A growing body of evidence suggests that preoperative hypoxia in patients with congenital heart disease (CHD) has significant impact on subsequent postoperative outcomes including, most importantly cerebral damage and, yet not the least, myocardial and renal dysfunction. Furthermore, the complexity, duration and number of surgical procedures required, constitute a considerable drawback for the developing brain. As a result the approach of complete repair in the neonatal period has been adopted in order to establish a normal circulation as soon as possible.

Although hypoxia does not appear to affect early stages of intrauterine life, oxygen becomes a prerequisite for the normal foetal development after the second trimester of gestation. Transient reductions of maternal oxygen supply are compensated through homeostatic redistribution of foetal blood flow to the brain, heart and adrenals while perfusion of the gastrointestinal tract, the kidneys and the lower limbs is reduced. If exposure to hypoxia during this stage is prolonged, up-regulation of adaptive mechanisms against oxidative stress takes place. Epigenetic regulation (DNA methylation and demethylation, microRNA's and histone modifications) may affect in-utero stress-induced neuronal and vascular cerebral developmental plasticity in foetuses with CHD, establishing hence a hypoxic/ischaemic sensitive phenotype in the maturing brain.

Reduced oxygen supply during midgestation affects cortical development in infants with CHD due to reduced neuroblast migration from the supraventricular zone (SVZ). Experimental evidence suggests that neural stem/progenitor cells from SVZ have the potential of migration to the injured site of the brain and differentiation into interneurons, restoring thus cortical tissue.

After birth, infants with CHD experience a complex of developmental and destructive neurological disturbances dominated by cerebral white matter injury (WMI) a condition similar to periventricular leucomalacia (PVL) of preterm infants. Regional brain biochemistry modifications resulting from injury or developmental processes detected by novel optical spectroscopy techniques and brain microstructure alterations estimated through magnetic resonance imaging (MRI) suggest that reduced cerebral oxygen supply slows myelination as a result of destruction of premyelinating oligodendrocyte progenitor cells (pre-OL). This type of glial cell begins to proliferate during the third trimester and presents intrinsic and extrinsic susceptibility to oxidative stress. Nonetheless brain microstructure may be altered in infants with CHD, even in the absence of visible injury on MRI.

A normothermic, full-term neonate responds to hypoxia with transient hyperventilation, which is sustained in the case of persistent hypoxaemia in the context of critical CHD. As a result more than half of newborns with severe CHD are found to bear acquired focal neurologic abnormalities before surgery. Preoperative MRI studies suggest that white matter vulnerability may be related to hypoxia-induced damage in utero. During the last decade, increased attention has been drawn to the fact that in the context of CHD perinatal and preoperative periods are critical for the development of cerebral injury. Apart from the nature of heart defects per se that affect the...
oxygen saturation of the blood supplied to the brain, the length of time of this deleterious exposure obviously renders timing of surgery very important.

Hypoxia associated with CHD leads to brain-sparing hemodynamic redistribution of cerebral blood flow as appears from Doppler measurements of anterior cerebral artery (ACA) pulsatility in foetuses with Transposition of the Great Arteries (TGA) and Hypoplastic Left Heart Syndrome (HLHS) (7). Although these flow adaptations do not ensure a normal postnatal neural and cognitive development, nonetheless, there is evidence that many of the pre- and immediate postoperative lesions resolve within 6 months following surgery (15).

Lynch et al. have previously reported that preoperative cerebral tissue oxygen saturation (ScO₂) in infants with TGA and HLHS is negatively correlated with a longer time interval between birth and surgery and is associated with an increased risk for postoperative WMI presenting as new or worsening periventricular leukomalacia (PVL) (16). These results are further supported by the results of a recent cohort study from the same group (17). Lynch et al. observed a substantial decrease in ScO₂ of −2.2% per day in this patient population. Decreased oxygenation was associated with an increase in oxygen extraction, without yet compensatory increase in cerebral blood flow.

In spite, however, the compiling evidence of the time related detrimental effect on the brain of preoperative hypoxia in patients with critical CHD, additional factors should be taken in account while planning treatment. Other organs e.g., liver, kidneys may similarly sustain early hypoxic insult and adequate time is required for them to recover, a prerequisite for surviving a successful repair procedure. Apparently, optimal operative strategy, as regards to timing, is defined as the time interval that provides the best chance of survival in conjunction with the least adverse effects (18).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

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