



OPERAČNÍ PROGRAM PRAHA
KONKURENCESCHOPNOST



EVROPSKÝ FOND PRO REGIONÁLNÍ ROZVOJ



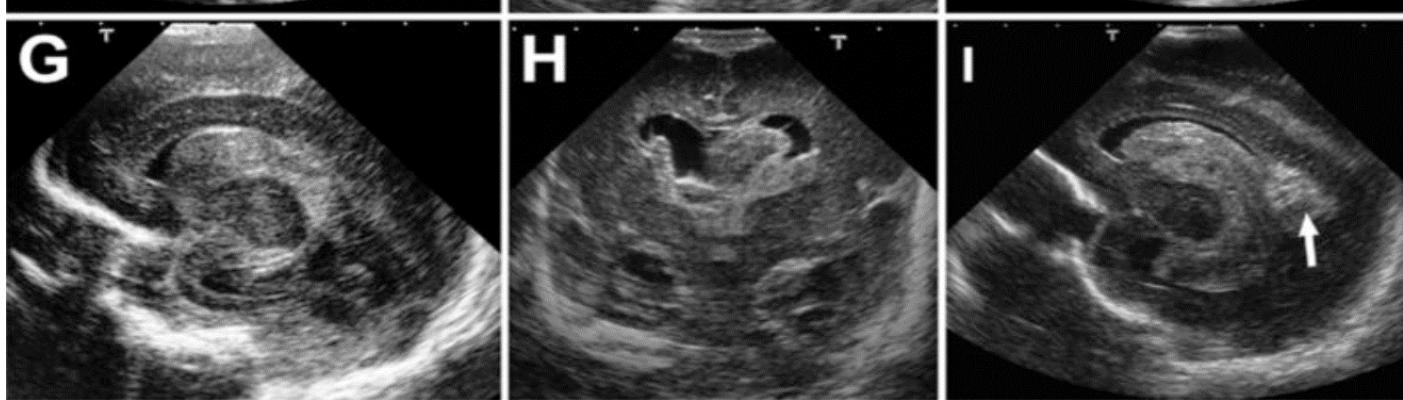
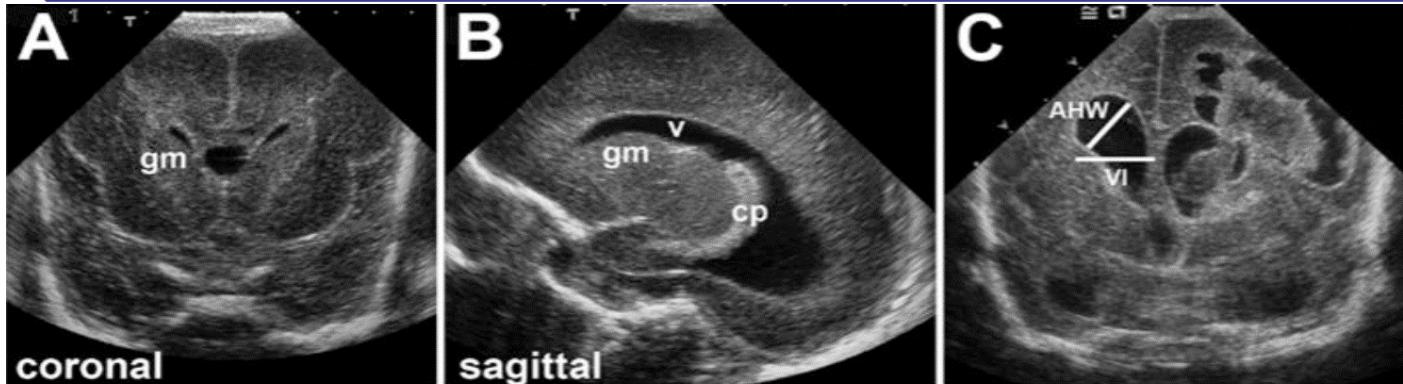
Selektivní pofylaxe intracerebrálního krvácení (IVH)

XXXIII. neonatologické dny s mezinárodní účastí

PRAHA & EU
INVESTUJEME DO VAŠÍ BUDOUCNOSTI

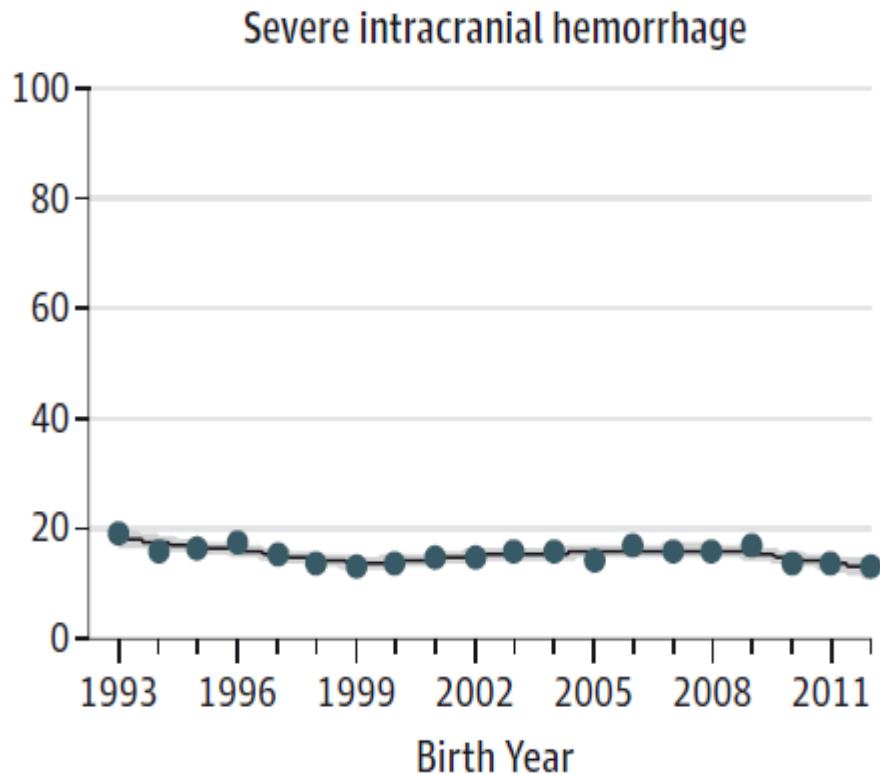
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Projekt „Péče o nezralé novorozence“, reg. č. CZ.2.16/3.1.00/21564

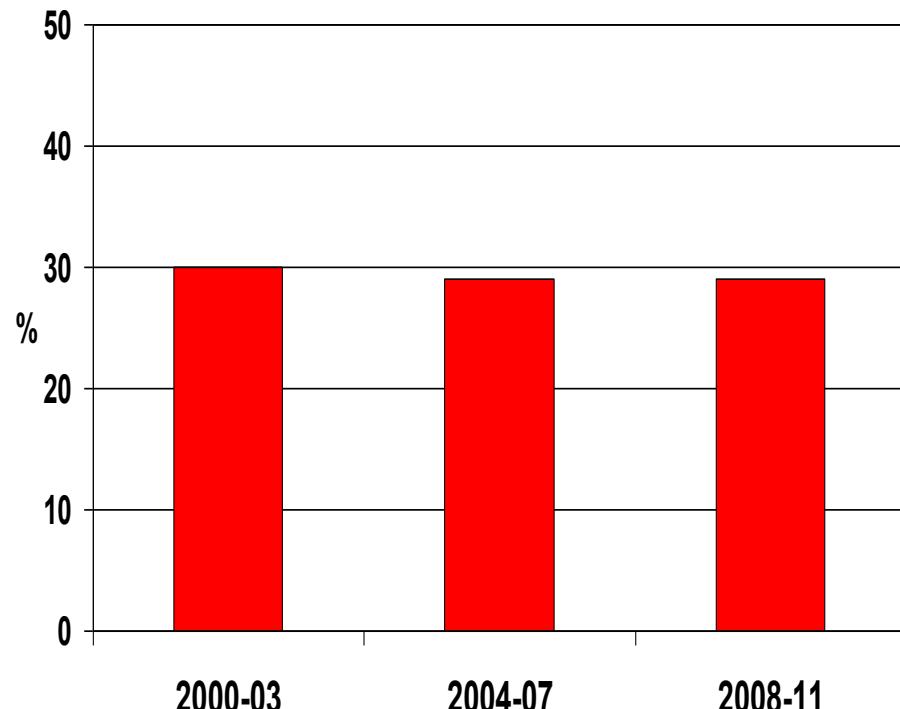


- Incidence a prognóza
- Hlavní příčina a mechanismus vzniku
- Možnosti prevence a profylaxe

NICHD – NRN data
Trend Data



NICHD NRN data
severe intracranial hemorrhage
GA 22+0-24+6



Závažná neurosenzorická poškození po IVH

New South Wales and Australian Capital Territory NICUs. Data collection

2701 born at 23–28 wks, in period 1998–2004, evaluation in 2–3 years

304 (11%) had IVH gr. 3-4, 62% died

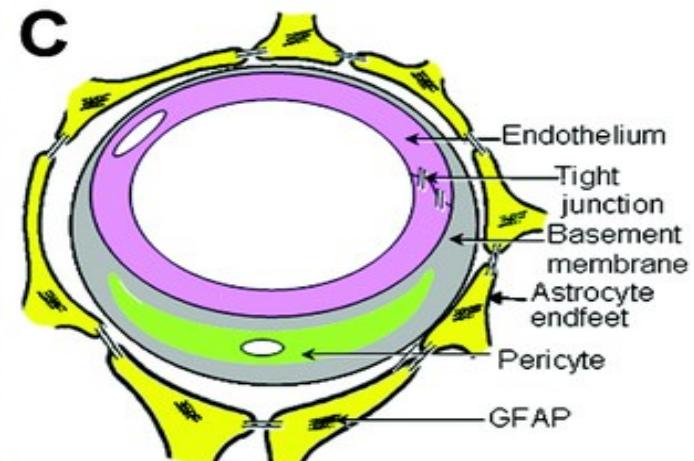
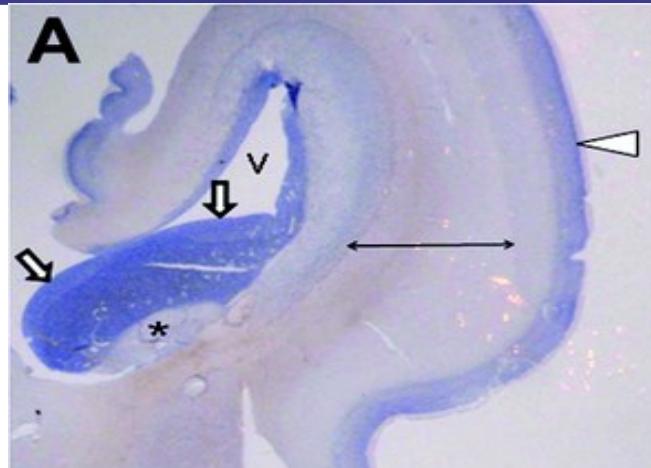
515 (19%) had IVH gr. 1-2, 16% died

	Developmental Delay	Cerebral Palsy	Deafness (bilat)	Blindness (bilat)
IVH gr 3-4	17.5%	30%	8.6%	2.2%
IVH gr 1-2	7.8%	10.4%	6.0%	
controls without IVH	3.4%	6.5%	2.3	

- Fragility of germinal matrix (GM) vasculature
- Disturbance of cerebral blood flow (CBF)
- Platelet and coagulation disorders

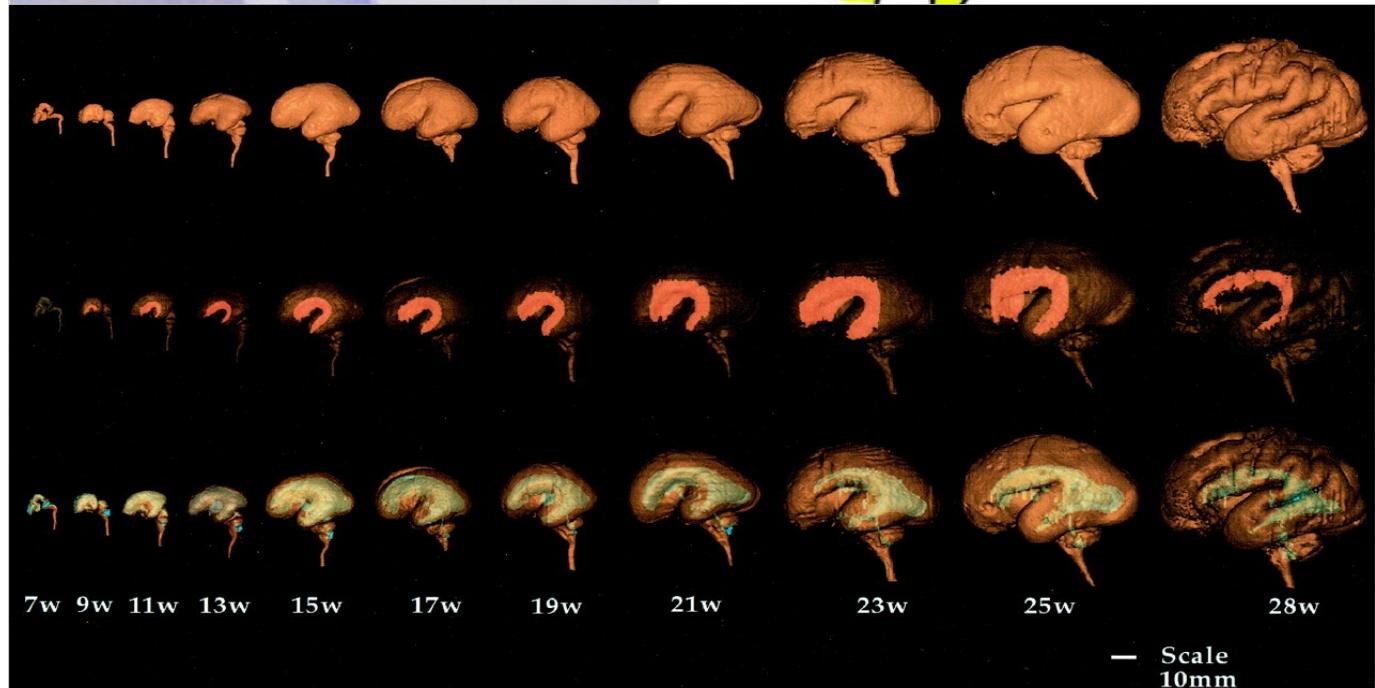
GM

* Caudate nucleus

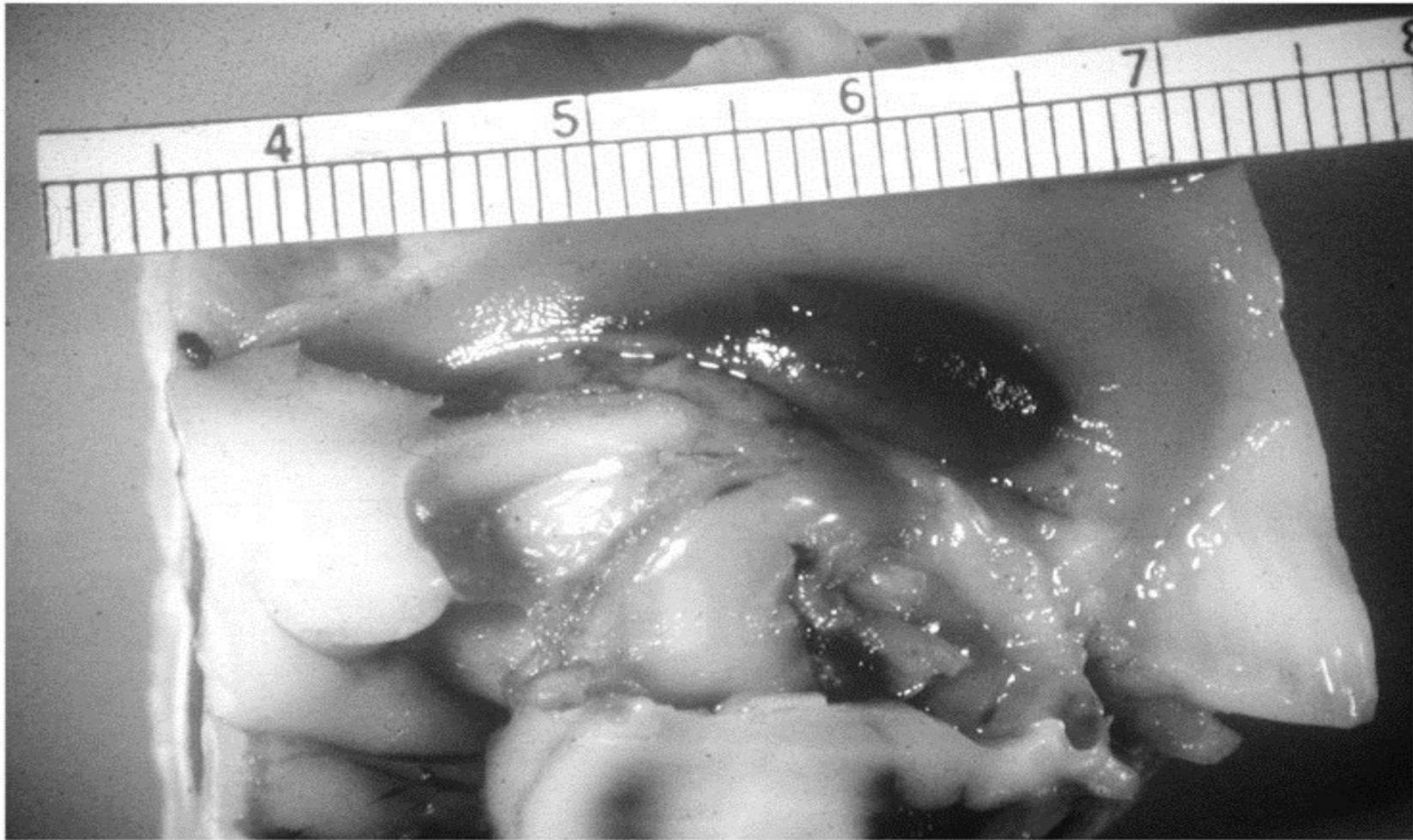


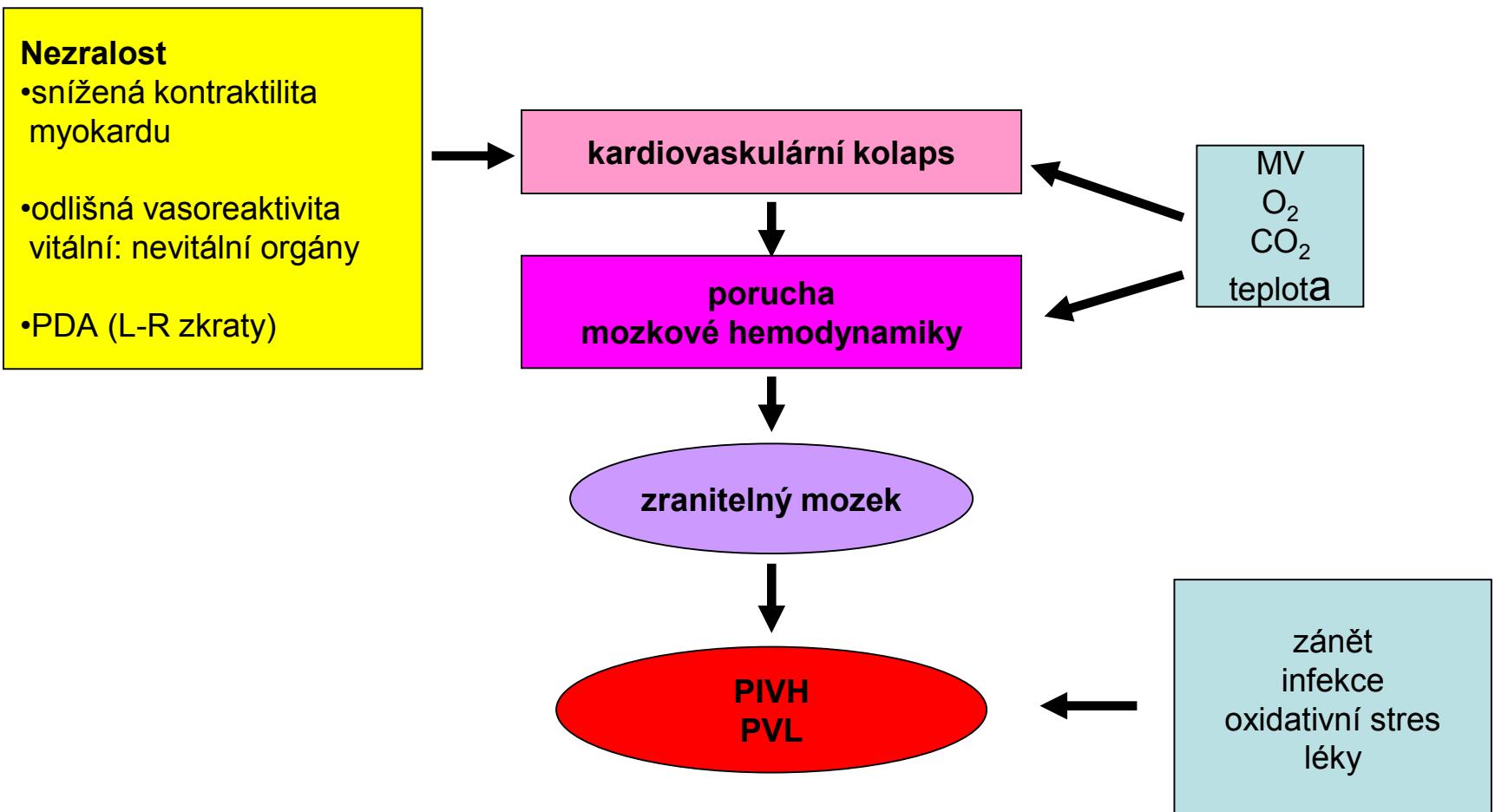
Endothelium (red)

Glial cell mass (green)



OPP Většina P/IVH se rozvíjí v průběhu
K 72 hodin po porodu





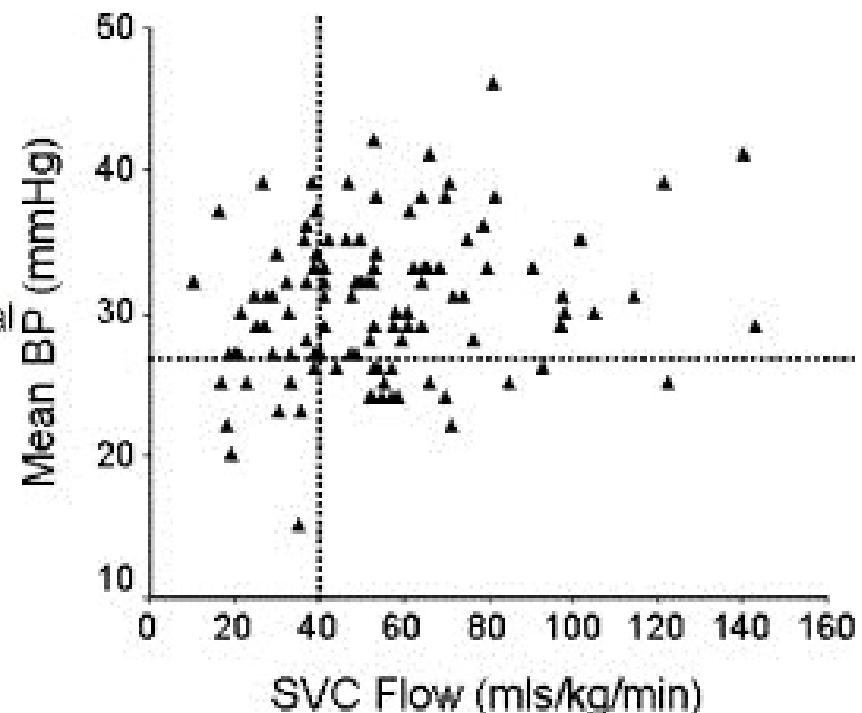
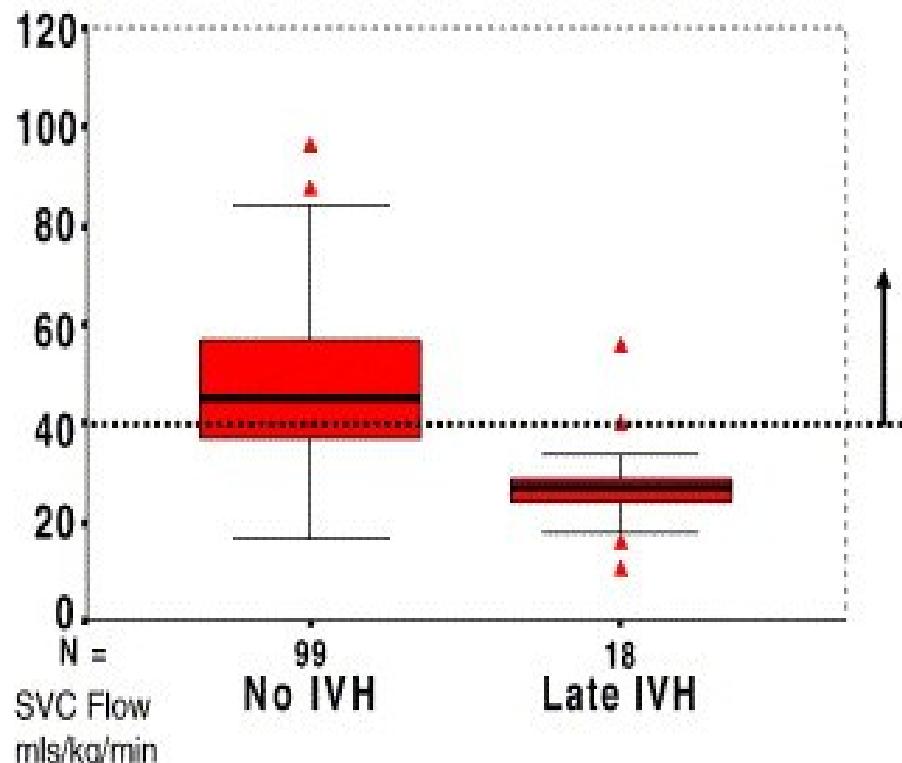
- Low Blood Pressure vs Low Systemic Blood Flow
- Fluctuation of CBF or Pressure Passivity

- Paradox of arterial pressure treatment
- Antihypotensive therapy was associated with an increased risk of death or NI at 18–22 months CA.

Batton et al NICHD NRN data, Fetal and Neonatal Ed 2016

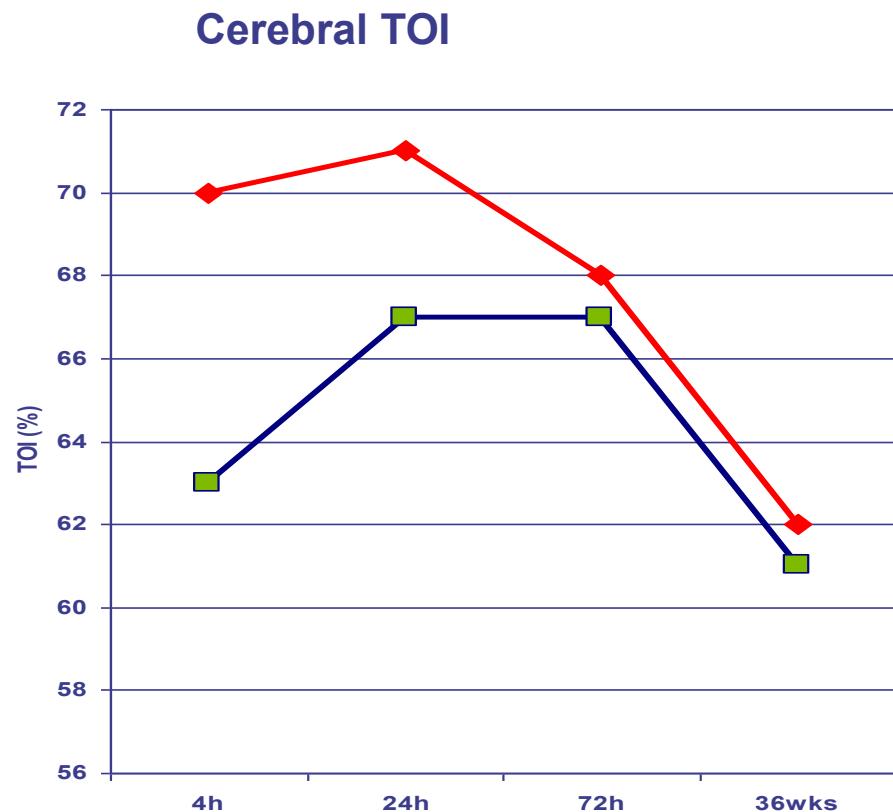
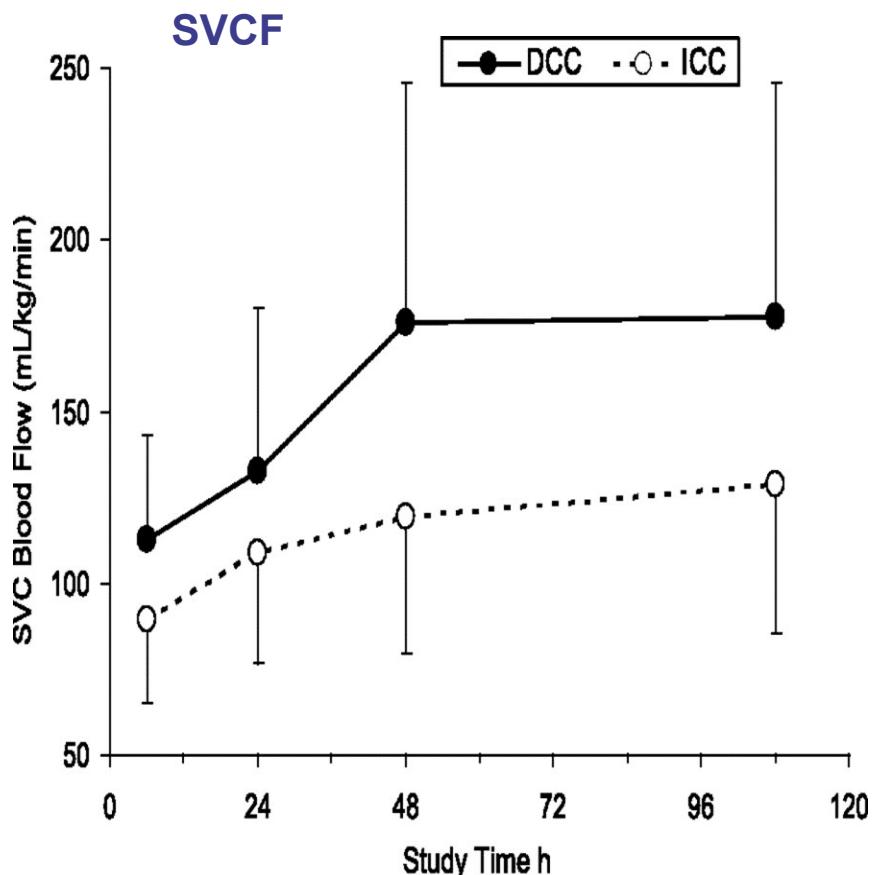
- Early low SVCF was associated with higher mortality and morbidity(PIVH, NEC and ROP) and with worse neurodevelopment in 3 years of life.

Osborne et al., Pediatrics, 2007



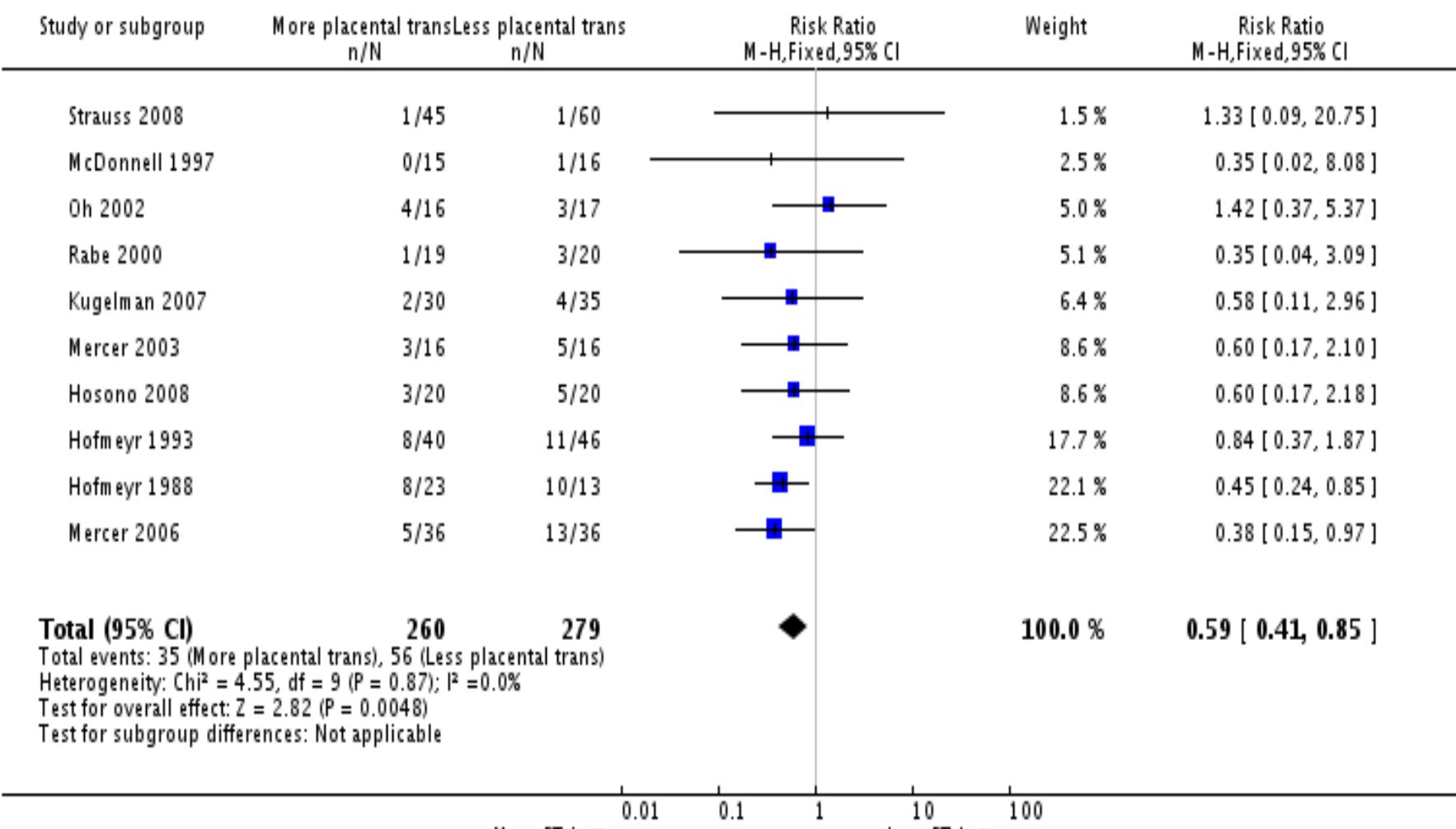
Kluckow M Early Hum Dev 2005

Delayed Cord Clamping (DCC 60–90 secs) improves systemic and cerebral blood flow



Sommers R et al. Pediatrics 2012;129:e667-e672

Baezinger O et al , Pediatrics 2007
WWW.OPPK.CZ



Risk factors:

- Low blood pressure vs Low Systemic Blood Flow
- Fluctuation of CBF or pressure passivity

Near infrared spectroscopy (NIRS) Spatially resolved spectroscopy (SRS)

- Noninvasive, continuous quantitative measurement of regional oxygen saturation (rcSpO₂, TOI)
- Coherence between MABP a rcSpO₂
- (> 0.5, **PRESSURE PASSIVE PERFUSION** of brain)



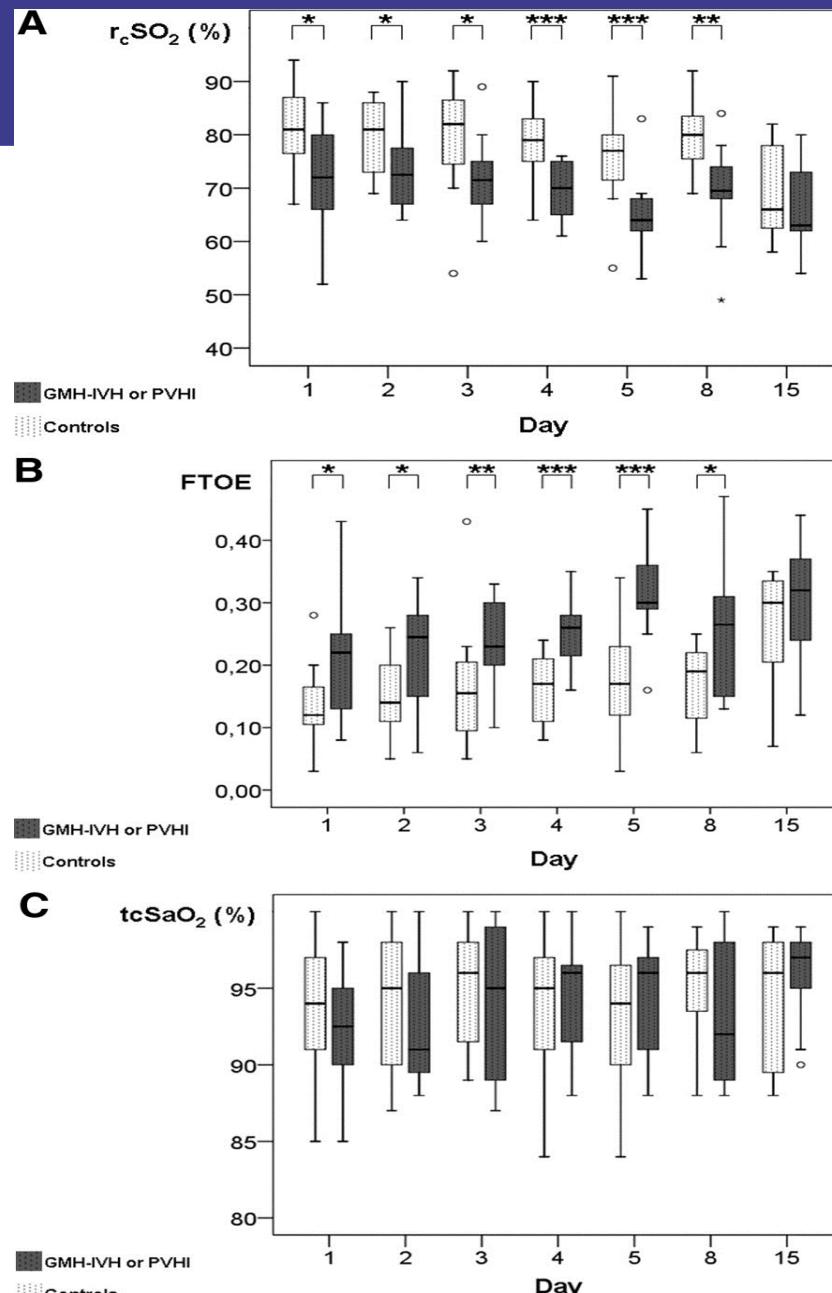
- USG CNS within 72 hrs after birth
- NIRS, 2 hour period: 1., 2., 3., 4., 5., 8., 15. DOL

	GMH-IVH N=17	Controls N=17
GA	29.4 (25.4–31.9)	29.9 (26.0–31.6)
BW	1260g (850–1840)	1310g (730–1975)

Preterm Infants with GM-IVH had lower rcSpO₂.
Decreased cerebral perfusion persists for 2 weeks.

Verhagen E A et al. Stroke 2010

OPP Krvácení do germinální matrix a do komor
K mozkových

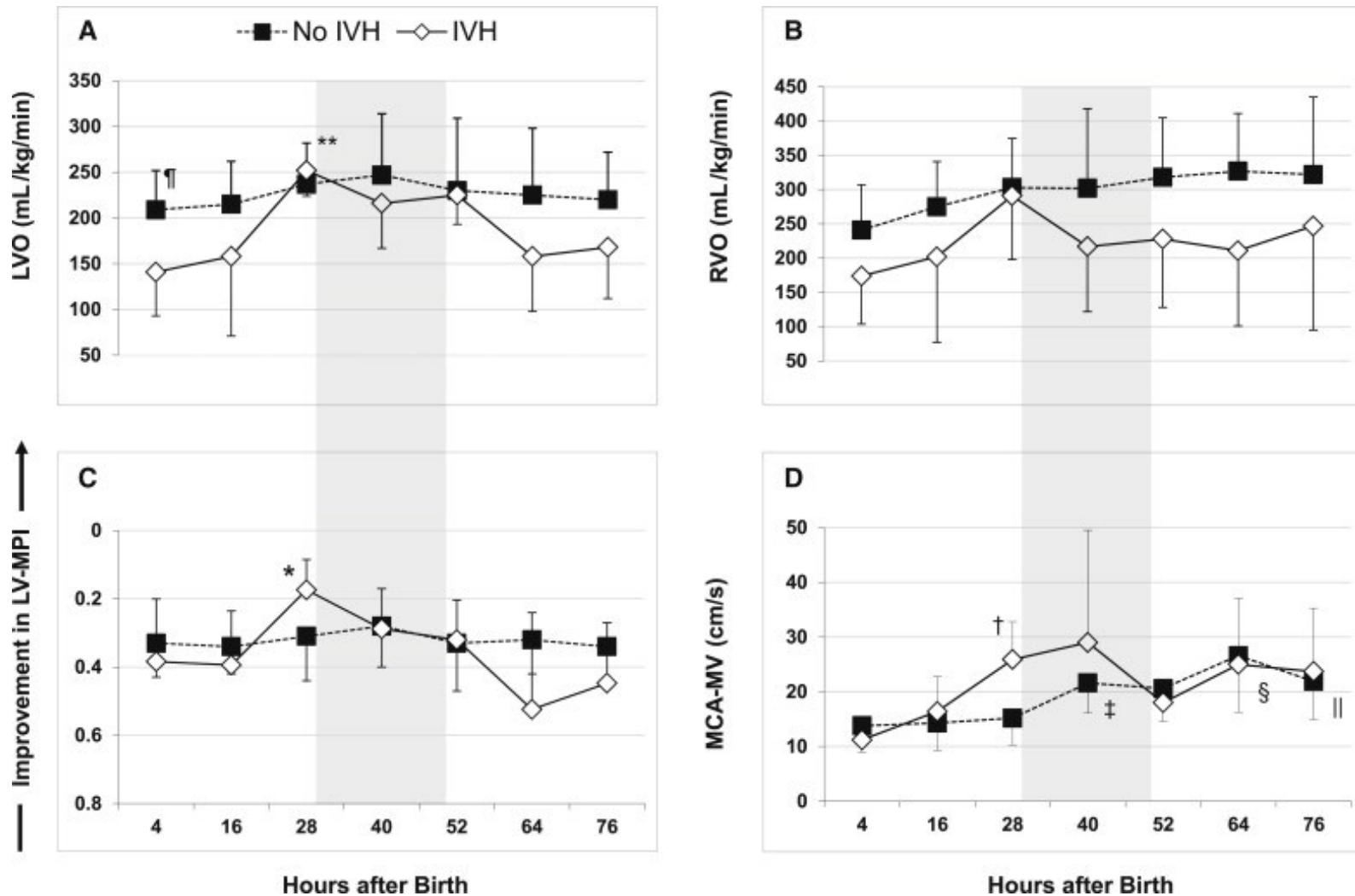


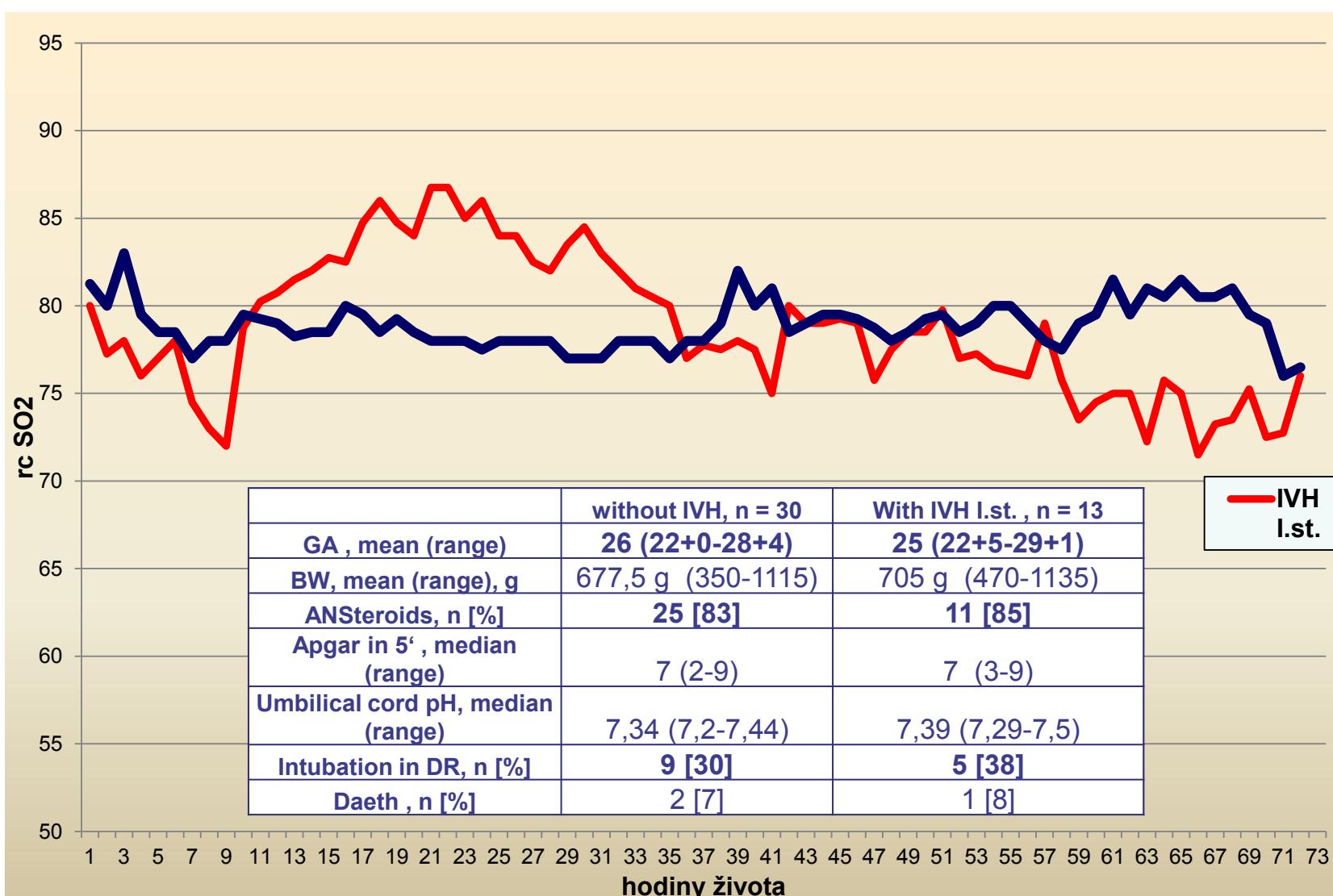
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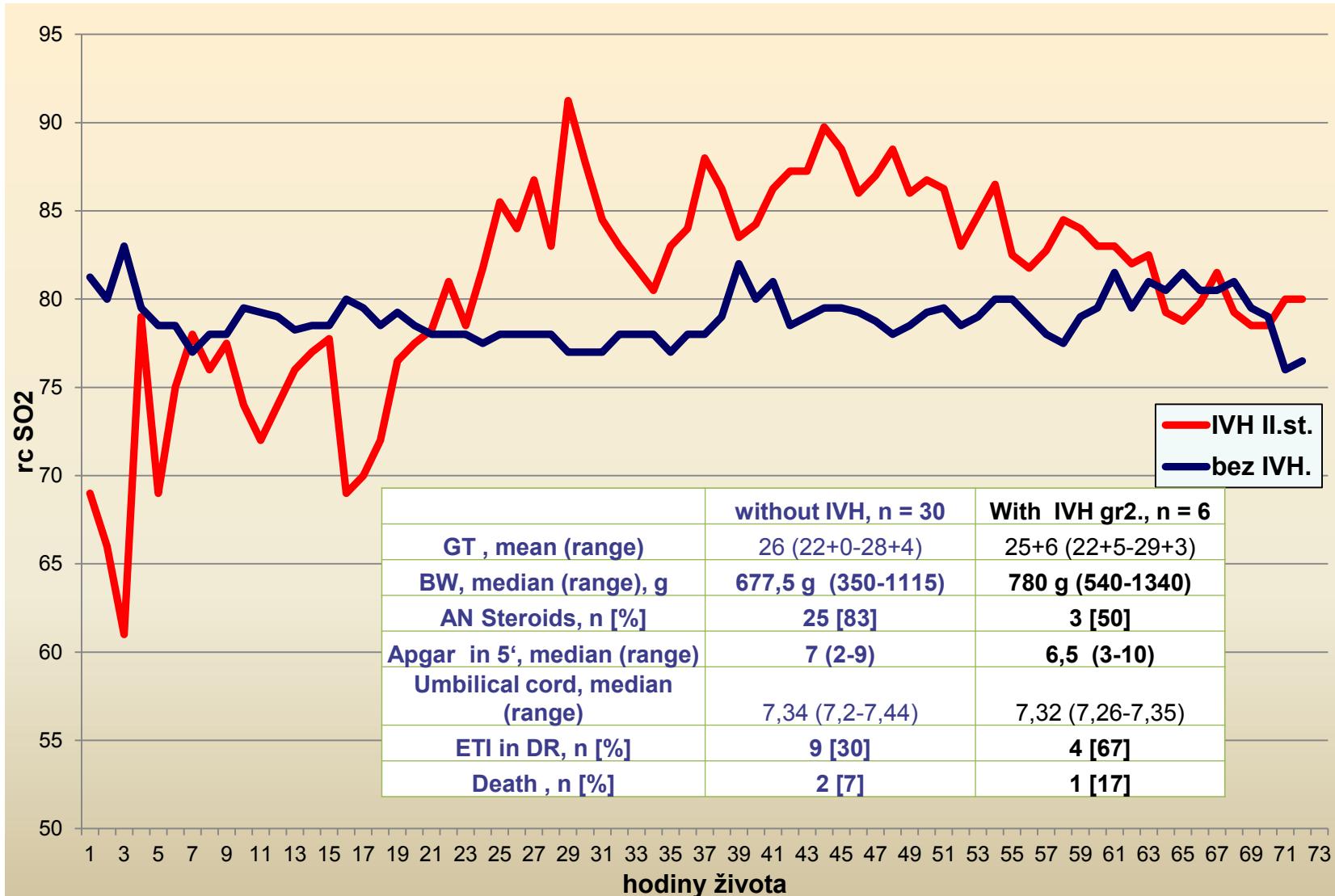
Verhagen E A et al. Stroke 2010

- LVO and cerebral oxygenation increase are related to IVH development in extremely preterm infants.
- *Noori S et al J Pediatr 2014*

N 22, GA 25.9 ± 1.9 , NIRS + FECHO 4–72h, 5 patients with IVH gr. 2–4

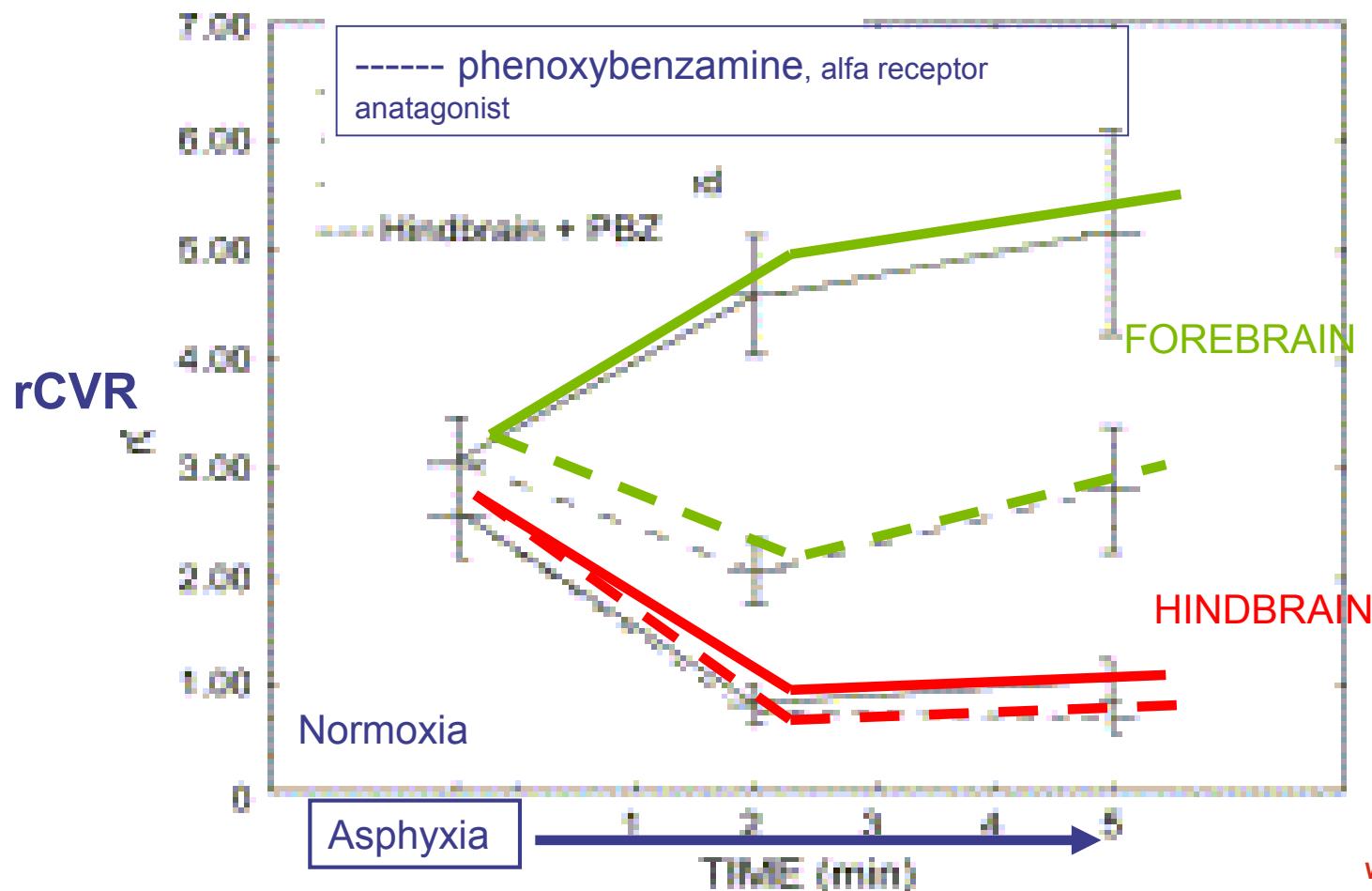




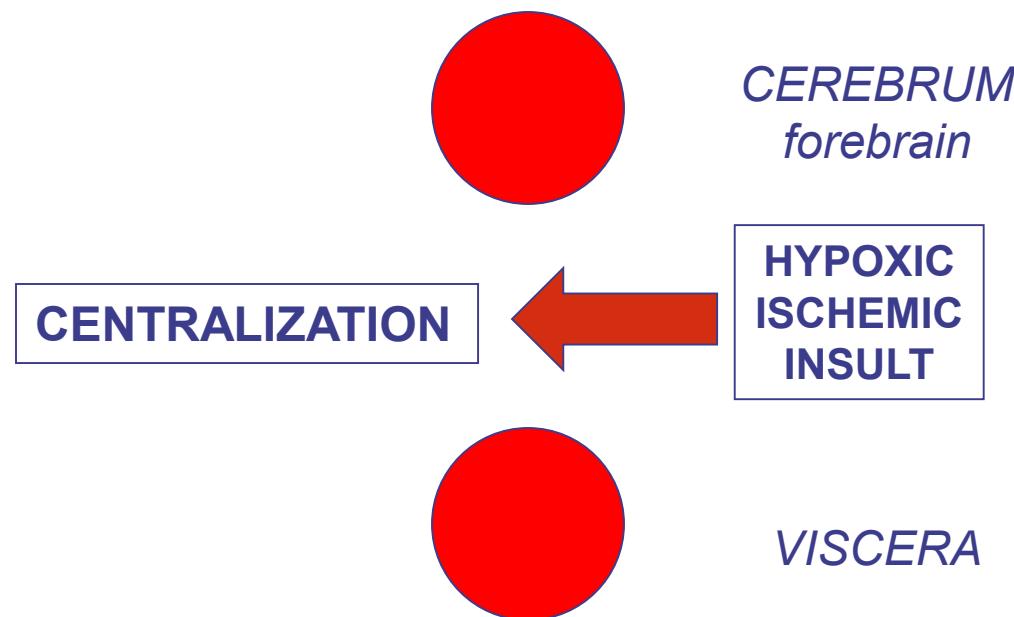


- Lower initial values of rcSO₂ and larger variability.
- Postnatal times crossing control values are positively related to the grade of IVH.
- HYPOPERFUSION ⇒ **REPERFUSION**
Reperfusion attacks can be repeated in more severe grades of IVH

Different vascular reaction is developmentaly determined and may contribute to IVH stroke

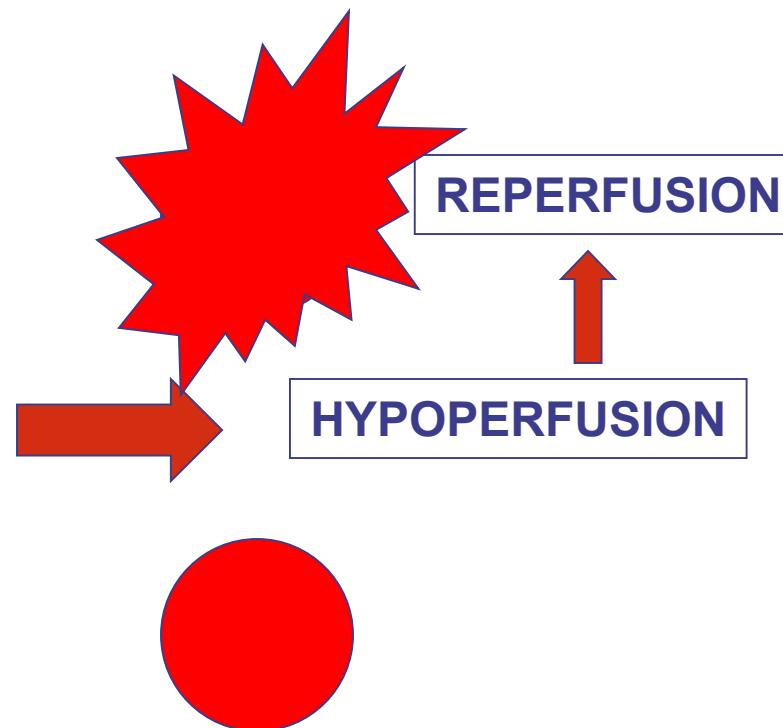


ADULTS

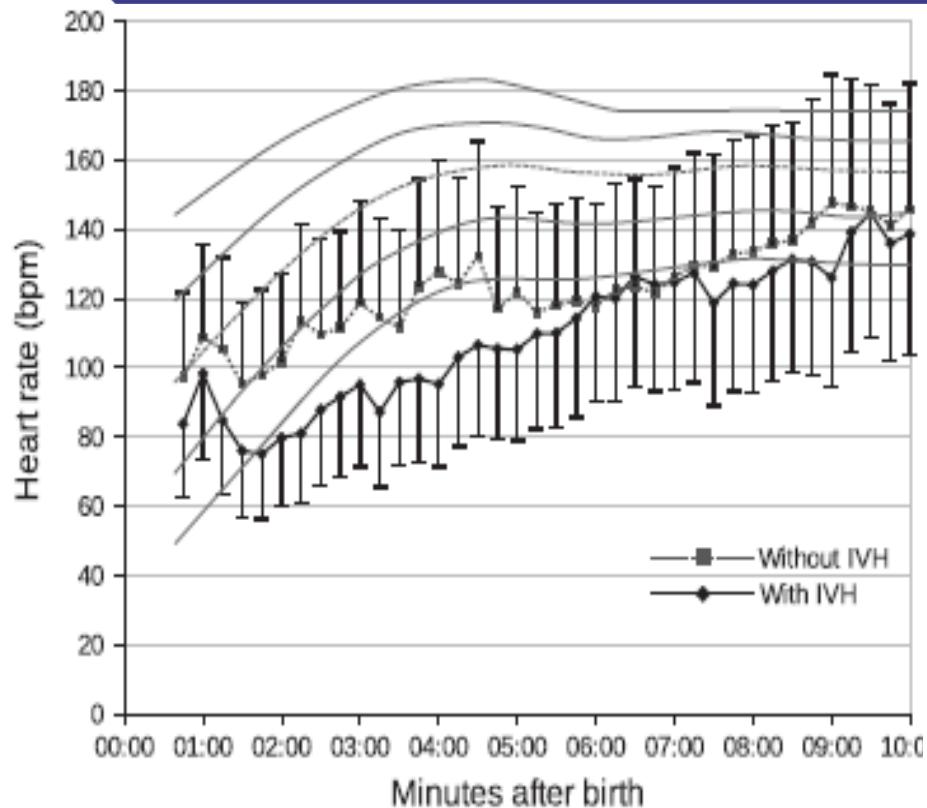


Premature NEWBORNS

GM vascular fragility in PRETERM

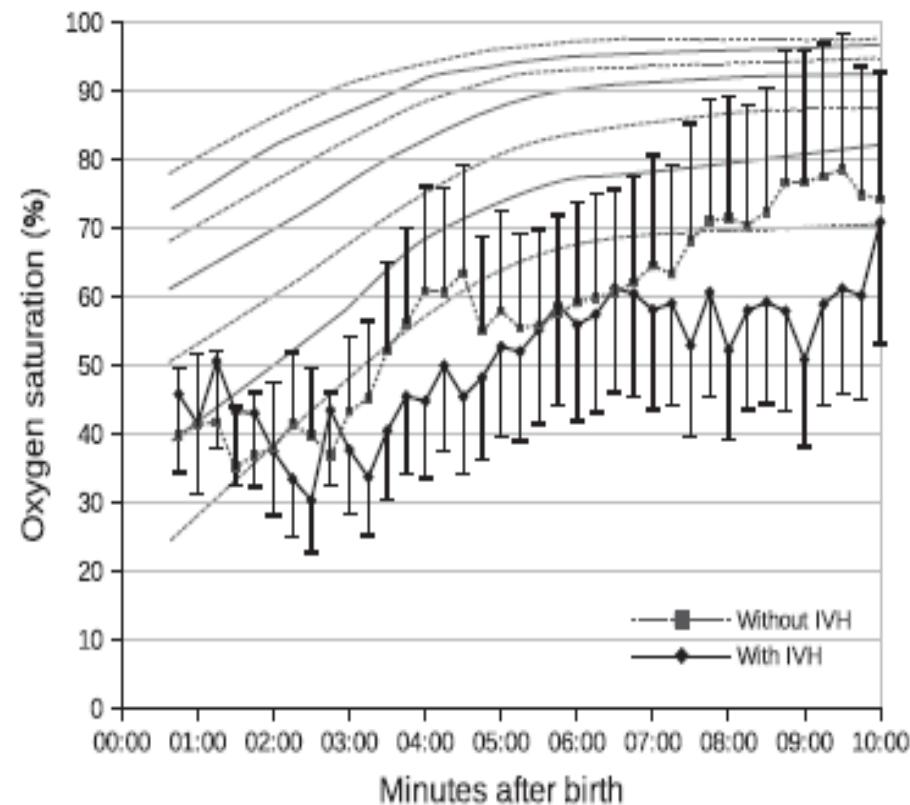


Proč mají extrémně nezralí novorozenci,
u nichž se později rozvine IVH,
nižší cerebrální oxygenaci?



2–5 minutes, lower HR and SPO₂
Ineffective PPV- delayed lung aeration

2:45, p = 0.006; 4:15, p = 0.043; 4:30, p = 0.024; 5:00, p = 0.043.



7–10 minutes, lower SPO₂
Repeated intubation procedure

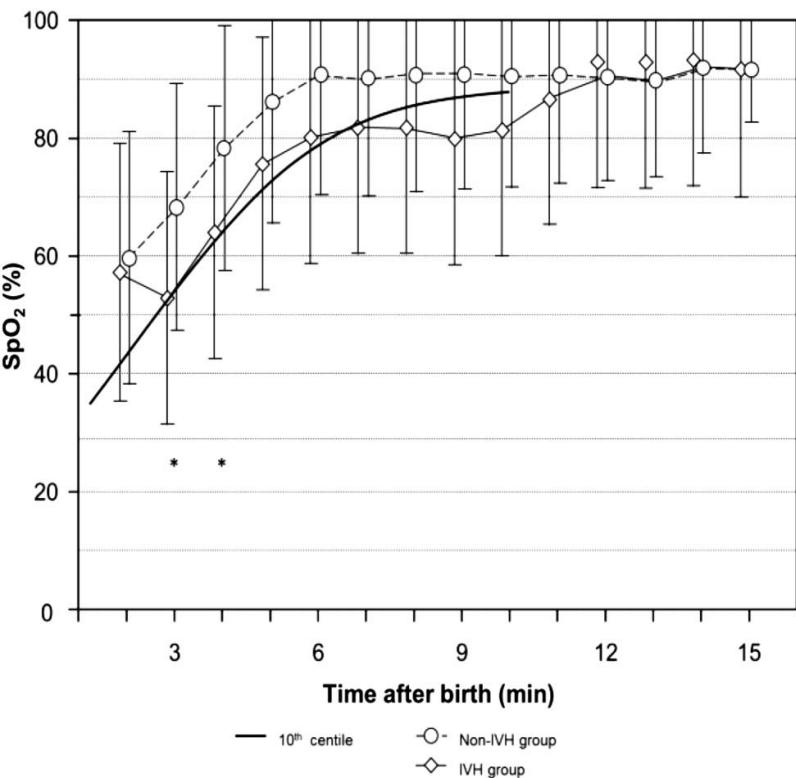
5:00, p = 0.047; 8:30, p = 0.041; 9:30, p = 0.013; 9:45, p = 0.049.

Table 1 Demographics of preterm neonates with and without IVH

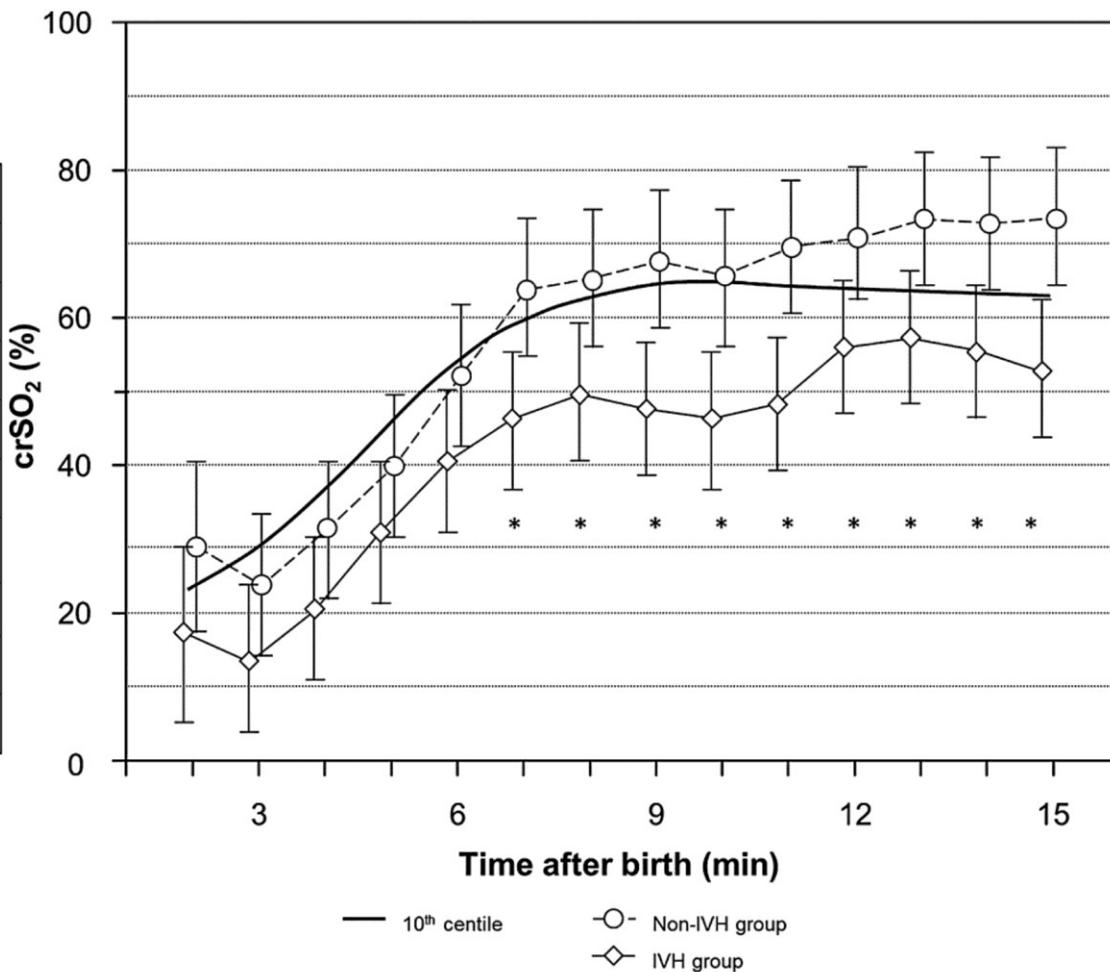
	IVH group	Non-IVH group	p Value
Neonates, n*	12	12	–
Gestational age, weeks	25.7±2.6	26.4±2.1	0.06
Birth weight, g	856.3±314.7	869.8±238.3	0.75
Apgar 1†	4 (1.5–6.8)	5 (3.3–7.5)	0.52
Apgar 5†	7 (6–7.8)	7 (6.3–8)	0.17
Apgar 10†	9 (8–9)	8 (8–9)	0.81
Male*	5 (42%)	2 (17%)	0.08
pH umbilical artery	7.27±0.11	7.31±0.06	0.46
Delayed cord clamping (60 s)*	6 (50%)	6 (50%)	1.00
Early cord clamping*	6 (50%)	6 (50%)	1.00
Indication for delivery/maternal risk factors			
Premature rupture of membranes	3 (25%)	2 (16%)	1.00
Pre-eclampsia	3 (25%)	4 (33%)	1.00
Preterm labour	6 (50%)	6 (50%)	1.00

Data are presented as mean±SD, unless indicated *n(%), †median (IQR).
IVH, intraventricular haemorrhage.

VLBWI < 32 wks, NIRS in DR, 12 with IVH
vs 12 controls



*Significant difference between IVH group and Non-IVH group



*Significant difference between IVH group and Non-IVH group

- Hlavní příčinou cerebrální hypoperfuze je **hypoxicko ischemický inzult**.
 - ✓ Může začínat již u plodu.
 - ✓ A/nebo vznikne v průběhu transitorní fáze přechodu placentárního dýchání na dýchání plícemi.

- ... nebo v kombinaci s jinými nežádoucími faktory jako jsou:
 - ✓ neodkladná intubace
 - ✓ hyperkapnie/hypokapnie, fluktuace CO₂
 - ✓ SIVH/death OR 1.62 (1.05 to 2.51), p=0.029
(Fabres J et al Pediatrics 2007, Ambalavanan N, et al. 2015)
 - ✓ stresující výkony a nepřiměřená manipulace

RR (95% CI)

SIVH	0.66 (0.53–0.82)
PDA	0.51 (0.37–0.71)
Death or severe NSI	1.02 (0.90–1.15)

Mechanism of effect:

Non-selective inhibitor of COX1 and COX2 → ↓prostaglandin synthesis:

- ✓ Attenuates hyperemic response
- ✓ Stabilizes blood brain barrier
- ✓ Promotes maturation of basal lamina
- ✓ Attenuates cerebrovascular CO₂ reactivity



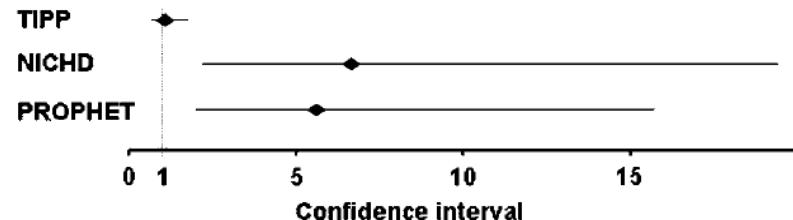
reduction of SIVH
+ PDA ligation

risk of ischemia-hypoxia

- brain
- gut
- retina

no evidence of better
neurodevelopment outcome

no evidence of higher
incidence of:
PVL
NEC/SIP
ROP



Main goal: to identify high-risk group for indomethacin prophylaxis

- Neocosur Network, 6538 VLBWI 2001–10, logistic regression model; *Luque et al 2014*
- VON database, 2917 infants \leq 34wks 2000–10, logistic regression model; Final model AUC=0.85.(0.81–0.88); *Singh R et al 2013*

Predictive clinical variables by IVH

	Neocosur Data	VON Data
Gestational age	0.001	0.001
Birth-weight	0.001	0.001
Apgar score (5')	0.001	0.001
Antenatal steroids	0.001	0.001
Male	0.001	0.94
Out-born		0.001
C-section (opposite results)	$\downarrow 0.001$	$\uparrow 0.03$
Mechanical ventilation	0.001	NS

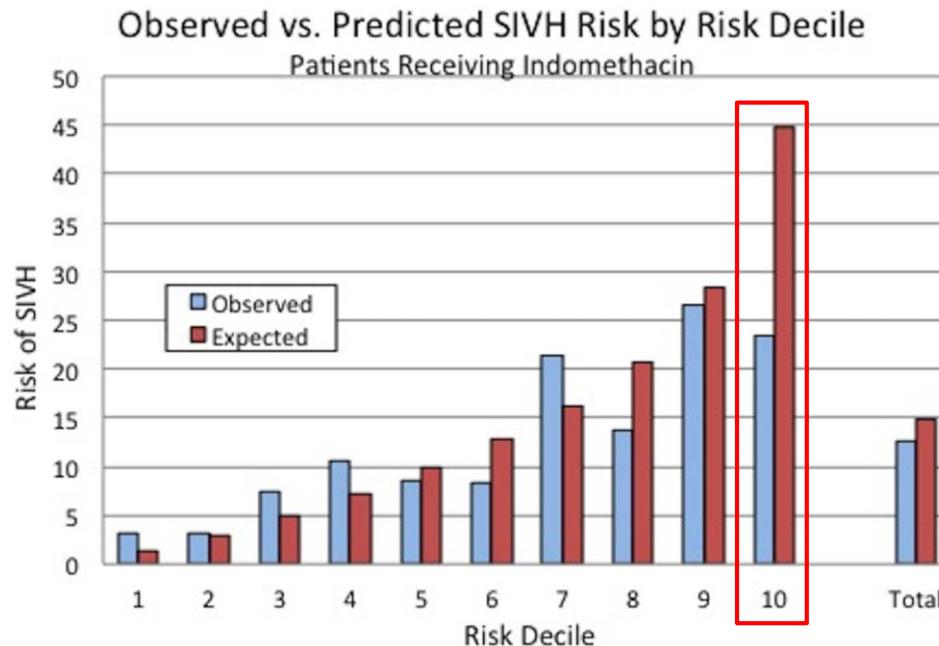
Gestational Age (weeks): Birth weight (grams):

Any Antenatal Steroids: Gender:

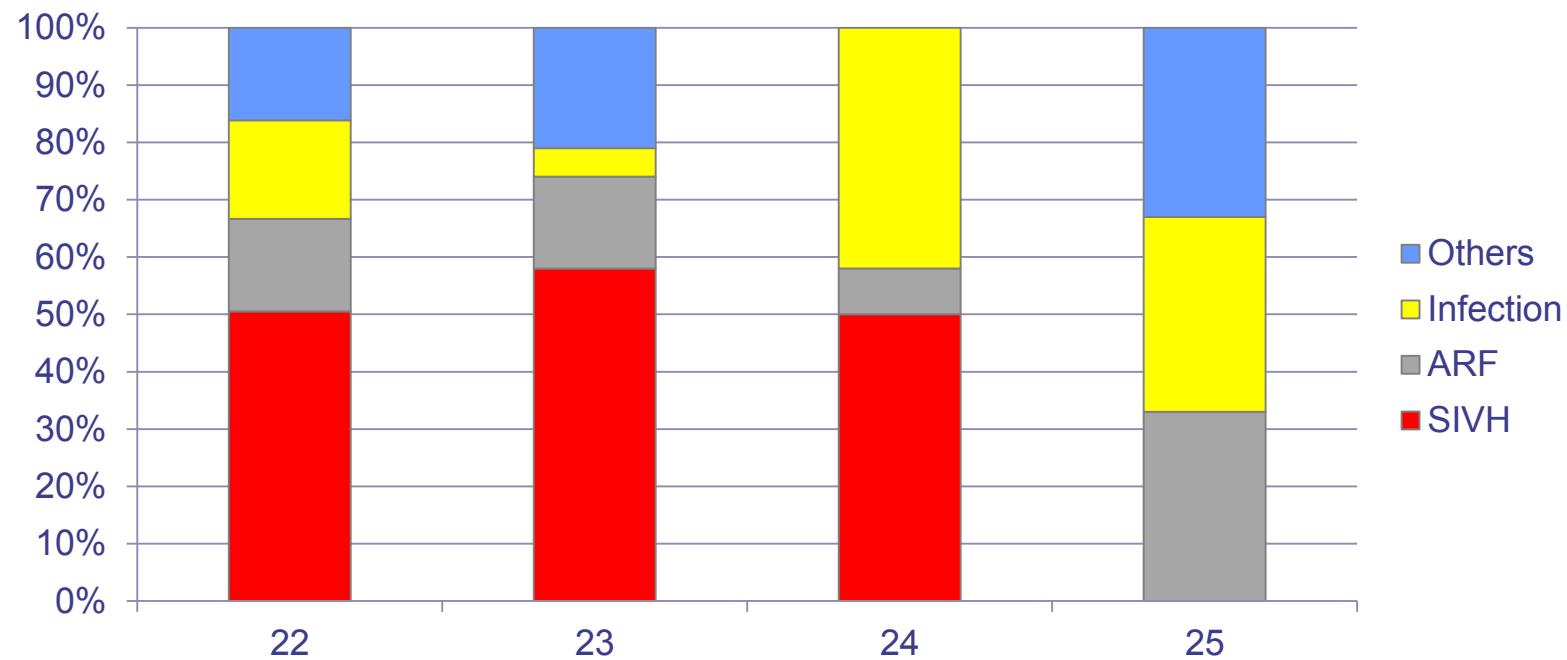
Mode of delivery: 5 minutes APGAR:

Location of delivery:

Risk: 49.25%



Všeobecná fakultní nemocnice v Praze, jednotka ARO-JIP
N 166, období 2010–2017



Všeobecná fakultní nemocnice v Praze, jednotka ARO-JIP

ELGA infants (22^{+0} – 25^{+0}), period 2010 – 2017,
N = 106, BW mean (range) 611g (340 – 850g) , GA mean (range) 23+6 (22+6-25+0)
PIVH gr. 2–4 N = 48, **severe IVH N = 32**, IVH gr. 2 N = 16
Risk score using AS, median (range) 36 (12 – 62)

Evaluation of Risk Score	www.neoqic.org
sensitivity (%)	82
specificity (%)	88
PPV	0.80
PNV	0.89
NNT	3.5 (5*)

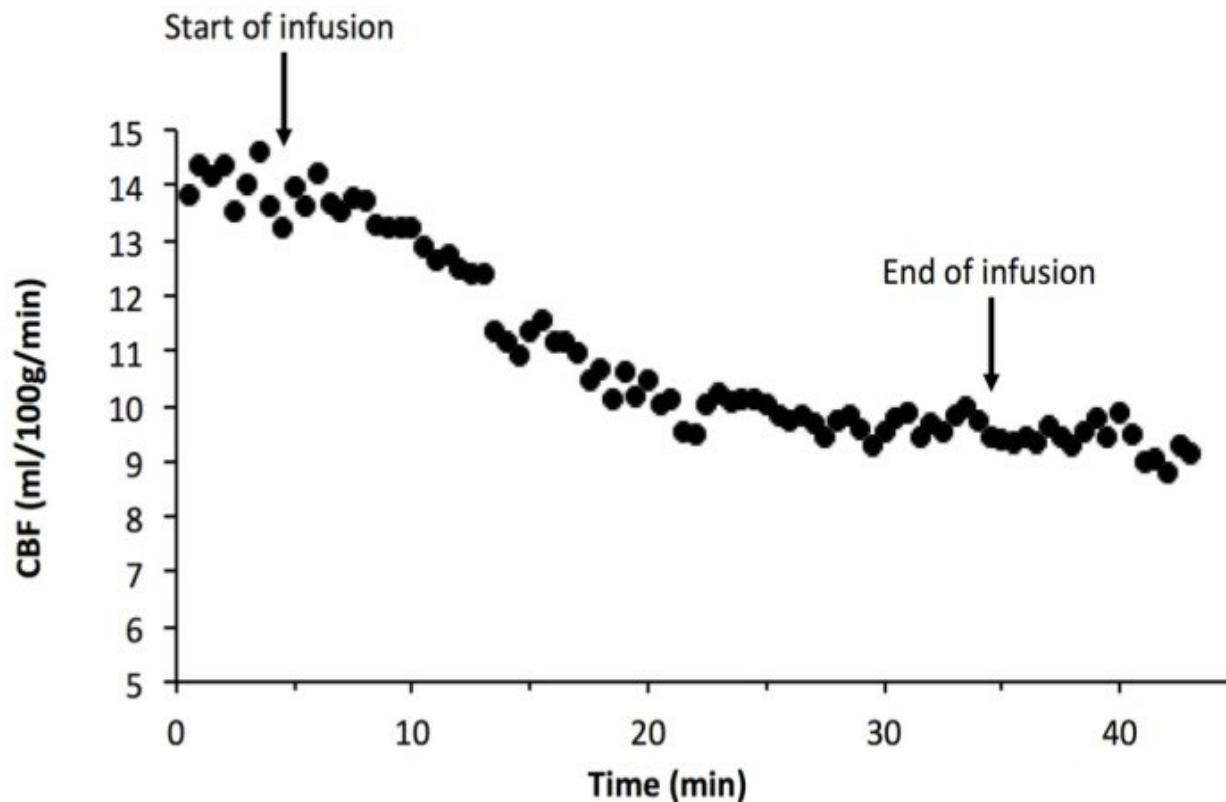
*The 33% of effectiveness is considered as a highly probable in patients with high risk score (RS $\geq 38\%$)

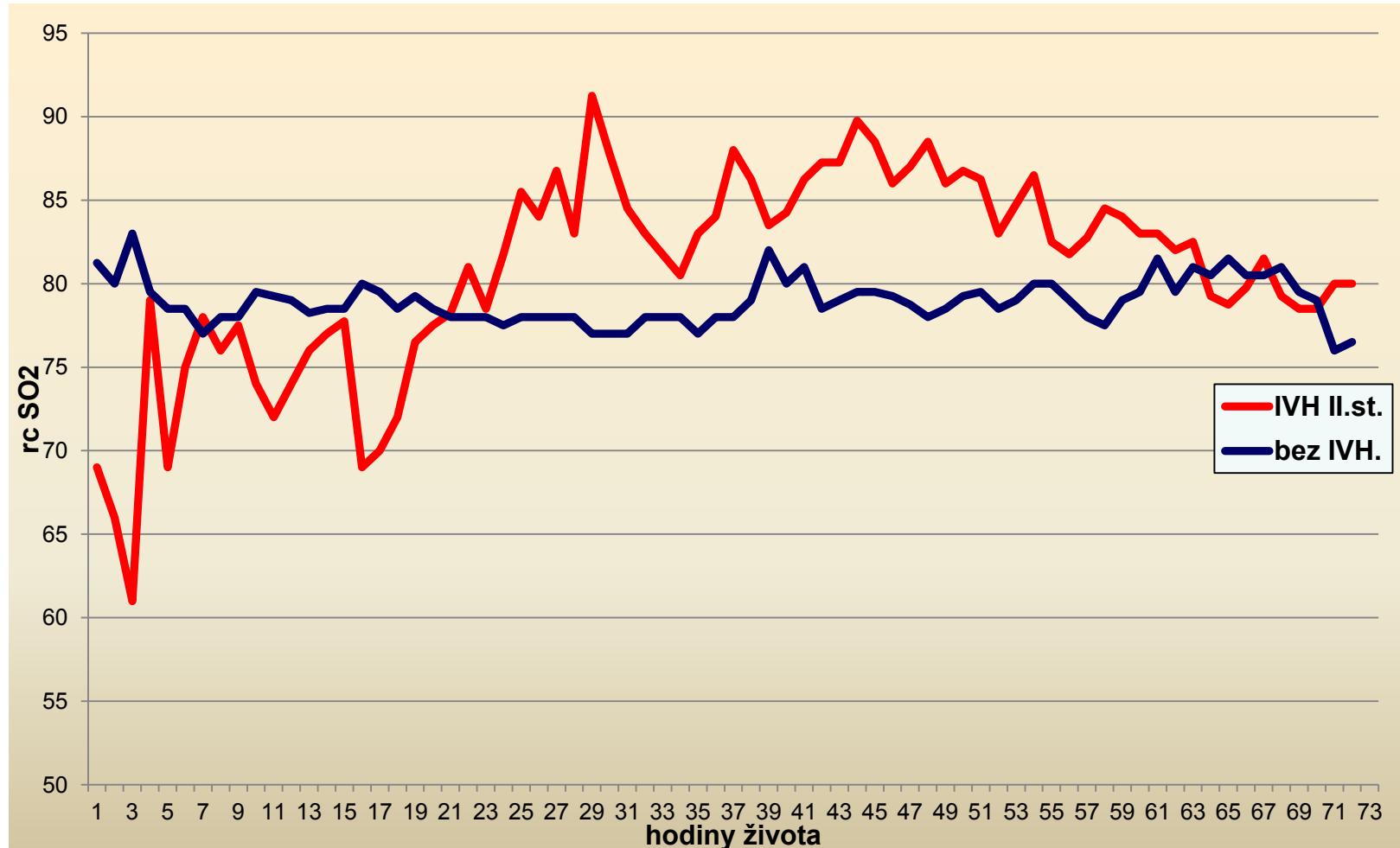
Všeobecná fakultní nemocnice v Praze, jednotka ARO-JIP

Patient	GA (wks)	BW (g)	RS (%)*	IVH (gr)	Diagnoses	Status
1 female	24+1	585	52	2, bilat.	mild BPD ROP st.3 anti VEGF	home
2 male	24+2	665	38	2, bilat	moderate BPD ROP st.2	home
3 male	24+2	605	39	2, l.sin	moderate BPD ROP st.2	Home
4 female	23+4	565	68	0	severe RDS, PIE	10 wks, IMC
5 female	25+1	785	38	0	RDS mild BPD,	8 wks IMC, CPAP
6 female	24+1	730	50	0	NEC, laparotomy,	4 wks NICU

*All had no ANS and were rescue intubated in delivery room

Infuze indomethacinu 0,1 mg / kg / 30 min
významně snížila cerebrální perfuzi





- PLACENTÁRNÍ TRANSFUZE opožděný podvaz pupečníku alespoň 1 min (milking u apnoe/> 30 s)
- VYHNOUT se prolongované bradykardii (≥ 180 s může být kritické) a nízkým hodnotám SpO₂ (< 10· percentil nomogramu) během ustanovování FRC.
- UŽÍVEJ bezpečné a efektivní techniky plicní aerace, které mohou **snížit potřebu „rescue“ intubace na PS**.
- Intubuj, když jsou srdeční akce a SpO₂ na bezpečných hodnotách.

- Léčit **nízký systémový průtoku** nebo nízký tlak s klinickými/laboratorními známkami snížené tkáňové perfuze.
- Vyhnut se **hyper- a hypokapnii, kolísání CO₂** → využívat SYNCHRONIZOVANÉ and OBJEMOVĚ CÍLENÉ ev KONTROLOVANÉ (**VG a VC**) ventilační mody.
- **IVH RR (95 % CI) 0.65 (0.42–0.99) NNT11.**
- **Snížení frekvence a délky odsávání** a vyhnout se zbytečným a stresujícím manipulacím.
- *Analgosedation and myorelaxation in MV ELGA infants with HIGH RISK of PIVH progression?*

Osobní názor

- Časná identifikace velmi rizikových pacientů
- Risk skóre > 38 %

- **Indomethacin (Liometacen)**
 - ✓ 3 x 0.1 mg/kg a 24 hodin
 - ✓ i. v. aplikace během 60 min.
 - ✓ 1. dávka ≈ 8–12h života

- ... pouze když se podaří implementovat komplex klinických opatření založených na znalosti patofyziologie tohoto multifaktoriálního závažného onemocnění!
- **Začínat u plodu a na porodním sále!**



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neonatologické oddělní GPK VFN v Praze a 1. LF UK**

2017