TGA: Reflections on an ‘optimal’ neonatal pre & perioperative management model expecting ‘normal’ neurologic development

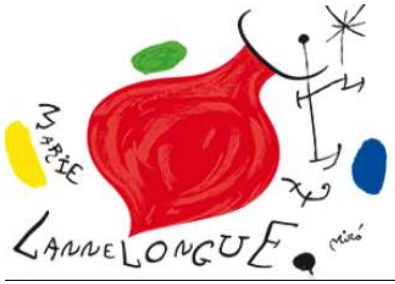
Mirela Bojan, MD PhD

Marie Lannelongue Hospital

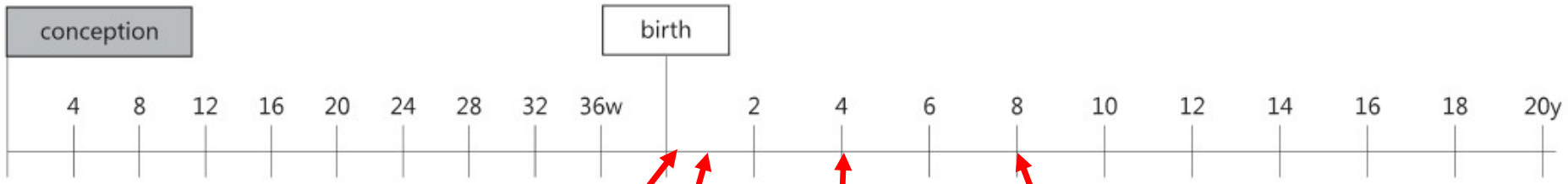
Department of Congenital Heart Disease

Le Plessis Robinson, France

m.bojan@hml.fr



Hôpital
Marie Lannelongue



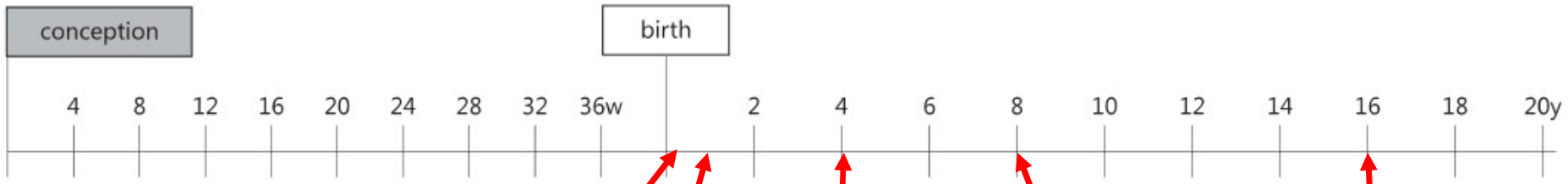
BCA study 1988 – 1992
n = 171 ASO

1993 Newburger, NEJM
OR = 11.4 for seizures
if DHCA

1995 Bellinger, NEJM
Lower PDI if DHCA
PDI ~ DHCA duration

1999 Bellinger, Circulation
Worse motor coordination, speach if DHCA

2003 Bellinger, JTCVS
Worse dexterity, speach,
impulsivity if DHCA



BCA study 1988 – 1992
n = 171 ASO

1993 Newburger, NEJM
OR = 11.4 for seizures
if DHCA

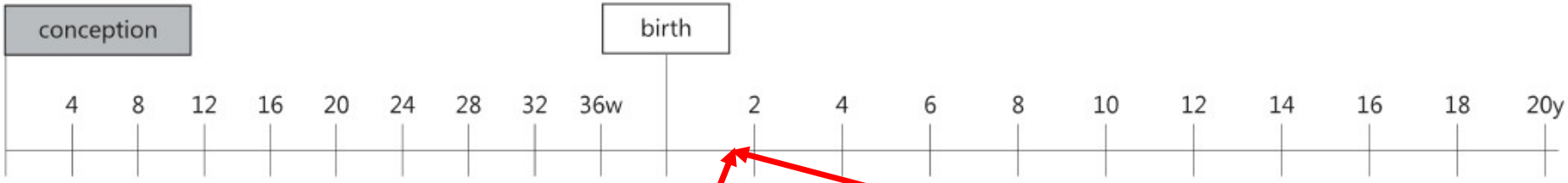
1995 Bellinger, NEJM
Lower PDI if DHCA
PDI ~ DHCA duration

1999 Bellinger, Circulation
Worse motor coordination, speach if DHCA

2003 Bellinger, JTCVS
Worse dexterity, speach,
impulsivity if DHCA

2011, Bellinger, Circulation
33% had MRI abnormalities
65% required remedial
academic or behavioural
treatment

The performance of the full cohort was below expectations in many respects, including academic achievement, fine motor function, visual-spatial skills, working memory, hypothesis generating and testing, sustained attention, and higher-order language skills



ICCON (International Cardiac Collaborative on Neurodevelopment Investigators)

1996 - 2009

n = 1770, ASO = 356

Preop factors explain about **30%** variability in PDI, MDI

- Genetic
- Extracardiac anomaly
- Birth weight
- Center

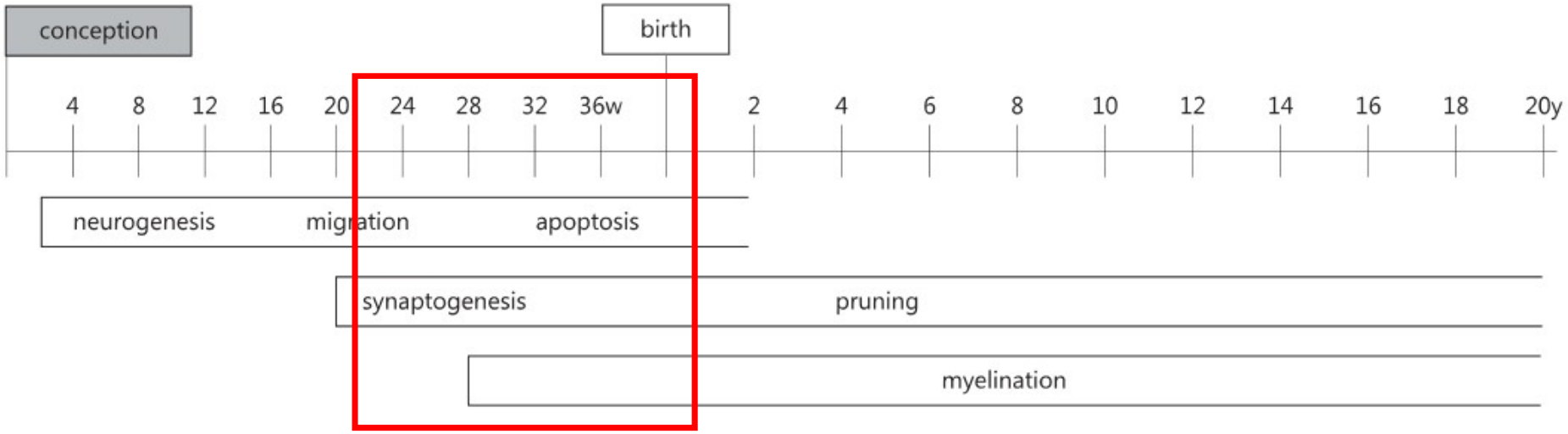
Operative and **postop** factors explain **5%** variability in PDI and MDI

- Total support duration
- ECMO or VAD
- Hospital length of stay > 9 days

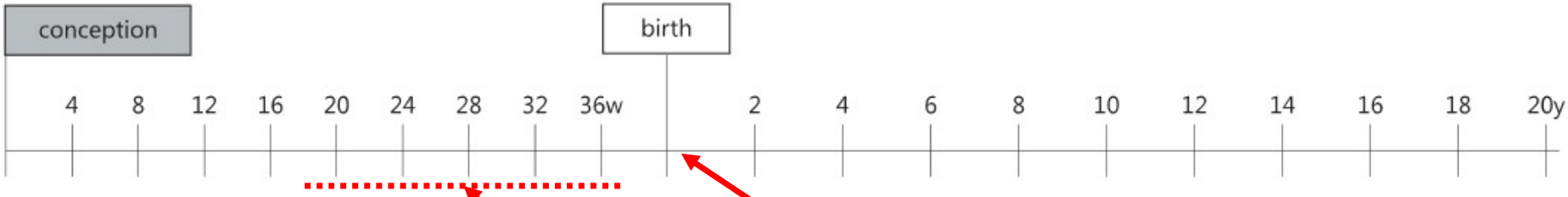
PDI : psychomotor developmental index
MDI : mental developmental index

2015 Gaynor, Pediatrics *2016 ICCON investigators, JTCVS*

Timing of key neurodevelopmental processes in the human brain



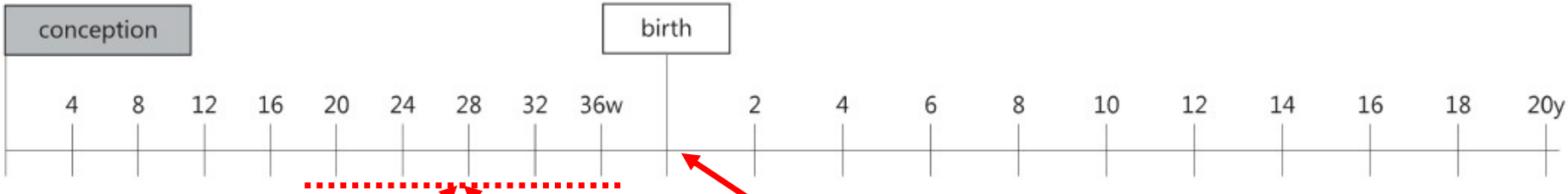
Tymofiyeva, Br J Radiol 2014



2014 Khalil, Ultrasound Obstet Gynecol
34% MRI abnormalities prior to surgery

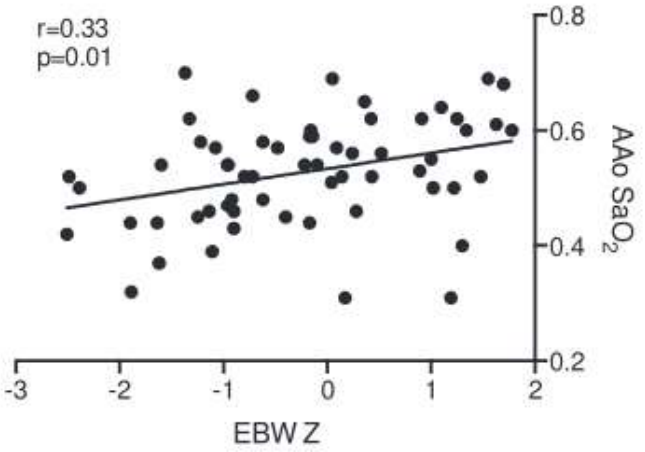
2016 Khalil, Ultrasound Obstet Gynecol
28% MRI abnormalities:

- Structural brain abnormalities
- Reduced brain volume
- Altered brain metabolism
- Decreased MCA pulsatility index



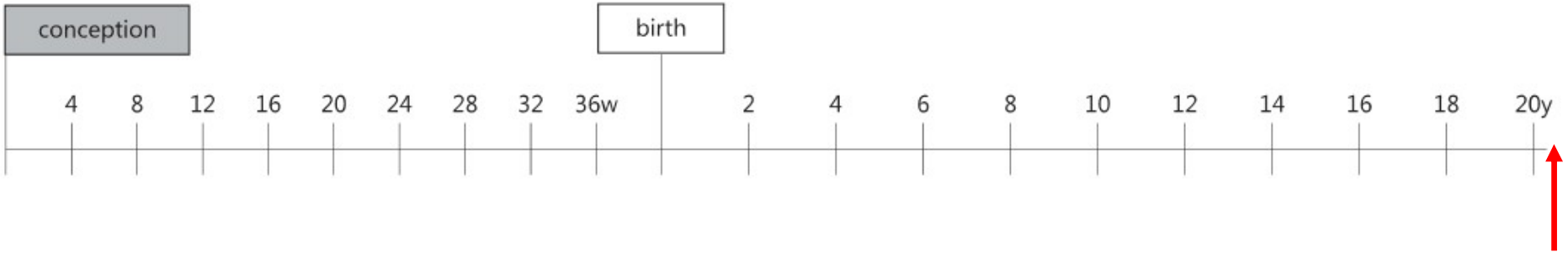
2014 Khalil, Ultrasound Obstet Gynecol
34% MRI abnormalities prior to surgery

2015 Sun, Circulation
SaO_2 in the ascending aorta correlates with fetal brain size



2016 Khalil, Ultrasound Obstet Gynecol
28% MRI abnormalities:

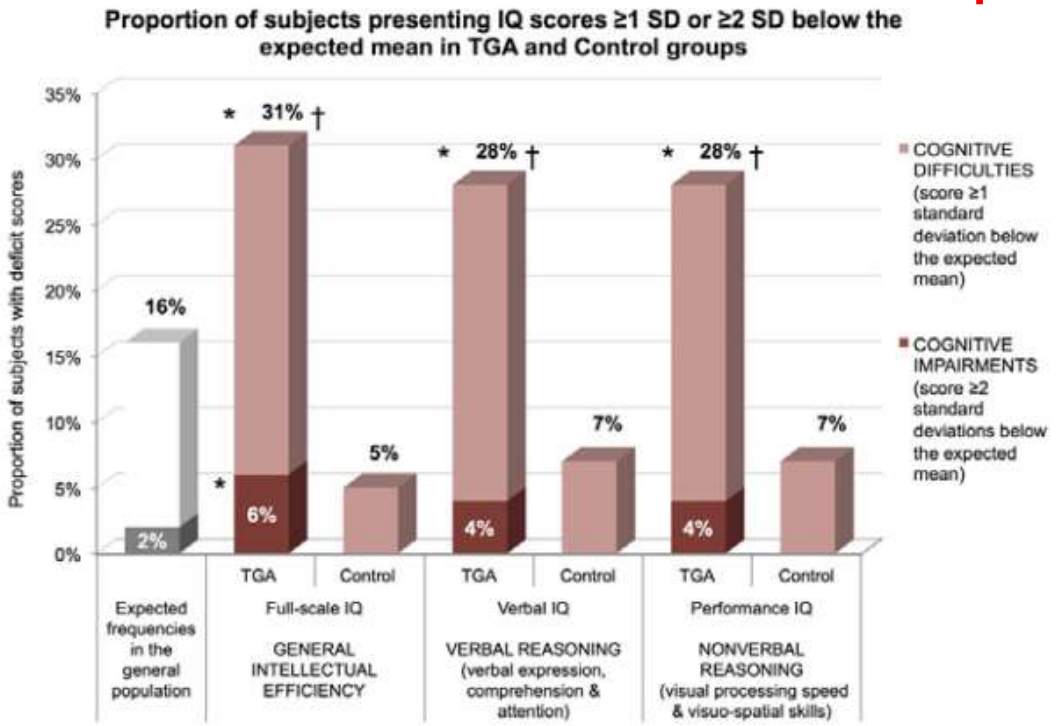
- Structural brain abnormalities
- Reduced brain volume
- Altered brain metabolism
- Decreased MCA pulsatility index



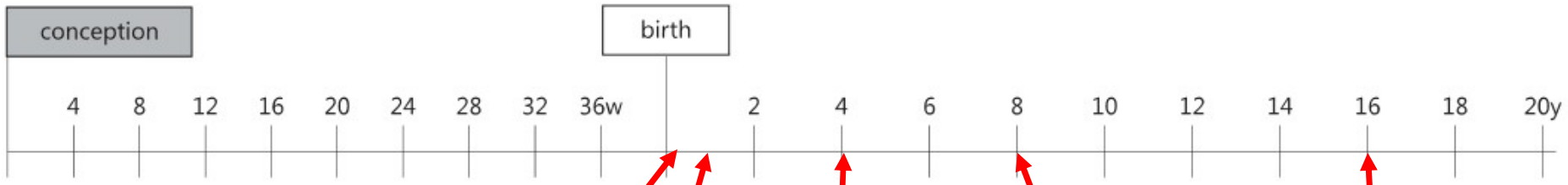
Marie Lannelongue 1984 – 1995
n = 67 ASO, 9.5% with DHCA

Risk factors for low IQ:

- lower parental socioeconomic and educational status
- older age at surgery
- longer hospital stay



2017 Kalfa, JTCVS



BCA study 1988 – 1992
n = 171 ASO

1993 Newburger, NEJM
OR = 11.4 for seizures
if DHCA

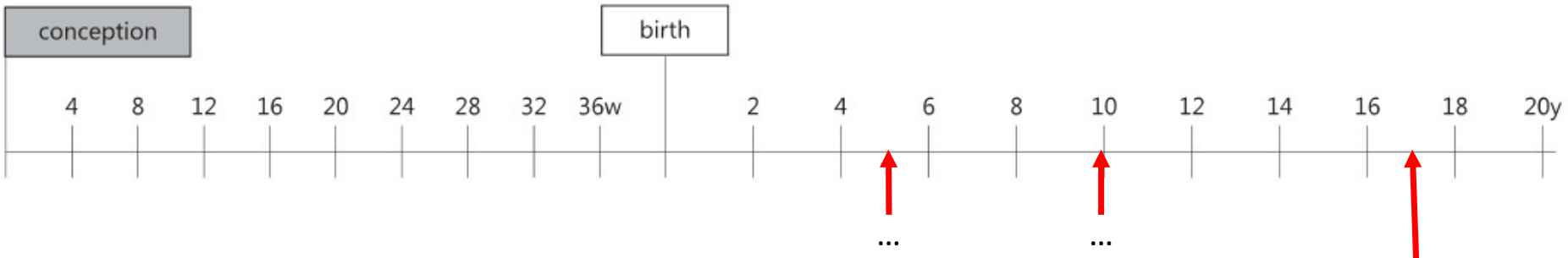
1995 Bellinger, NEJM
Lower PDI if DHCA
PDI ~ DHCA duration

1999 Bellinger, Circulation
Worse motor coordination, speach if DHCA

2003 Bellinger, JTCVS
Worse dexterity, speach,
impulsivity if DHCA

2011, Bellinger, Circulation
33% had MRI abnormalities
65% required remedial
academic or behavioural
treatment

There was a link between VSD and adverse neurological outcome (underwent ASO 11 days later)

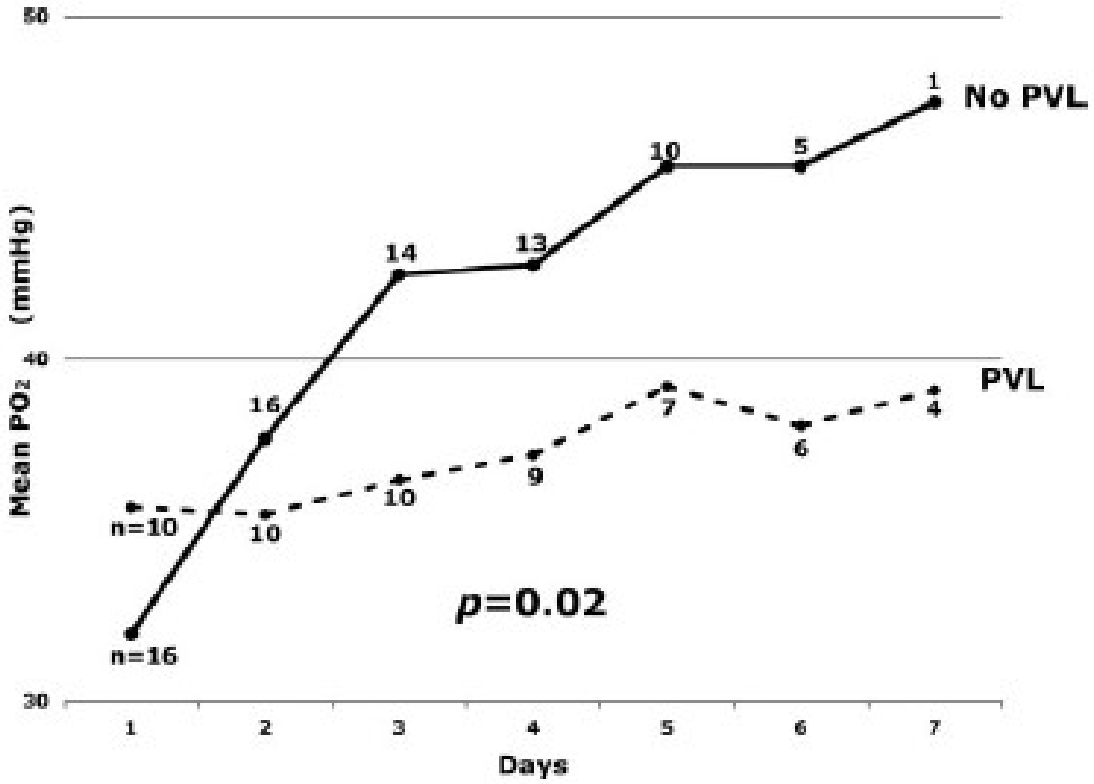


Aachen, 1986 – 1992
n = 96 ASO, low-flow or DHCA

10% neurologic deficit
14% IQ < 85, 11% IQ < 70
57.5% white matter injury
24% reduced brain volume
The only risk factor for neurologic dyfunction and MRI abnormalities was perinatal hypoxia and acidosis

2014 Heinrichs, JTCVS

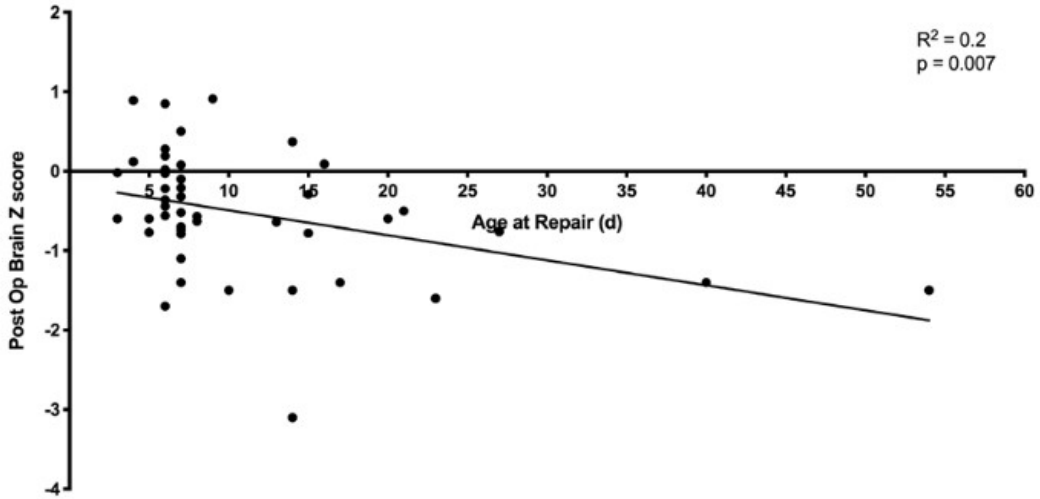
Preoperative cyanosis and periventricular leucomalacia

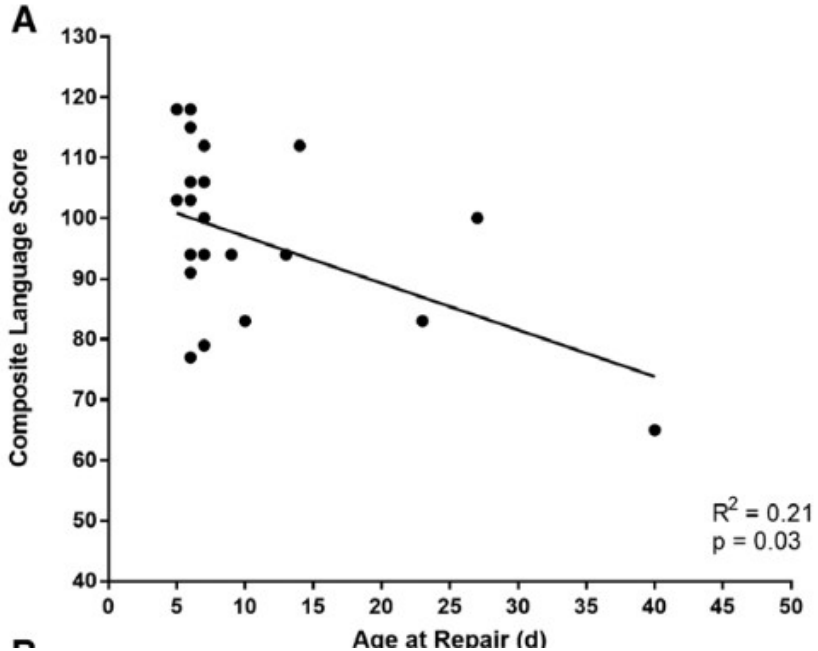


(n = 26)

2009 Petit, Circulation

Neonatal cyanosis and adverse neurodevelopmental outcomes





(n = 45)

2019 Lim, Circulation

Neonatal cyanosis and adverse neurodevelopmental outcomes

Variables	Early (n=32)	Late (n=13)	*P* Value
Gestational age at birth, wk	39 (35 to 41)	39 (36 to 41)	0.44*
Prenatal diagnosis	66%	38%	0.11†
VSD requiring patch closure, individuals	3	4	–
Birth weight, kg	3.3 (2.5–4.2)	3.4 (2.9–4.1)	1.0*
Birth weight *z* score	0.2 (–1.7 to 1.7)	0.1 (–0.9 to 1.4)	0.85*
Preoperative body weight *z* score	0.1 (–1.9 to 2.3)	0.02 (–1.7 to 1.2)	0.42*
Postoperative body weight *z* score	–1.1 (–2.7 to 0.8)	–1.7 (–4.6 to 0.3)	0.05*
Change in body weight *z* score	–1.3 (–1.7 to –0.1)	–1.7 (–4.6 to –0.4)	0.16*
Preoperative saturation, %	86 (70 to 98)	80 (74 to 93)	0.006*
Preoperative intubation, days	1 (0 to 7)	3 (0 to 21)	0.03*
Preoperative ECMO, individuals	0	4	–
Preoperative NEC, individuals	0	2	–
Age at arterial switch operation	7 (3 to 13)	17 (14 to 54)	<0.0001*
Cardiopulmonary bypass time, min	142 (86 to 362)	140 (84 to 197)	0.92*
Aortic cross-clamp time, min	90 (52 to 280)	80 (49 to 142)	0.61*
Deep hypothermic circulatory arrest time, min	0 (0 to 16)	0 (0 to 0)	0.58*
Total support time, min	142 (86 to 362)	140 (84 to 197)	0.92*
Open chest postoperative	44%	31%	0.02†
Days of open chest	0 (0 to 8)	0 (0 to 7)	0.49*
Days of intubation	3 (1 to 18)	2 (1 to 12)	0.47*
Total hospital length of stay, days	15 (7 to 55)	26 (8 to 106)	0.04*
Postoperative length of stay, days	10 (5,49)	11 (6 to 55)	0.44*
Incidence of seizure, individuals	1	2	–
Age at postoperative MRI, days	14 (4 to 30)	25 (21 to 70)	<0.0001*
Total postoperative brain volume, mL	344 (275 to 424)	363 (304 to 408)	0.29*
Postoperative brain weight *z* scores	–0.4 (–1.7 to 0.9)	–0.8 (–3.1 to 0.37)	0.008

2019 Lim, Circulation

Prenatal diagnosis of TGA decreases the risk of brain injury

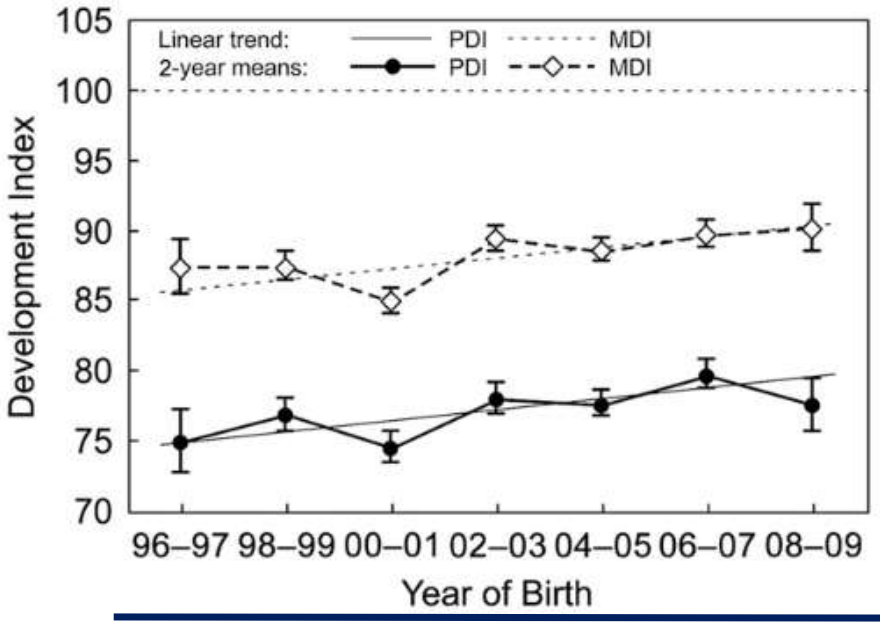
No. With Injury/Total No. With Cardiac Diagnosis (%)		
Postnatal Diagnosis	**Prenatal Diagnosis**	***P* Value[a]**
Any injury		
31/68 (46)	6/28 (21)	.03
White matter injury		
17/68 (25)	3/28 (11)	.09
Stroke		
20/68 (29)	4/28 (14)	.09
Hypoxic-ischemic injury		
1/68 (1)	0	.71

(n = 96)

2016 Peyvandi, JAMA Pediatrics

Is there evidence of improvement over time ?

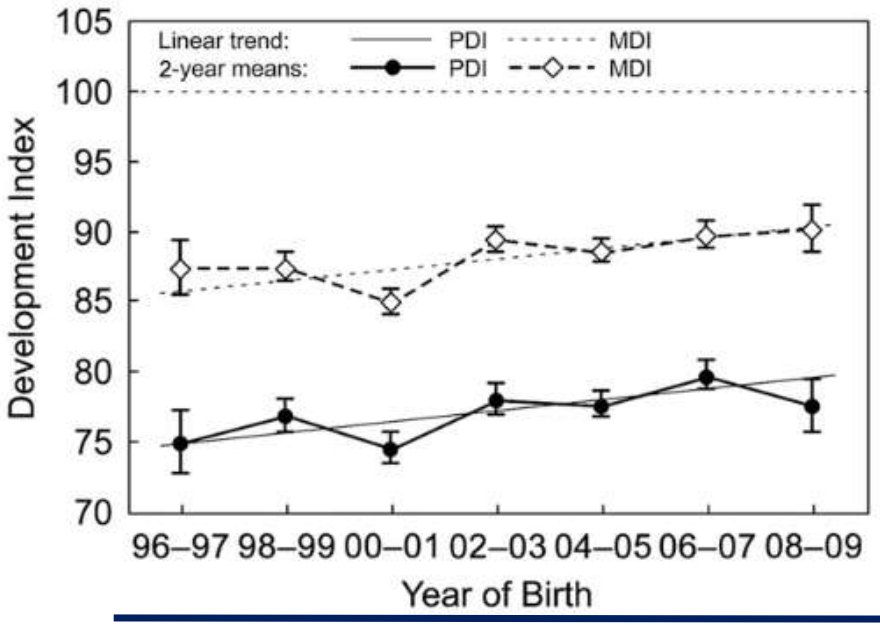
PDI improved by 0.39 points / year
MDI improved by 0.38 points / year



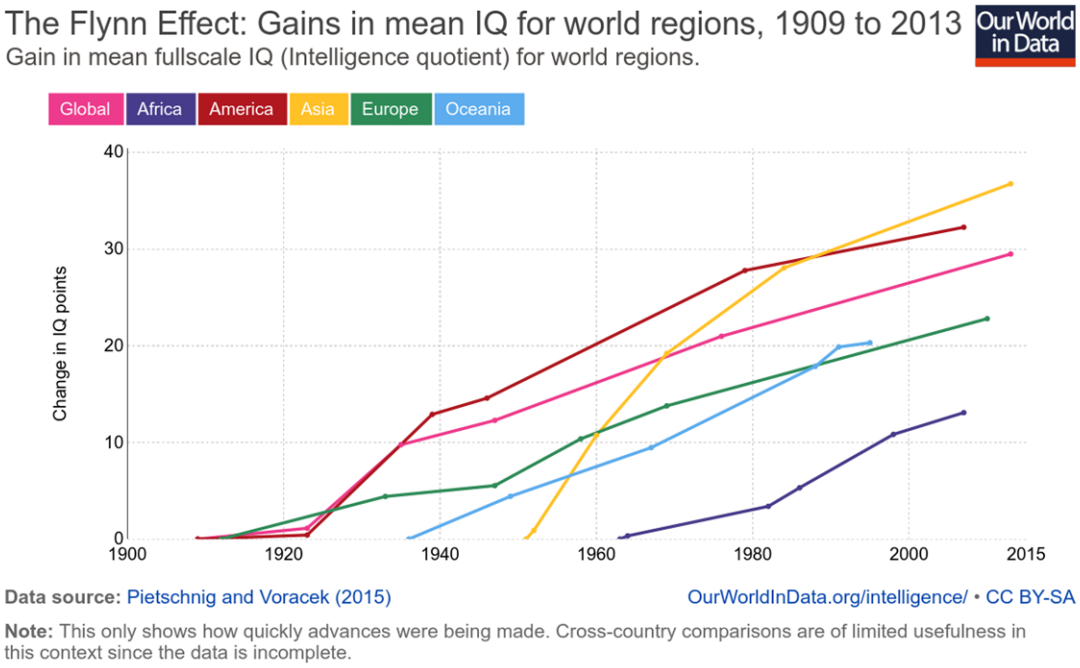
2016 ICCON investigators, JTCVS

Is there evidence of improvement over time ?

PDI improved by 0.39 points / year
MDI improved by 0.38 points / year



Flynn effect in the general population : + 0.3 – 0.5 points / year



2016 ICCON investigators, JTCVS

Other prospective cohorts investigate development of children with surgery for TGA, TOF and VSD

Long-term early development research in congenital heart disease (LEADER-CHD): a study protocol for a prospective cohort observational study investigating the development of children after surgical correction for congenital heart defects during the first 3 years of life

2017 Ferentzi, BMJ Open

Multicenter prospective clinical study to evaluate children short-term neurodevelopmental outcome in congenital heart disease (children NEURO-HEART): study protocol

2019 Ribera, BMC Pediatrics

Operative management for ASO : risk factors of neurological injury

Embolic stroke : venous lines
cooling and rewarming

Inflammation: duration of CPB
transfusions

Neurotoxicity of anesthetic agents

Operative management for ASO : risk factors of neurological injury

Embolic stroke : venous lines cooling and rewarming	Favour normothermia
Inflammation: duration of CPB transfusions	Miniaturisation of the CPB circuits
Neurotoxicity of anesthetic agents	Dexmedetomidine ?

Dr Yves Durandy

Normothermia for ASO

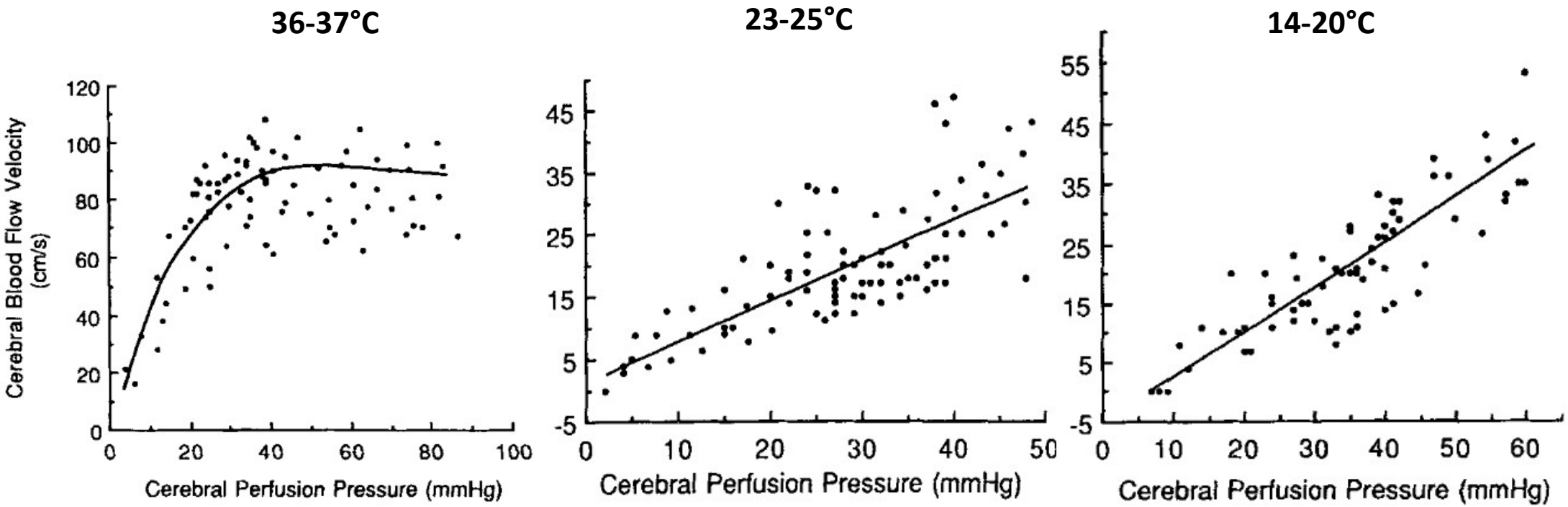
	N-CPB	H-CPB	*P* value
VASOACTIVE INOTROPIC SCORE			
PICU arrival	9.7 ± 5.9	13.4 ± 7.9	<0.005
After 4 h	7.0 ± 5.2	11.1 ± 7.3	<0.001
After 24 h	2.8 ± 3.6	5.2 ± 4.9	<0.005
ARTERIAL pH			
PICU arrival	7.33 ± 0.09	7.30 ± 0.09	0.046
After 4 h	7.35 ± 0.07	7.32 ± 0.07	0.022
After 24 h	7.37 ± 0.05	7.35 ± 0.05	0.01
LACTATE			
PICU arrival	1.9 ± 1.1	2.9 ± 2.7	0.01
After 4 h	1.7 ± 0.6	2.4 ± 2.2	0.03
After 24 h	1.1 ± 0.5	1.6 ± 1.5	0.048
Mechanical ventilation (hours)	22 ± 27	48 ± 57	0.003
PICU stay (hours)	61 ± 46	87 ± 69	0.021

	N-CPB	H-CPB	*P* value
IN OPERATING ROOM (mL/kg)			
RBC	8.6 ± 7.0	12.2 ± 7.0	0.007
FFP	3.4 ± 4.8	5.7 ± 6.8	0.034
Cryoprecipitate	1.3 ± 4.1	3.3 ± 5.9	0.031
Platelets	2.7 ± 4.9	5.1 ± 6.4	0.018
FIRST 24 h IN PICU (mL/kg)			
RBC	6.4 ± 9.5	7.0 ± 9.9	0.371 (NS)
FFP	4.6 ± 6.9	5.7 ± 6.8	0.202 (NS)
Cryoprecipitate	1.3 ± 3.2	2.7 ± 4.7	0.046
Platelets	1.9 ± 3.6	3.6 ± 4.9	0.029
CHEST DRAINS LOSSES (mL/kg)			
PICU arrival	1.5 ± 1.4	2.5 ± 2.7	0.013
After 4 h	7.8 ± 6.0	10.9 ± 8.7	0.025
After 24 h	23.0 ± 12.0	27.9 ± 15.2	0.043

(n = 99, 10 ASO)

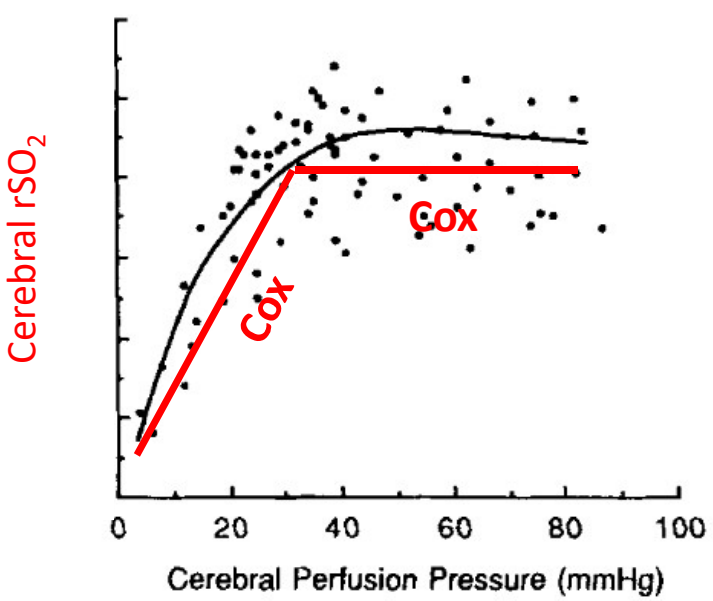
Corno, Front Ped 2018

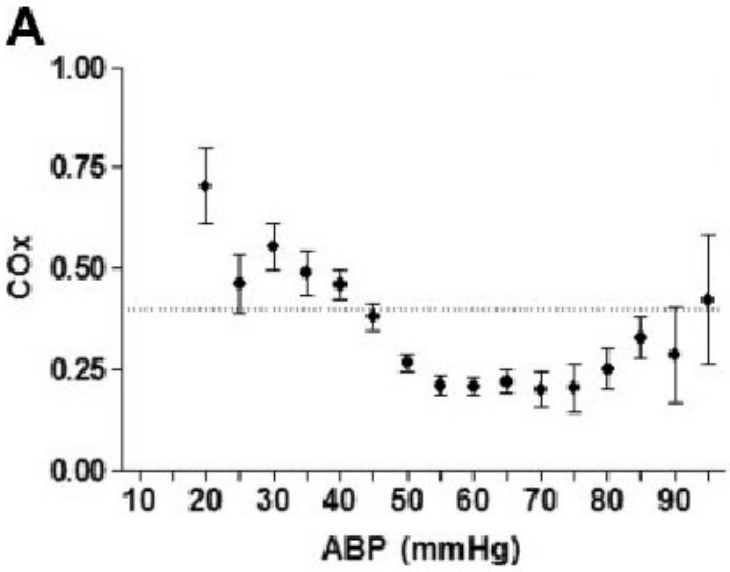
CPB temperature and the maintenance of the cerebral blood flow autoregulation



1992 Taylor, Anesth Analg

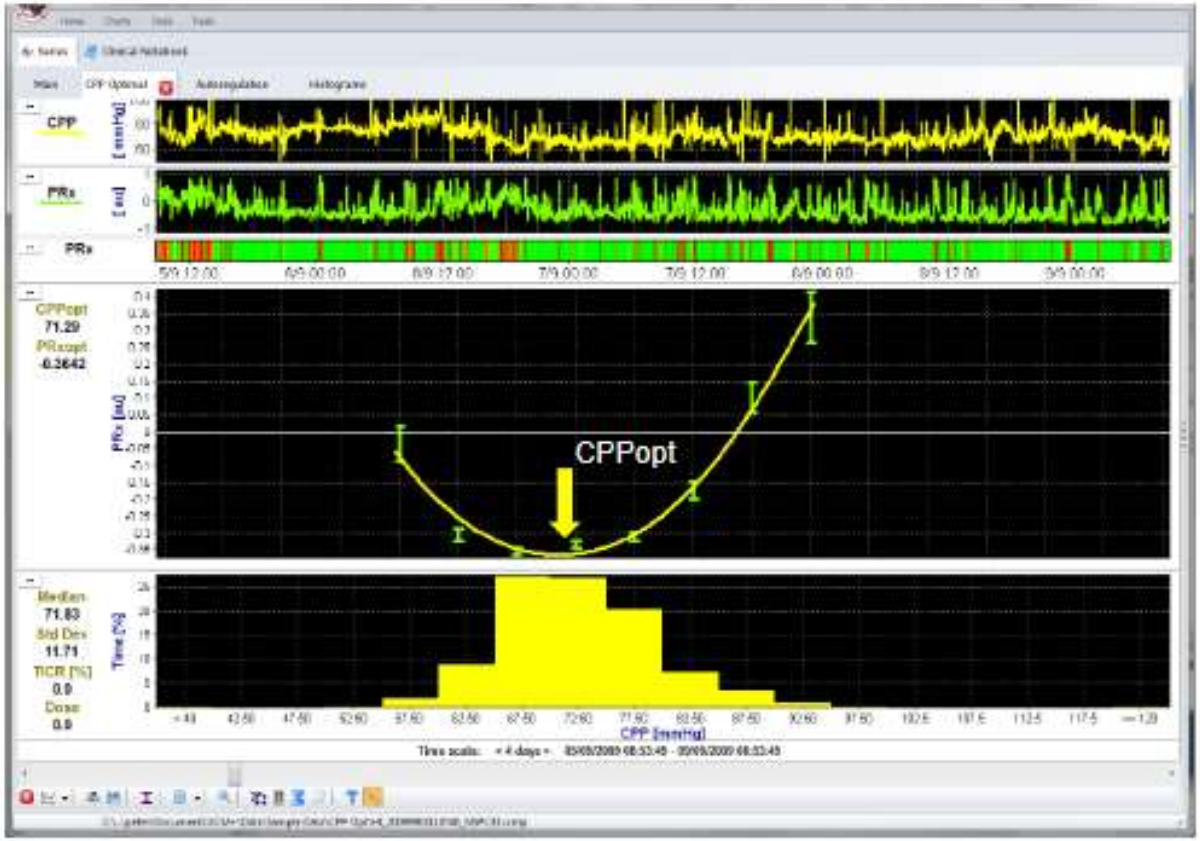
Monitoring CBF autoregulation with cerebral NIRS





2010 Brady, Stroke

Monitoring CBF autoregulation with cerebral NIRS



2005 Smielewsky, Acta Neurochir

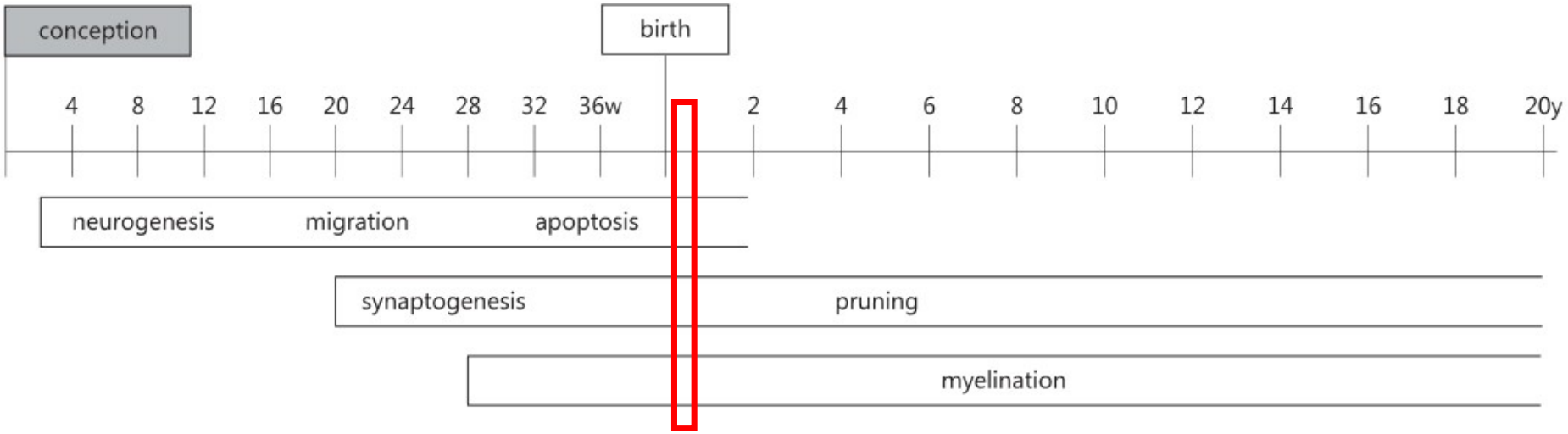
Continuous Cerebral Perfusion for Aortic Arch Repair: Hypothermia Versus Normothermia

	Hypothermia (≤ 28°C), N = 70	Normothermia (≥ 34°C), N = 40	*p* Value
Cerebral perfusion			
PTFE graft	4	27	
Aortic cannulation	66	13	
Techniques of repair			
Direct anastomosis	13	20	
RV/PA conduit	30	6	
Pericardial patch	6	7	
Pulmonary artery patch	20	6	
Subclavian artery patch	1	1	
Status at end of operation			
Aortic clamp (min)	87.9 ± 31.2	61.7 ± 29.3	0.0001
CPB time (min)	173 ± 71.3	112.3 ± 64.8	0.0001
Flow of cerebral perfusion (mL/kg/min)	47.9 ± 23.3	52.7 ± 27.9	0.18
Perfusion pressure (mm Hg)	53.7 ± 8.3	49.3 ± 8.6	0.012
Duration of perfusion (min)	32 ± 11.9	26.3 ± 9.1	0.0015
Delayed sternal closure (%)	75	65	0.32

no clinical or electrical EEG anomaly

2011 Ly, ATS

Anesthetic neurotoxicity in neonates



Tymofiyeva, Br J Radiol 2014

1999, Ikonomidou, Science : **ketamine** increases neuroapoptosis by 15 – 40 x in neonatal rats

2003, Jevotovic-Todorovic, J Neuroscience: clinical concentrations of **NO_2, isoflurane** and **midazolam** during 6 hours increase neuroapoptosis by 20 - 60 x in neonatal rats

Agent	GABA	NMDA	μ-Opioid	α_2-Adrenergic
Halogenated anesthetics (sevoflurane, isoflurane, desflurane)	+			
Nitrous oxide		−		
Benzodiazepines	+			
Propofol	+			
Barbiturates	+			
Etomidate	+			
Chloral hydrate	+			
Ketamine		−		
Opioids			+	
Dexmedetomidine				+

GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate; +, agonist; −, antagonist.

1999, Ikonomidou, Science : **ketamine** increases neuroapoptosis by 15 – 40 x in neonatal rats

2003, Jevotovic-Todorovic, J Neuroscience: clinical concentrations of **NO_2, isoflurane** and **midazolam** during 6 hours increase neuroapoptosis by 20 - 60 x in neonatal rats

Agent	GABA	NMDA	μ-Opioid	α_2-Adrenergic
Halogenated anesthetics (sevoflurane, isoflurane, desflurane)	+			
Nitrous oxide		–		
Benzodiazepines	+			
Propofol	+			
Barbiturates	+			
Etomidate	+			
Chloral hydrate	+			
Ketamine		–		
Opioids			+	
Dexmedetomidine				+

GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate; +, agonist; –, antagonist.

Neurotoxicity of anesthesia in early infancy

2009 Wilder, Anesthesiology (n = 5357)
Single anesthesia exposure < 4 years of age did not increase the risk of 5-year learning dysabilities
Repeat anesthesia : HR = 1.59
≥ 3 anesthetics : HR = 2.60

2016 Sun, JAMA, the PANDA study (n = 105 sibling pairs)
Single anesthesia exposure < 3 years of age has no impact on IQ scores later in childhood

2019 McCann, Lancet, the GAS study (CRT, n = 722):
Slightly less than 1 hour of general anesthesia exposure < 5 month of age does not alter the 5-year neurodevelopmental outcome when compared with awake spinal anesthesia

Dexmedetomidine as a neuroprotectant in anesthetic neurotoxicity

2009, Sanders, Anesthesiology
DEX attenuates iso-flurane induced neurocognitive impairment in neonatal rats

Postoperative management

PDI

Variable	Operative Management Final	Postoperative Final
Total support duration per min	−0.025 [−0.042 to −0.007] (0.005)	−0.003 [−0.021 to −0.016] (0.78)
ECMO or VAD	.	−4.5 [−8.6 to −0.4] (0.03)
Hospital length of stay, d	.	(< 0.001)
0–9 (reference)	.	.
10–15	.	−1.2 [−3.8 to 1.4] (0.37)
16–26	.	−3.7 [−6.6 to −0.8] (0.01)
27–286	.	−9.7 [−12.9 to −6.5] (< 0.001)

MDI

Variable	Operative Management Final	Postoperative Final
Total support duration per min	−0.023 [−0.038 to −0.007] (0.004)	−0.008 [−0.024–0.009] (0.35)
ECMO or VAD	2.4 (0.02) [0.4–4.3]	3.7 [1.6–5.7] (< 0.001)
Hospital length of stay, d	.	−6.3 [−9.9 to −2.7] (< 0.001)
0–9 (reference)	.	(< 0.001)
10–15		-
16–26		−3.9 [−6.2 to −1.7] (< 0.001)
27–286		−4.2 [−6.8 to −1.7] (0.001)
		−7.9 [−10.8 to −5.1] (< 0.001)

2016 ICCON investigators, JTCVS

Conclusions

Neurodevelopmental impairment is a prevalent complication of ASO, and there has been little improvement during the last decades

Genetic abnormalities and preoperative management (duration and amplitude of desaturation) have huge impact on the future neurodevelopment

There are several advantages of providing normothermic CPB during ASO

Further investigations are necessary in order to develop a strategy to limit the neurotoxicity of anesthesia during neonatal cardiac surgery