ANAESTHESIA AND BABIES

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Age is an important risk factor when discussing anaesthesia morbidity and mortality. The risks of anaesthesia are greater in neonates and infants, even in expert hands[1,2]. This presentation will consider the physiology of the neonate and the premature infant in an attempt to explain this particular vulnerability. In addition to the dramatic physiological changes in the transition from intrauterine to extrauterine life at birth, the newborn infant undergoes a period of rapid maturational development, particularly in the first few months of life. Recent research indicates that experiences during this period of rapid development may have lifelong effects[23].

Physiology of the neonate

The full term neonate is defined as a child born between 37-40 weeks gestation and less 1 month of age, the premature neonate a child born before 37 weeks gestation, the infant a child from 1 month to 1 year of age. Prematurity is defined as a gestational age of less than 37 weeks - extreme preterm infants are born between 23 weeks (limit of viability) and 27 weeks. Premature infants may be low birthweight (<2.5kg), very low birth weight (VLBW) (<1.5kg) or extremely low birth weight (ELBW) (<1.0kg).

Cardiovascular function [3]

Transitional circulation. Fetal life is characterised by the presence of fetal shunts (ductus arteriosus, sinus venosus and foramen ovale). These enable blood to bypass the non-aerated lungs such that in the foetus, less than 10% of the right ventricular output passes through the lungs. Pulmonary vascular resistance (PVR) is high, systemic vascular resistance (SVR) low. At birth, the situation is reversed - clamping of the umbilical vessels results in a dramatic increase in SVR at the same time as the first breaths are taken and PVR drops. Pulmonary blood flow increases, pulmonary venous return and pressure in the left atrium increase; the flap valve covering the foramen ovale closes. The arterial duct constricts in response to oxygenation, later fibrous occlusion occurs over several weeks. Patent arterial duct (PDA) is seen in 50% of VLBW infants due to inadequate constrictor muscle in the immature duct and deficient metabolism of prostaglandins that maintain ductal patency. Left to right shunting results and is a risk factor for respiratory distress syndrome, intraventricular haemorrhage, nectrotising enterocolitis and poor outcome.

Pulmonary vessels in the fetus are well muscularised when compared to similar arteries in the adult. The oxygen tension in fetal lung is 3kPA; the high PVR in fetal life results mainly from hypoxic pulmonary vasoconstriction. Physiological control of PVR is also modulated by the balance between endothelial derived factors such as endothlin[1] and leucotrienes (vasoconstrictor) and nitric oxide (NO) and prostaglandins (vasodilator). At birth, the newborn lung is exposed to oxygen and vasodilatory mediators and the PVR is dramatically reduced. Further reduction of PVR takes place due to involution of smooth muscle in the pulmonary arterial walls. The PVR remains relatively high in neonates (estimated PVRI 3-5 Wood units/m^2) only reaching adult levels (PVRI 0.8-1.9 Wood units/m^2) at about 2 months of age. The relatively high PVR in neonates explains why infants with significant left to right shunts may not become symptomatic until a few months of age. The pulmonary vasculature of the neonate remains sensitive to vasoconstrictor effects, for instance due to hypoxia, hypercarbia and acidosis. Severe pulmonary hypertension may ensue, with reopening of the fetal shunts (foramen ovale/ductus arteriosus), profound hypoxia and cardiovascular compromise. Conditions which predispose towards this condition, Persistent Pulmonary Hypertension of the Newborn (PPHN), include congenital diaphragmatic hernia, meconium aspiration, asphyxia, hypoxia and sepsis. Management includes optimising oxygenation and ventilation (avoiding over/underinflation, loss of synchronisation), sedation, inotropic support, inhaled nitric oxide and high frequency oscillatory ventilation (HFOV) and occasionally extracorporeal membrane oxygenation (ECMO).

Immature myocardium. The right ventricle and left ventricles in term neonates are symmetrical with the right ventricle forming the apex of the heart. Chamber proportions change in response to the haemodynamic workload of the heart - by three months the left ventricle is dominant, as in adults. The cardiac myocytes multiply in number in the first seven months of life (hyperplasia), thereafter cardiac weight increases due to hypertrophy of cardiac myocytes.

The immature myocyte is spherical in shape with disorganised intracellular contractile elements, immature sarcolpasmic reticulum and disorganised supporting extracellular matrix. The myocardium therefore has limited functional reserve, is dependent on extracellular calcium for contraction (ionised hypocalcaemia is poorly tolerated) and is relatively stiff and non-compliant. Functional reserve

increases in the first few days of life with an increase in stroke volume. The Frank-Starling relationship regulates cardiac output as in adults and neonates do increase cardiac output with careful volume loading, especially after the first few weeks of life. Contractility in neonates is high due to high sympathetic tone, especially around the time of birth, and this also explains the high resting heart rate of neonates. Cholinergic innervation is also well developed at birth and vagally mediated cardiac reflexes are well developed even in premature infants. Analysis of heart rate variability indicates that parasympathetic control becomes more important with age (reduction in heart rate). Heart rate is an important determinant of cardiac output and the heart rate should be maintained in the normal range (120-180bpm, term neonate). Afterload is also a major determinant of left and right ventricular output. The SVR in a healthy term neonate has been estimated to be 244mmHg/l/min (mean 723mmHg/l/min in healthy young adults).The neonatal heart is exquisitely sensitive to increases in SVR or PVR. Ventricular interdependence may exaggerate the effects of increased afterload. Neonates respond to inotropes in a predictable manner - dopamine, dobutamine and adrenaline are commonly used, milrinone especially useful after cardiac surgery.

Cardiovascular immaturity results in neonates being more sensitive to the negative inotropic effects of anaesthetic agents than older children. Volatile anaesthetics all reduce myocardial contractility due to an effect on intracellular calcium release; contractility decreases in a dose dependent manner, the effect more marked with halothane than isoflurane or sevoflurane. The infant baroreceptor reflex is poorly developed and abolished by anaesthesia. Atropine may counteract the reduction in cardiac output seen with volatile agents and will protect against vagally mediated reflexes.

Respiratory function[4,5]

Control of ventilation. Periodic breathing is a feature of newborn infants. The ventilatory response to hypercapnia is blunted in the first few weeks of life. Neonates respond to hypoxia by a brief increase in ventilation followed by apnoea. The apnoeic response to hypoxia is probably due to respiratory muscle fatigue or upper airway obstruction. However, by three weeks of age in the term infant, with maturation of the chemoreceptor centres, hypercapnia and hypoxia cause a sustained increase in breathing, as seen in adults.

Anaesthetic agents depress ventilation in a dose dependent manner. Neonates are thus at risk from postoperative apnoeas, especially if born prematurely, especially if anaemic. There is little evidence with respect to term neonates, but it generally accepted that the risk of postoperative apnoea after routine minor surgery is low at 44 weeks post conception. However, in premature neonates the probability of postoperative apnoeas decreases to less than 1% only at 60 weeks post conception[6].

Lung development. Development of the lung starts early in embryonic life, but continues well into childhood. Of note, airway branching is completed at 16 weeks gestation terminal sacs first appear at 24 weeks, surfactant producing type II pneumocytes appear between 24-26 weeks, capillary networks surrounding the terminal sacs at 26-28 weeks. Alveolar development begins at 32 weeks reaching 10% of the adult number at birth. Alveolar development is complete by 18 months of age.

Respiratory mechanics. The newborn lung is small in relation to body size. The metabolic rate is high, tidal volumes small but similar per kg body weight as adults (7ml/kg), thus the respiratory rate is high (30-40 breaths per minute) and there is little respiratory reserve. Lung compliance is low and the ribs soft and elastic; chest wall compliance is higher compared with adults. Chest wall stability increases by about 1 year of life. Thus the distending pressures on the lung are low and the newborn infant is prone to lung collapse, especially under general anaesthesia. Anaesthetic agents also depress the pharyngeal dilator muscles leading to upper airway obstruction. PEEP or CPAP and the appropriate airway support should be utilised in the anaesthetised infant. The diaphragm is the predominant respiratory muscle in neonates but is more easily fatigable than in adults. Ventilation under anaesthesia should be at least assisted and abdominal distension should be avoided.

Respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD) occur in the premature neonate due to the immaturity of lung development, surfactant deficiency and adverse lung mechanics, compounded by ventilator induced lung injury and oxygen toxicity. Strategies to avoid BPD include use of CPAP, surfactant, HFOV, avoiding volutrauma, hypocarbia and reducing oxygen exposure[22].

Oxygen transport. Infants have a high metabolic requirement for oxygen (6-8ml/kg/min vs 4-6ml/kg/min in adults). Tissue oxygen delivery is achieved by a relatively high cardiac output (300ml/kg/min vs 60-80ml/kg/min in adults) and high respiratory rate (30-40bpm). However, oxygen transport oby haemoglobin shows developmental changes with time.

Fetal haemoglobin (HbF) is suited to the hypoxic conditions found during fetal life. It has a low P50 (18-20mmHg vs 27mmHg in adults) and allows effective tissue oxygenation of the fetal tissues. However, at birth HbF still forms 70-80% of total haemoglobin - relatively poor tissue oxygenation is compensated for by a relatively high

haemoglobin concentration. HbA2 production increases from birth, being the dominant haemoglobin by the first few months of life. The P50 continues to rise during infancy to levels higher than found in adults, probably reflecting increased levels of[2,3] diphosphoglycerate (2,3 DPG) during a period of rapid growth. Coupled with a relatively high cardiac output, tissue oxygen delivery is extremely efficient in infants compared to adults. These factors affect the triggers for transfusion or the haemoglobin level at which a child should be considered significantly anaemic:

	P50 (mmHg)	Hb required for equivalent tissue oxygen delivery (g/dl)		
Neonate<2 months	24	17.6	14.7	11.7
Infant >2 months	30	9.8	8.2	6.5
Adult	27	12	10	8

Hepatic function and drug handling.

The liver in the newborn infant contains 20% of the hepatocytes found in adults and continues to grow until early adulthood. The liver is the principle site of drug metabolism, some evidence of which can be found in fetal life, albeit at low levels. Phase I processes (metabolic, e.g. the cytochrome P450 system) are significantly reduced at birth whilst phase II processes (conjugation) may be well developed (sulfation) or limited (glucuronidation). Paracetamol is excreted by sulfation in the neonate, glucuronidation in adults. In general, drug effects are prolonged in neonates and drugs should be titrated to effect, given by bolus rather than infusion, or plasma levels monitored as appropriate. Maturation of enzymatic processes increases over the first few weeks of life and the half-life of drugs such as morphine reaches adult levels at 2 months of life. However, infants require significantly less morphine than older children, especially in the first week of life[(7)]. Plasma protein binding is reduced in neonates (low levels of a1-acid glycoprotein) and drugs that are plasma protein bound (such as local anaesthetics) may demonstrate increased toxicity in infants.

Children have been described as 'therapeutic orphans' in that many drugs, especially new drugs, have not been studied in this age group - hopefully this will be rectified in future.

Infants have reduced hepatic stores of glycogen and immature gluconeogenic enzyme systems. Coupled with a high metabolic rate, this makes them susceptible to hypoglycaemia following starvation. Blood sugar should be measured during surgery and glucose containing solution continued if the child has been hypoglycaemic or receiving parenteral nutrition preoperatively

Renal function[(8)]

Nephrogenesis is completed at 36 weeks gestation and no further nephrons are produced (impaired nephrogenesis in premature infants has been related to hypertension in adult life). Further increase in renal mass is due to the growth of tubules. The GFR at term is low and reaches adult values only at 2 years of age. Renal autoregulation of blood flow is functioning in neonates, albeit at lower levels of blood pressure. Creatinine at birth reflects the mother's creatinine and falls to reflect renal function of the infant by 1 week of age. Tubular function matures over the first few months of life; infants usually produce urine that is isotonic to plasma, but if required, can concentrate their urine to achieve an osmolality of 500-700mOsmol/kg H_2O. Adult values (urinary osmolality typically 1200-1400mOsmol/kg H_2O) are reached by a year of age. Infants tolerate fluid restriction poorly. The neonate's limited renal function is appropriate to the period of rapid growth after birth - growth has been termed the 'third kidney'. However, in the postoperative (catabolic) infant, renal insufficiency may become apparent and the neonate does not handle fluid or sodium overload.

Fluid and electrolyte balance[(9)]

The extracellular fluid compartment is expanded in neonates, with total body water representing 85% of body weight in premature babies, 75% of body weight in term babies, compared to 60% body weight in adults. Contraction of the extracellular fluid compartment and weight loss in the first few days after birth is a normal physiological process, due in part to a diuresis induced by atrial naturetic peptide (ANP) secondary to increased pulmonary blood flow and stretch of left atrial receptors. After this period of negative water and sodium balance, water and sodium requirements increase to match those of the growing infant. Fluids should therefore be restricted until the postnatal weight loss has occurred. Liberal fluid regimens in the first few days of life have been shown to be associated with worse outcomes in premature infants (increased patent ductus arteriosus, necrotising enterocolitis and death)[(24)].

Of interest to anaesthetists, the expanded extracellular fluid compartment results in an increased volume of distribution of commonly used drugs and increased dose requirements, despite increased sensitivity (muscle relaxants, intravenous induction agents).

Temperature control[5]

Thermoregulation in the neonate is limited and easily overwhelmed by environmental conditions. Heat production is limited and there is a greater potential for heat loss (high body surface area to body weight ratio, increased thermal conductance, increased evaporative heat loss through the skin). The newborn infant is able to vasoconstrict to reduce heat loss and to increase heat production through brown fat metabolism (non shivering thermogenesis, inhibited by volatile agents), however this is at the expense of increased oxygen consumption and the possibility of increased complications. The preterm baby is particularly vulnerable in this respect as the immature skin is thin and allows major heat (and evaporative fluid) losses. The principle of anaesthesia in these infants is close liaison with the neonatologist and minimal handling. Surgery is frequently performed in the neonatal unit for this reason.

Central nervous system, nociception and the stress response

The brain forms 10% -15% of body weight at birth, only 2% of body weight by the age of 8 years. The brain is reliant on glucose for metabolism but the child is also able utilise ketones under normal conditions. The CMRO2 is higher in young children due to the demands of growth and autoregulation of cerebral blood flow is present, even in premature neonates.

The lower limit for cerebral autoregulation in neonates is not known, but is thought to be around a cerebral perfusion pressure of 30mmHg. Appropriate mean arterial blood pressure for premature neonates are controversial but it generally accepted that the mean arterial pressure equates to the gestational age of the child during the first day of life, rising to a minimum of 30mmHg by 3 days.

Survival of extreme preterm infants has improved considerably in recent years, but this has been associated with high levels of disability. Marlow et al followed the progress of the cohort of children born in the UK at less than 25 weeks during 1995. At 30 months of age, 24% of survivors had severe disabilities; at 6 years of age, 21% had severe disability, and when compared with their classmates, 41% had significant cognitive impairment[20]

A major determinant of cerebral impairment is intraventricular haemorrhage (IVH), particularly complicated by ventricular enlargement, parenchymal infarction or cystic periventricular white matter injury (PVL). Major IVH usually occurs within the first few days of life. Factors that have been shown to reduce the incidence of IVH or later neurodevelopmental delay include: delayed delivery to allow the administration of prenatal maternal steroids, postnatal surfactant to reduce lung disease, neuromuscular paralysis to avoid ventilator asynchrony, avoidance of hypotension or fluctuating blood pressure, avoidance of morphine infusions in hypotensive infants, early indomethacin to encourage duct closure in PDA, and the avoidance of postnatal steroids. It has been estimated that there is one additional case or cerebral palsy for each 7 infants treated with dexamethosone. Avoidance of postnatal dexamethosone is currently the single most important factor to improve neurological outcomes in premature infants[21]

Developmental aspects of pain[10]

Neonates, including premature neonates, show well developed responses to painful stimuli. Indeed, the foetus shows a stress response (and behavioural changes) to nociceptive stimulation from 18-20 weeks gestation, which can be attenuated by the administration of fentanyl[12]. It has long been known that attenuation of the stress response to surgery improves postoperative morbidity and mortality.

The neonatal period is characterised by marked sensitivity to sensory stimuli of all types, with low thresholds of response to mechanical and noxious stimulation. The nociceptive responses of neonates are significantly different to adults; at birth, a noxious stimulus (eg heel prick), will elicit an exaggerated movement of the whole body and movement of all four limbs. These responses are less pronounced after 29-35 weeks post conception, but repeated stimulation results in sensitization.

The process of maturation of the nociceptive system is complex and involves interactions between the peripheral and central nervous systems, changes in receptor, ion channel and neurotransmitter expression and the effects of neurotrophins. Experimental evidence has shown widespread, functional opioid receptors in the spinal cord of newborn animals (rather than located to lamina I and II of the spinal cord as in adult life). It appears that there is a great deal of neuronal fine tuning during early neonatal life which may be influenced by the activity of endogenous opioids. However, this raises the question of the long term effects of exogenous morphine administration to neonates at the time of neuronal plasticity[11].

Long term effects of early pain experiences[23]

Animal and human work has indicated that early pain experiences can have long term effects, possibly through developmental changes in the nociceptive circuitry. For instance, painful procedures induce behavioural changes in preterm infants in NICU[13] Infants who undergo circumcision without analgesia show exaggerated responses to later immunisation compared to controls[14]. Infants who undergo major surgery in the first three months of life exhibit greater analgesic requirements, stress response and pain scores when undergoing repeat

surgery compared to controls that have not had previous surgery[15].

Long term effects of early exposure to anaesthetic agents

Recent work from Olney et al has investigated the effects of exposure of the developing brain to drugs that block NMDA receptors or potentiate GABA receptors. Anaesthetic drugs commonly used in paediatric practice (midazolam, nitrous oxide, isoflurane) were administered to 7 day old rats for 6 hours. They were found to cause widespread apoptosis (programmed cell death) with deficits in hippocampal synaptic function and persistent memory/learning impairments[16]. Similar findings had been previously noted with ketamine[17]. The relevance to clinical practice is at present unclear - indeed, surgery without effective anaesthesia and pain relief would equally have significant adverse effects. Others have questioned the experimental conditions used and found that smaller doses of ketamine that those used by Olney do not induce apoptosis in rat pups[18]. The jury is still out and animal models may not accurately reflect the situation in humans, but clearly, there is room for more research![19]

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Erratum: In Update in Anaesthesia number 19, PERIOPERATIVE FLUIDS IN CHILDREN:

Page 36 (page 1 of article) paragraph 2 should read:
Breast milk may be given to within 3 hours, formula milk to within 4 hours.

Page 37 (page 2 of article), paragraph 2: The word "in-vitro" should be substituted for "in-vivo".