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The Premature Fetus: Not as Defenseless as We Thought, but Still Paradoxically Vulnerable?

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Key Words
Asphyxia • Cardiovascular responses • Cerebrovascular responses • Fetal sheep • Prematurity

Abstract
Traditionally, it has been believed that the cardiovascular and hormonal responses to asphyxia in preterm fetuses are immature, and this immaturity contributes to their apparent vulnerability to neural injury. However, these data were derived from studies using relatively mild insults, which did not allow for the greater cardiac glycogen reserves and anaerobic capacity of the brain near midgestation. Here, we review the maturation of the cardiovascular and cerebrovascular and cerebral responses to asphyxia in experimental animals and how these relate to the apparent vulnerability of the human premature brain. Most such investigations have been performed in the chronically instrumental fetal sheep. Recent studies have demonstrated that the premature fetus has highly adaptive and relatively mature responses to asphyxia, and that in absolute terms the preterm brain is very resistant to asphyxial injury. These data suggest that the premature fetus is able to survive much more prolonged periods of asphyxia than the near-term fetus, but that, paradoxically, such survival is associated with exposure to prolonged periods of hypotension and hypoperfusion and consequently greater risk of severe neural damage.

Introduction

Neural injury of the preterm fetus and infant continues to be a significant problem. As recently reviewed, it is now clear that more than 70% of cerebral palsy is related to prepartum events, many of which occur in the midgestational period [1]. Further, the improved care of very premature infants in intensive care units has led to a progressive improvement in survival that has not been matched by a corresponding improvement in age-specific morbidity. Thus, the number of premature infants surviving with neurodevelopmental impairment has increased [2]. In many premature infants, the very early development of cerebral lesions after birth implicates a prenatal insult [3]. Periventricular white matter injury (periventricular leukomalacia) and hemorrhage into white matter (periventricular-intraventricular hemorrhage) are the major
Fig. 1. Schematic showing the current ‘vulnerable fetus’ paradigm for the high rate of neural injury in the premature brain. The fetus is exposed to a number of adverse factors including asphyxia, hypotension, and chorioamnionitis. Limited fetal defenses and critical developmental events occurring near midgestation, such as active proliferation and differentiation of multipotential cells and pre-oligodendrocytes, in turn, are postulated to increase the vulnerability of the fetus to cerebral damage. Immaturity of the fetal cardiovascular and cerebrovascular responses is believed to be an important factor, compromising the ability of the preterm fetus to maintain oxygen delivery to the brain. We propose an alternative view of the contribution of these fetal responses to neural injury.

Maturational Changes in Fetal Responses to Asphyxia

Limited previous data have suggested that there are maturational differences in the fetal responses to hypoxia; however, the insults used in early experimental studies were relatively moderate. In the premature fetal sheep before 100 days (0.7) gestation, isocapnic hypoxia [7] and hemorrhagic hypotension [8] are not associated with the hypertension, bradycardia, or peripheral vasoconstriction which are seen in the near-term fetus. Similarly, hypoxic release of cortisol also appears to be greatly reduced before 100 days [9]. Furthermore, although the 0.6 gestation fetus is able to increase cerebral blood flow (CBF) during moderate hypoxia, in contrast to the near-term fetus, this increase is not sufficient to fully maintain oxygen availability to the brain. Cerebral oxygen consumption is therefore sustained in part by an increase in fractional oxygen extraction [10]. The mechanisms mediating this blunted hypoxic vasodilatation in immature fetuses are not known.

Based on these data, it has been suggested that peripheral vasomotor control starts to develop at 0.7 gestation, coincident with maturation of neurohormonal regulators and chemoreceptor function [11, 12]. However, when interpreting these results it is important to consider that the premature brain has both reduced basal oxygen consumption [13] as well as a much greater capacity to maintain cellular energy requirements through anaerobic metabolism [14]. It is likely that the degree of hypoxia attained in these earlier studies did not reduce tissue oxygen availability below the critical threshold for this developmental stage.

The responses to asphyxia depend on the severity of the insult. During moderate asphyxia, the near-term fetus responds with redistribution of blood flow away from the periphery to essential organs such as the brain and the heart [15]. During profound asphyxia, corresponding with a severe reduction of uterine (or umbilical) blood flow to less than 25%, the cardiovascular responses of the normal fetus are substantially different. Bradycardia is sustained and there is a generalized vasoconstriction involving essentially all organs [15]. Under these conditions, CBF does not increase or might even decrease despite initially increased fetal blood pressure. This restriction of CBF is due to a significant increase in cerebral vasoconstriction [15, 16]. This is accompanied by redistribution of blood flow within the brain towards the brainstem, which would maintain autonomic function at the expense of the cerebrum [12]. As asphyxia continues, the contributors to mortality and neurodevelopmental impairment in premature infants [4]. Such white matter damage is strongly associated with impairment in cortical development [5]. Established clinical associations include evidence of hypoxic-ischemic insults such as asphyxia, hypotension, or hypocarbia (which causes cerebral vasoconstriction) and exposure to chorioamnionitis [4]. The current paradigm of neural injury in the premature infant may be termed ‘the vulnerable fetus’ (fig. 1). In this paradigm, the fetus is exposed to potential adverse events at a critical period of cardiovascular and cellular immaturity [4, 6].

The present review will highlight recent data that suggest an alternative view of the role of the fetal responses. We hypothesize that the premature fetus has both high cardiac and neural tolerance to asphyxia but that these adaptations permit the fetus to survive extraordinarily prolonged insults, which result in exposure to severe hypotension and hypoperfusion, and that it is the increased duration of the resulting hypoxia-ischemia which is the significant link with an increased risk of neural injury.
initial rise in blood pressure is followed by hypotension, with a parallel fall in CBF. The combination of impaired CBF and very low oxygen content severely reduces cerebral oxygen consumption [15].

Survival during profound asphyxia is a function of cardiac glycogen levels which are maximal near midgestation in the fetal sheep (and humans), and which decline towards birth [17]. Typically, the near-term fetus will survive 10–12 min of severe asphyxia [16]. In contrast, the premature fetus at 0.6 gestation can survive up to 30 min (fig. 2) [18, 19]. While the premature fetal response to hypoxia appears to be different to that at term, the response to asphyxia is similar to that seen in more mature fetuses, with sustained bradycardia, accompanied by circulatory centralization, initial hypertension, and then a progressive fall in blood pressure [16, 19]. Similar to the term fetus, there was no initial increase in blood flow to the brain and again this was due to a significant increase in vascular resistance rather than hypotension [19].

As shown in figure 2, once blood pressure begins to fall below baseline, CBF falls in parallel, similarly to the near-term fetus [16, 19]. The fall in pressure is partly a function of failure of redistribution of blood flow at this time with a rise in femoral blood flow. The mechanisms mediating this loss of redistribution are unknown, but are likely to relate to profound local peripheral acidosis. In the latter half of a maximal interval of asphyxia in the preterm fetus, there is a progressive decrease in cardiac output, with a fall in both central and peripheral perfusion. This phase is likely to be much shorter in duration at term, as glycogen stores in the term fetus are depleted more quickly [16]. Thus, as a consequence of its extended survival, unlike the term fetus, the preterm fetus is exposed to pro-

Fig. 2. The relationship between mean arterial blood pressure (MAP) and carotid and femoral blood flow (CaBF and FBF) during complete umbilical cord occlusion for 30 min in the 0.6 gestation fetal sheep. The start and end of occlusion are shown by the shaded area. Note that the CaBF begins to fall only when MAP is below baseline levels, and thereafter paralleled the changes in MAP very closely. It is interesting that this rapid decline in CaBF also corresponds with failure of peripheral vasoconstriction (shown by the secondary rise in FBF during occlusion) [19].
found and prolonged hypotension and hypoperfusion during ongoing asphyxia. This is the major difference in the responses to asphyxia between the term and preterm fetus.

It can be speculated that during this final phase of asphyxia in the preterm fetus there is a catastrophic failure of redistribution of blood flow within the brain which places previously protected areas, such as the brainstem, at risk of injury. This hypothesis is consistent with clinical reports showing a pattern of subcortical injury after asphyxia in the preterm fetus [20]. Following asphyxia, a brief period of arterial hypertension and hyperperfusion is followed by a prolonged period of hypoperfusion, despite normalization of blood pressure. This secondary fall in CBF is paralleled by a reduction in total blood volume, as indicated by near-infrared spectroscopic measurements. Furthermore, there is a transient reduction in cerebral oxygenation, indicating a true reduction in perfusion relative to cerebral requirements [19]. This post-asphyxial hypoperfusion and impaired cerebral oxygenation might contribute to further cerebral injury.

**Cellular Maturation and Sensitivity to Injury**

Surprisingly little work has been accomplished to define the precise effect of maturation on sensitivity to injury. The immaturity of oligodendrocytes and their precursors has been highlighted by many investigators, since the period of greatest risk for periventricular leukomalacia in premature infants is at a time when oligodendrocyte precursors are actively proliferating and differentiating [4]. In vitro studies have suggested that developing oligodendroglia are particularly vulnerable to free radical toxicity because of a developmental lack of antioxidant enzymes to protect against oxidative stress [21, 22]. Although this phenomenon might affect the differential sensitivity between cell types, in isolation such data do not prove that the premature brain is necessarily more vulnerable to injury than near-term fetuses or newborn infants. Indeed, the reverse appears to be the case in short-term studies of defined hypoxic-ischemic insults. The near-term fetal sheep develops severe selective hippocampal neuronal loss after just 10 min of umbilical cord occlusion [23]. In contrast, after 10 or even 20 min of cord occlusion at 0.6 gestation there is rapid recovery of EEG activity and no neuronal (or glial) loss [18, 23]. However, when asphyxia is continued for 30 min at 0.6 gestation, there is prolonged suppression of the EEG [19], and, on preliminary analysis, selective neuronal and white matter injury in subcortical structures sparing the cortex [24].

These differences are primarily related to neural maturation, since a similar relationship is seen with pure ischemic insults, with greatly reduced neural injury in the preterm fetus after short periods of ischemia [25, 26]. At 0.65 gestation, a maturation approximately equivalent to the 28-week human fetus, 30 min of cerebral ischemia leads to the development of subcortical infarction involving the deeper layers (V and VI) of the cortex and underlying white matter tracts [26]. In contrast, the same insult in the near-term fetal sheep leads to severe neuronal loss which is greatest in the superficial layers (II, III and IV) of the cortex [25]. This difference is consistent with the stages of anatomical maturation. As neurons migrate into the cortex during development, the deeper layers are populated first and thus mature first, while the superficial layers include immature, migrating neurons which are less metabolically active and are still using primarily anaerobic pathways [27], and which have less mature receptors for excitatory neurotransmitters [28].

**Long-Term Consequences**

The experimental studies discussed above have examined relatively short-term outcomes, typically 72 h after asphyxia. There are only limited data on the long-term consequences of different insults. Clinically, apparently isolated periventricular leukomalacia in premature infants is associated with markedly reduced gray matter volume at term [5]. It is likely that the impact of asphyxial insults at midgestation may be further amplified if, for example, immature and multipotential cell lines that can still divide are either lost or undergo premature differentiation, or if the development of neuronal connections is affected. Consistent with this, moderate hypoxia near midgestation in the fetal sheep not only reduced neuronal numbers in the hippocampus and cerebellum after 35 days recovery but also reduced the number of neural processes in regions that were still immature at the time of hypoxia, such as the cerebellum [29].

**Conclusions**

There appears to be a paradoxical relationship between the vulnerability of the fetus to asphyxia and subsequent neural injury. The data discussed above suggest that even the near-midgestation fetus demonstrates relatively mature and effective cardiovascular defenses against asphyxia, and is able to survive much longer insults than is possi-
ble near term. Furthermore, the premature brain is surprisingly resistant to defined ischemic or asphyxial insults. However, the greater cardiac glycogen reserves of preterm fetuses provide means to survive much longer periods of profound asphyxia. This ability to survive prolonged exposure to severe asphyxia with secondary cerebral hypoperfusion paradoxically increases the risk of gray and white matter injury. It is critical that future studies examine the long-term impact of well-defined prenatal insults on neural growth and development.

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