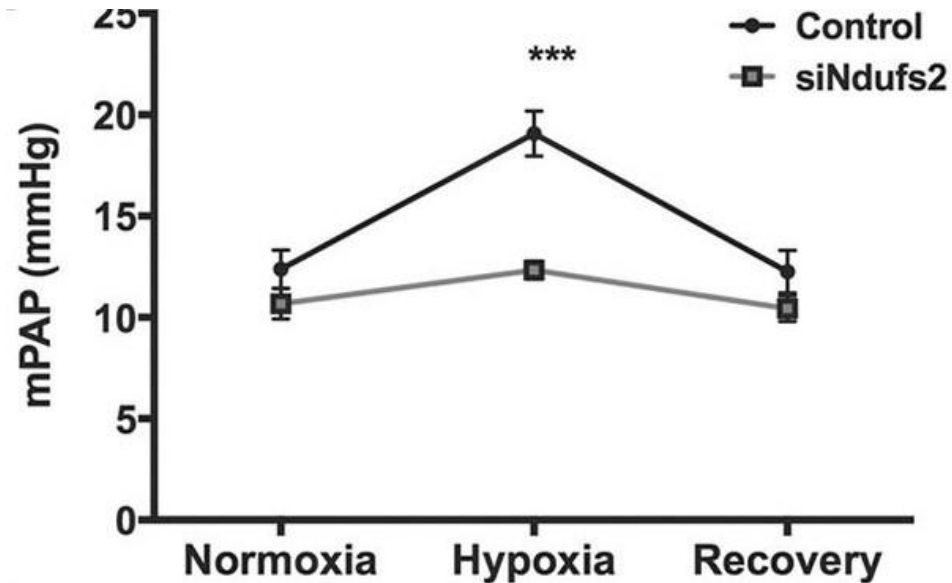
redox-sensitive fluorescence resonance energy transfer (HSP-FRET)



Elektrontransportní řetězec



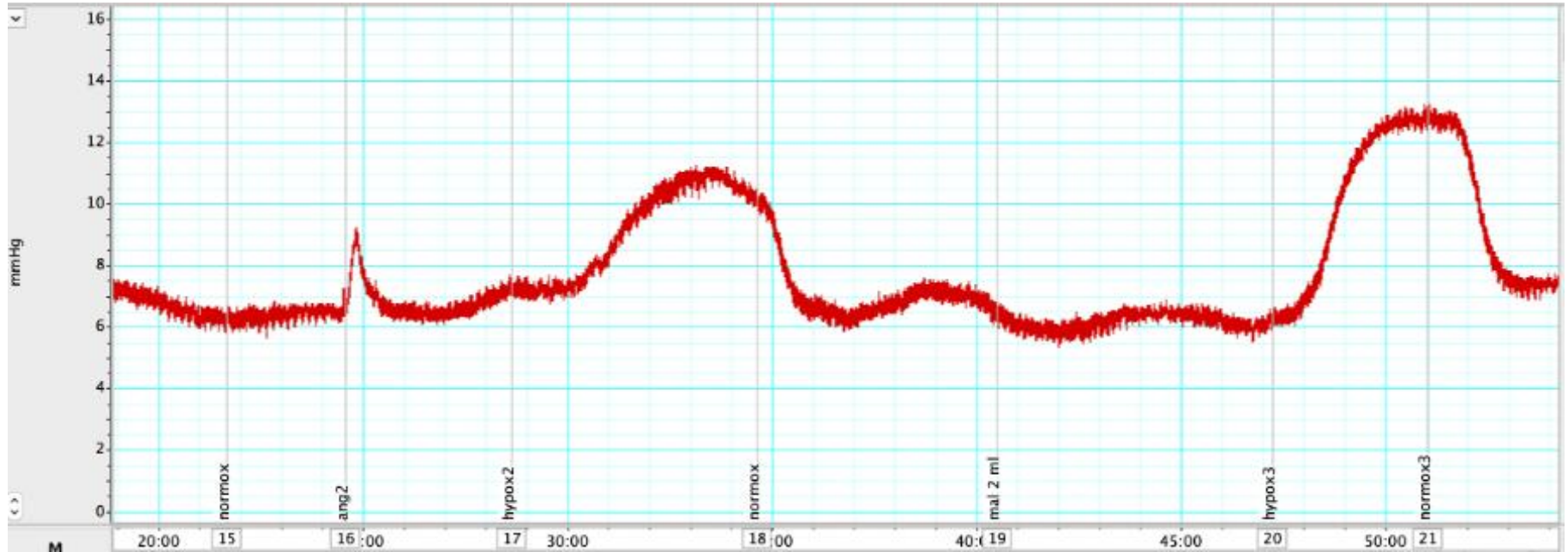
Ndufs2 silencing oslabuje HPV *in vivo*



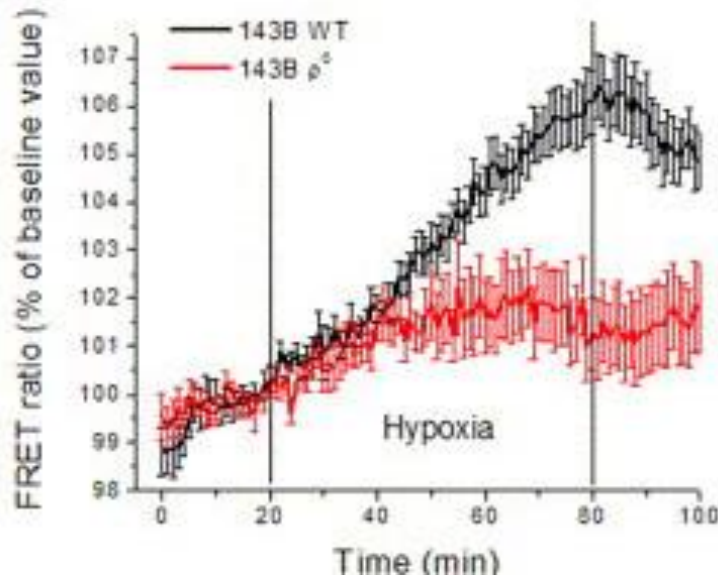
dufs2 = hl. podjednotka mitochondriálního komplexu I



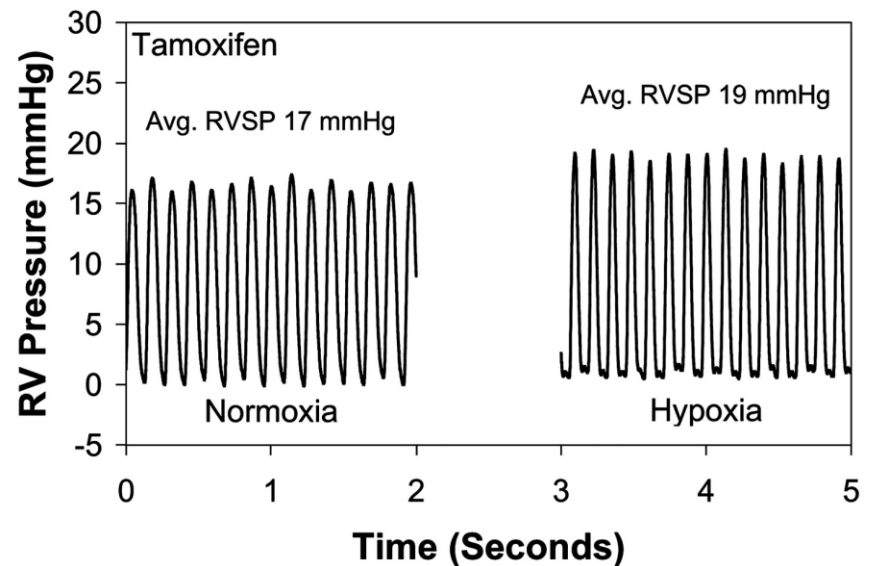
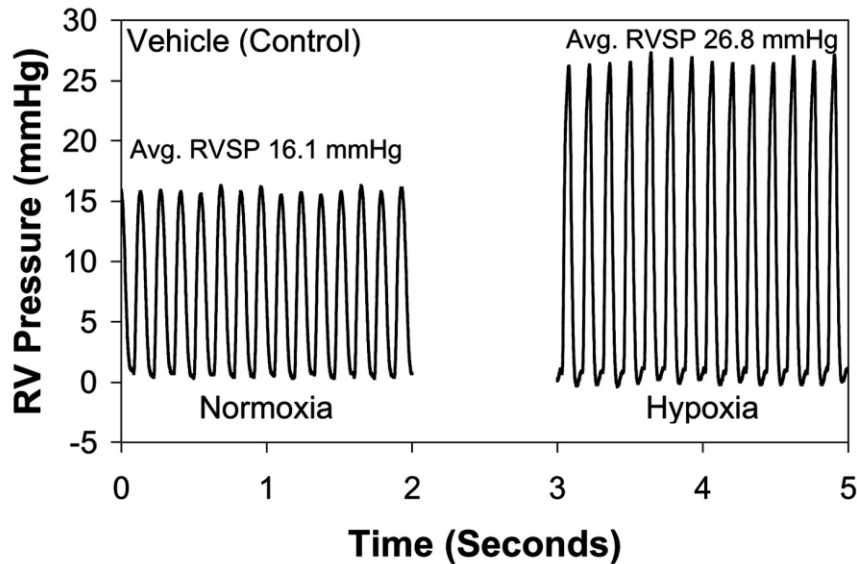
Inhibice komplexu II malonátem nesimuluje HPV

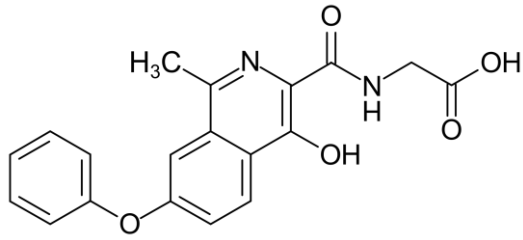


Knock-out Rieskeho Fe-S proteinu (RISP) komplexu III: snížená tvorba ROS v mitochondriích při hypoxii



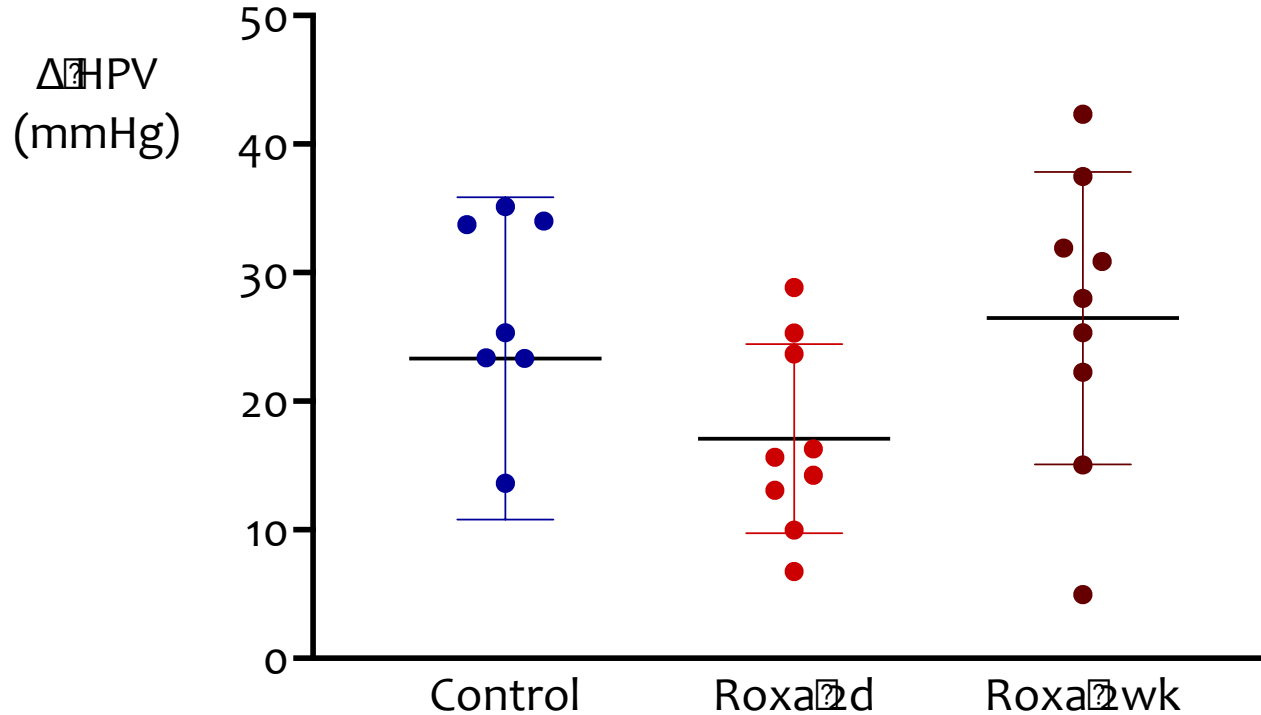
Tamoxifenem aktivovaná deplece RISP komplexu III v PASMC iinhibuje HPV





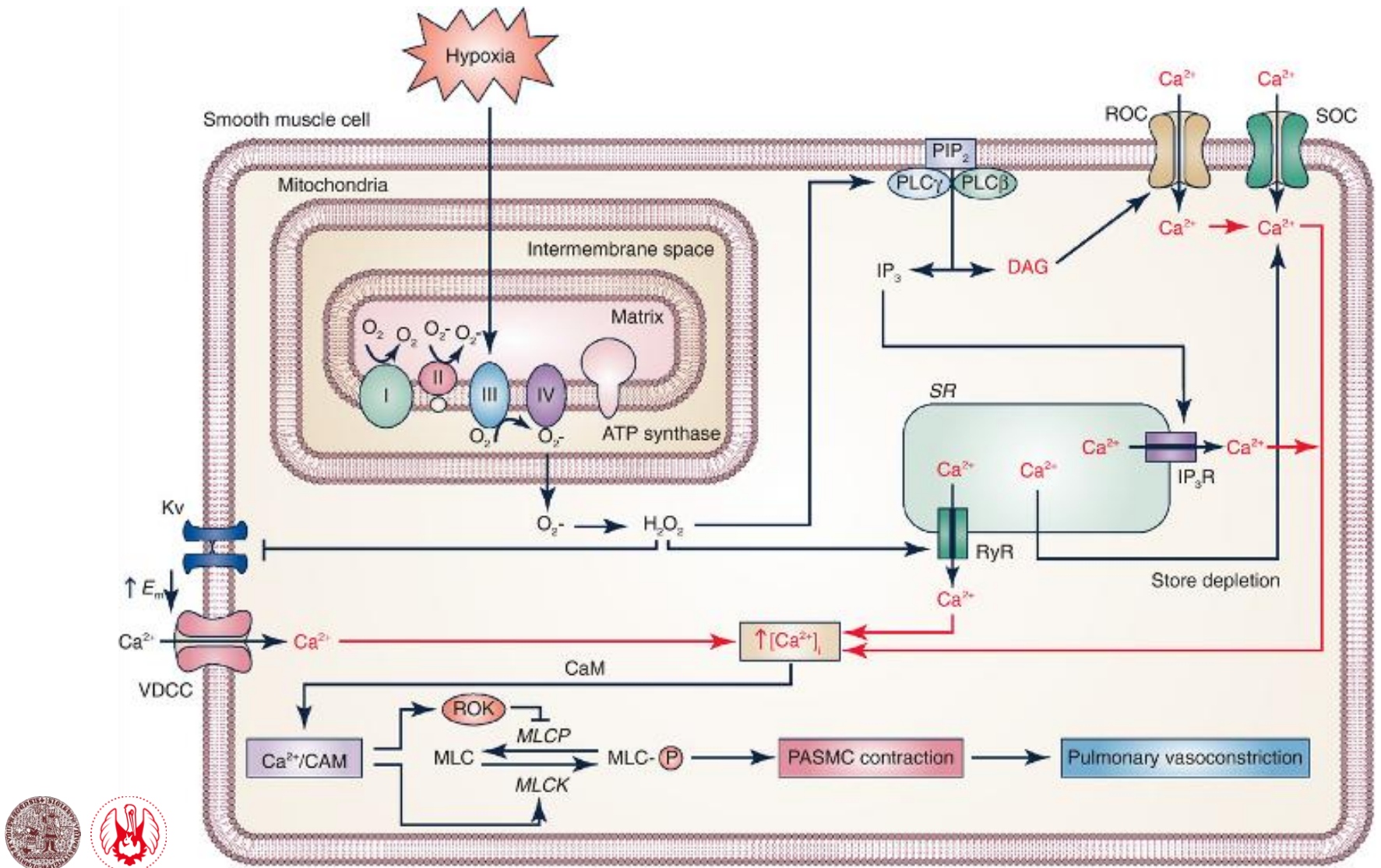
HIF?

roxadustat neovlivňuje HPV

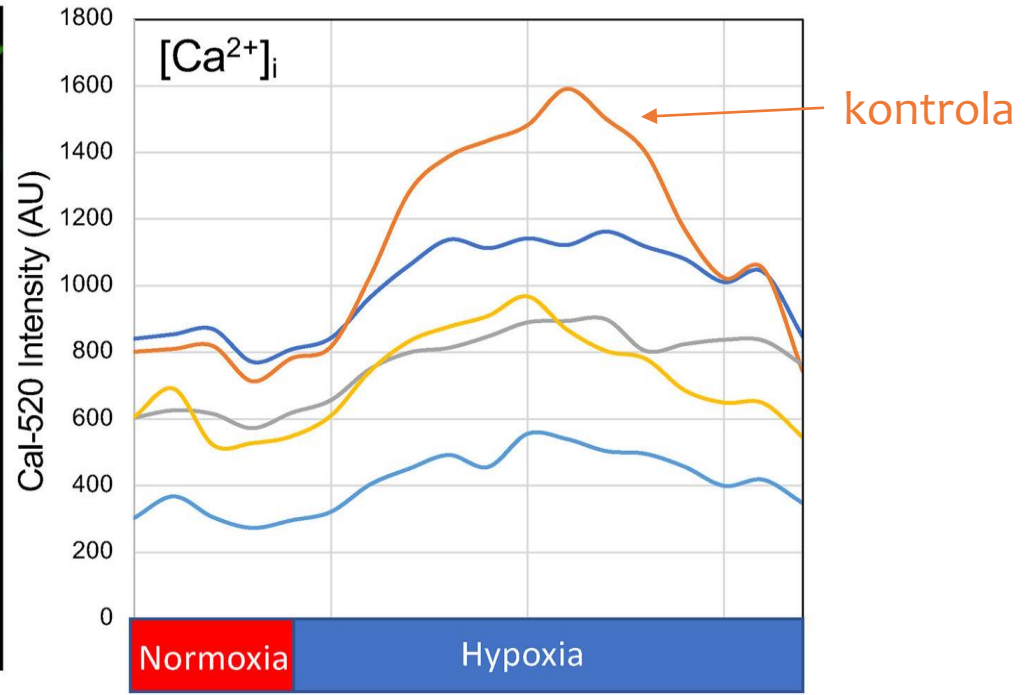
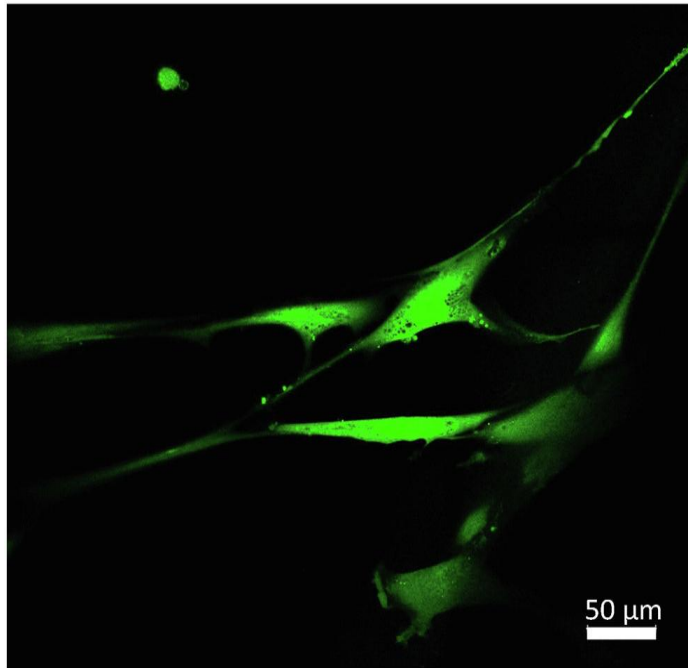


Roxadustat = stabilizátor HIF- α

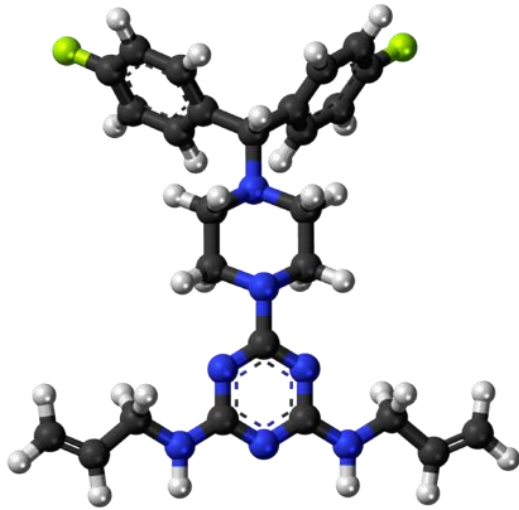




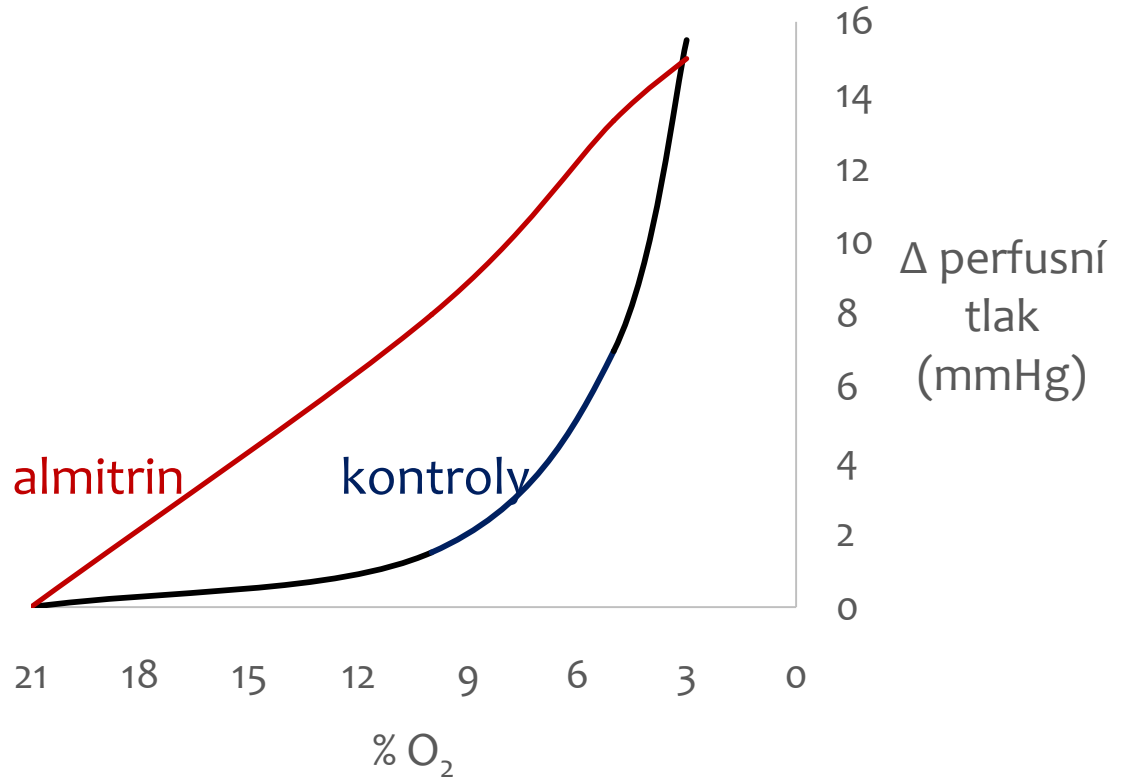
SARS-CoV-2 inhibuje „HPV“ v lidských PASMC



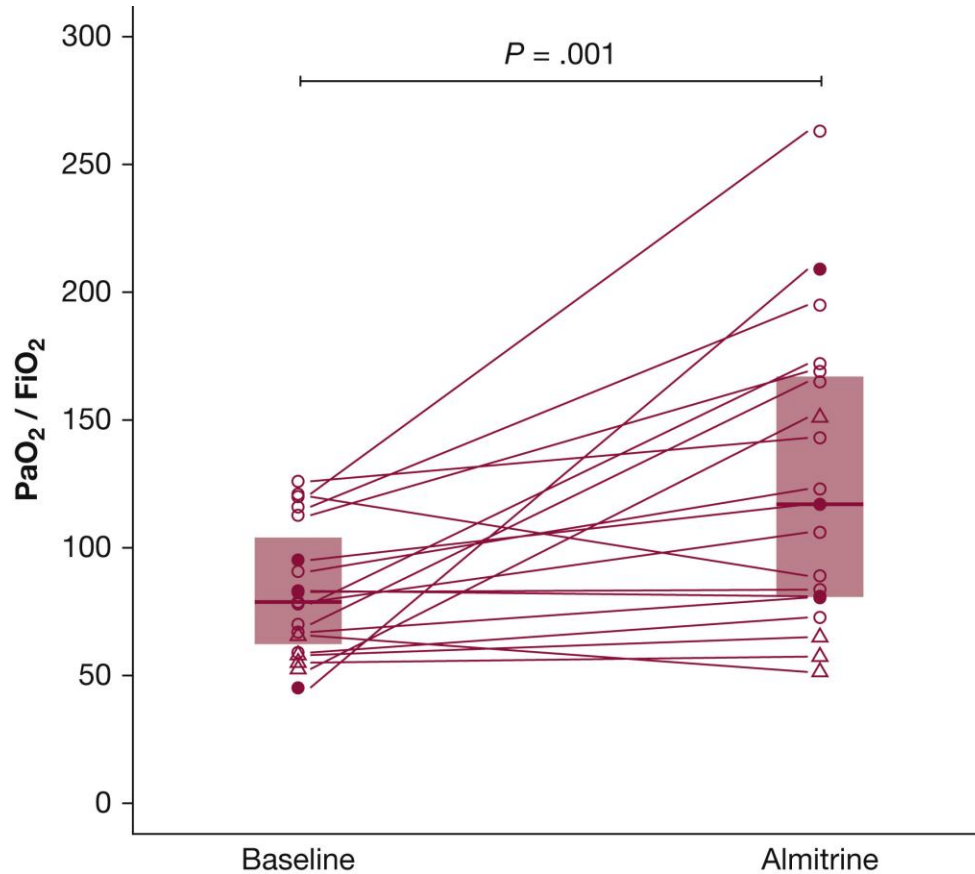
Almitrin zvyšuje citlivost HPV



stimulant karotických
tělísek



Almitrin zlepšuje oxygenaci při COVID-19



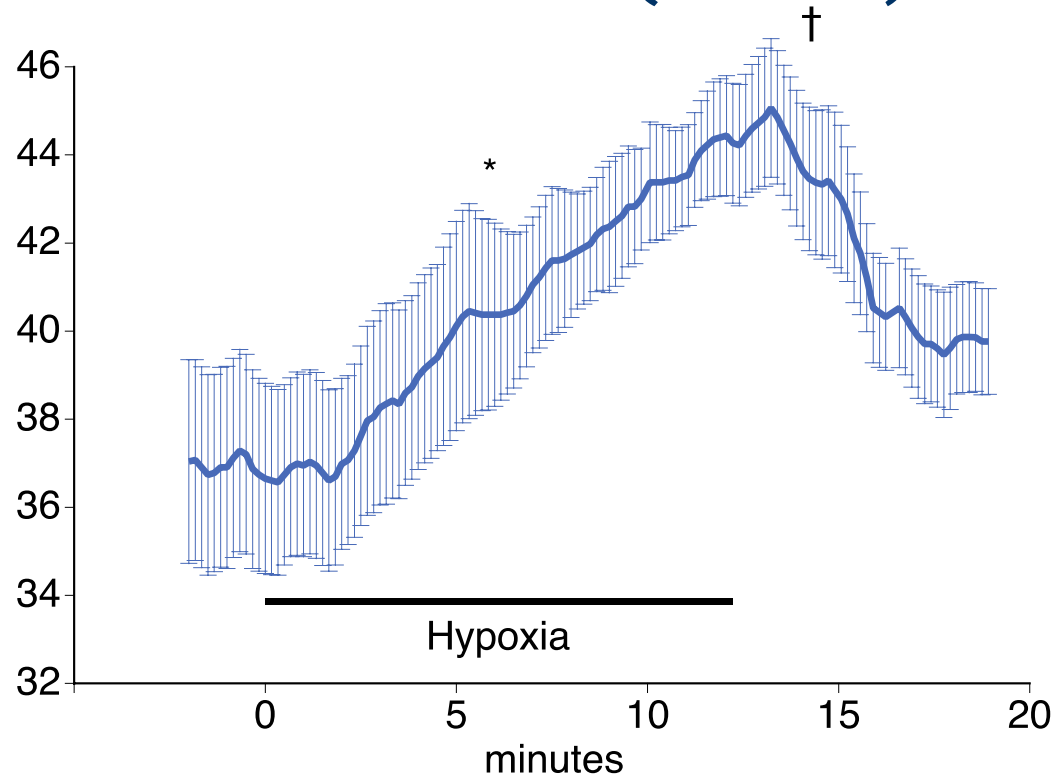
Placenta: (m.j.) stejná funkce jako
postnatální plíce

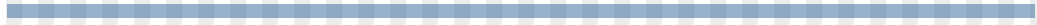




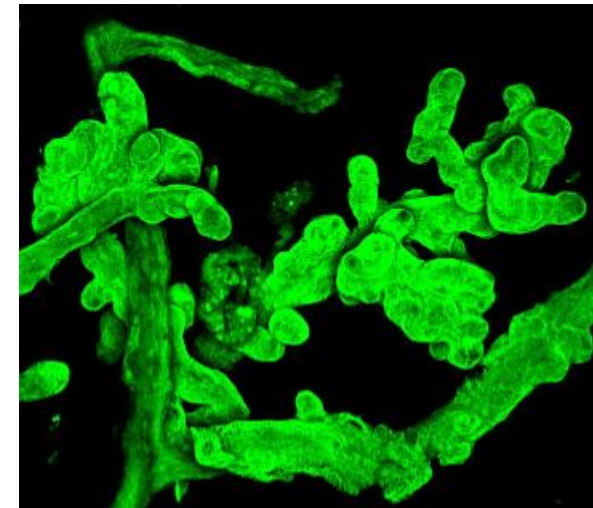
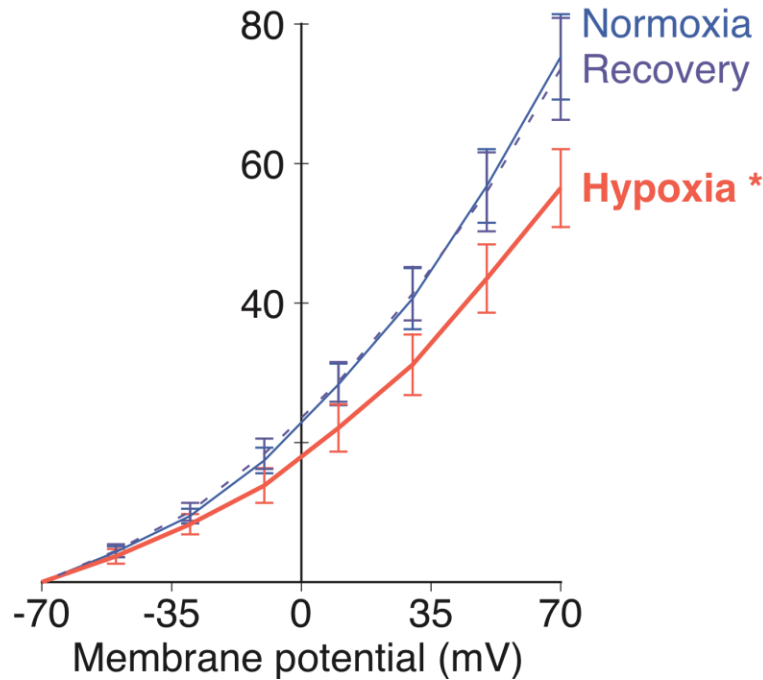
Hypoxická fetoplacentární vazokonstrikce (HFPV)

Fetoplacental
perfusion
pressure
(mmHg)

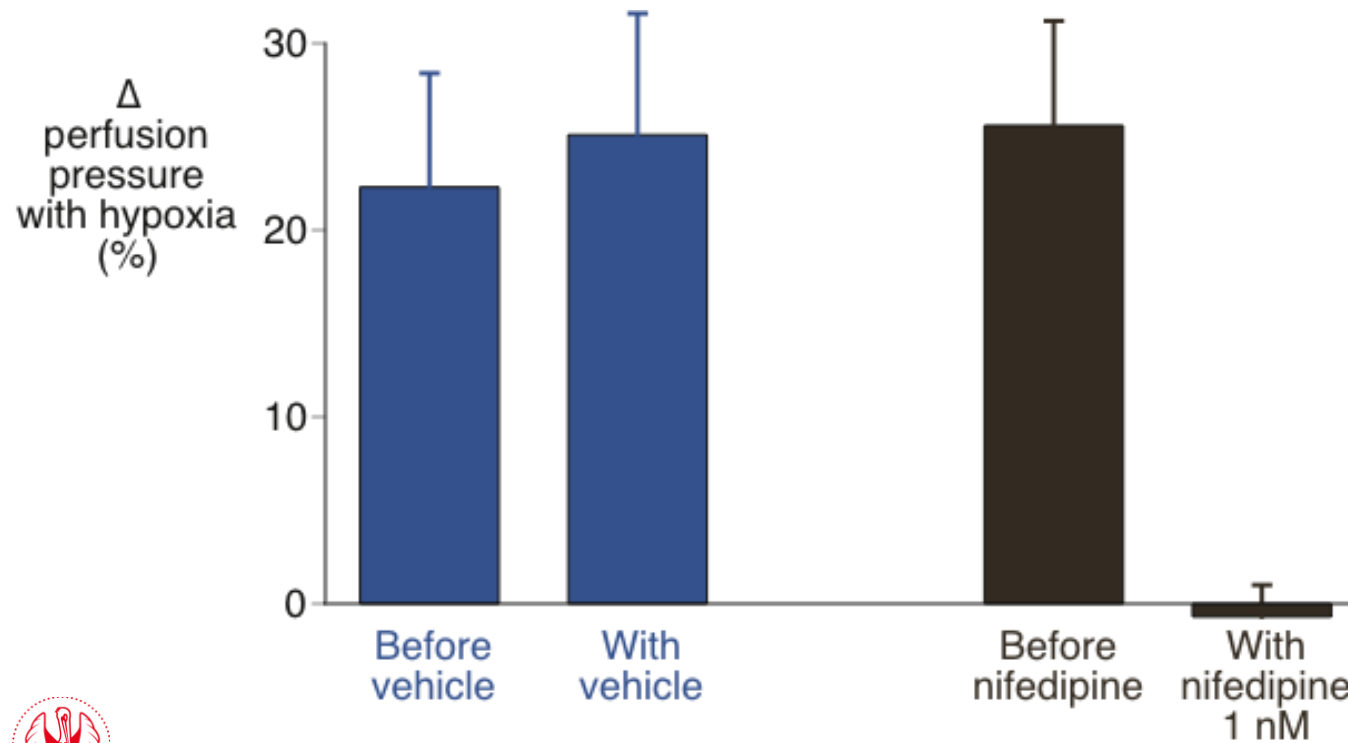




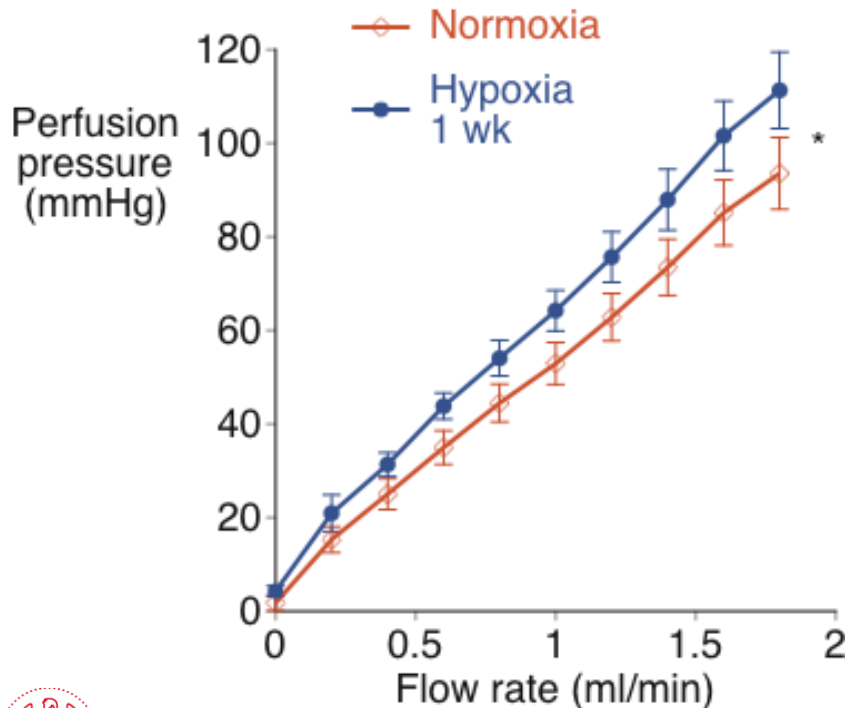
Hypoxie inhibuje K^+ kanály v buňkách hladkého svalu fetoplacentárních cév



Esenciální role napětím řízených Ca^{2+} kanálů v HFPV



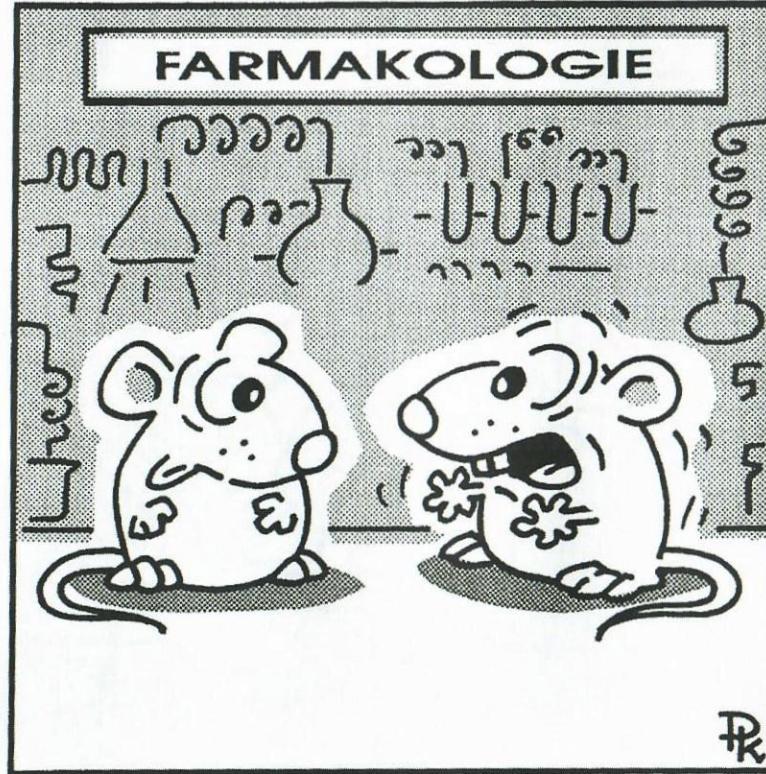
Chronická hypoxie zvyšuje fetoplacentární cévní rezistenci



→ hypotrofie novorozenců



plicní hypertenze → neonatologie



„Copak to ještě nechápeš? Jsme v rukou naprostých šilenců!
Napřed tě něčím strašně nakazí a pak se tě snaží vyléčit!“



Hypoxická plicní vazokonstrikce (HPV)

- o co jde?
- proč by nás měla zajímat?
- mechanismy

- akutní x chronická

- placenta

