

The Applied Physiology of the Neonate

Many see birth as a moment of profound change. In reality, birth is just a dramatic moment in the gradual transition from a bundle of cells into the highly organised systems that make up our adult bodies.

For the neonate, and the preterm neonate in particular, its physiology may be ill equipped to cope with life without a placenta, unlike older children. They have diseases related to incomplete adaptation to *ex-utero* life and their physiological response to disease also differs from older children.

In this article, the physiological changes that occur at birth are reviewed and common neonatal diseases are discussed, examining the clinically relevant physiology. Strategies used in the management of sick babies or those with surgical diagnosis are outlined.

Adaptation at birth

Fetal life is easy

The fetus has few demands placed upon it. The placenta supplies oxygen, glucose, nutrients and fluid. It removes carbon dioxide, urea and other products of metabolism. In short, the fetus would not be aware that its lungs were absent, if it had minimal renal or liver function, or even if its brain were not working. Only one ventricle need be present in the heart, the intestines might be absent and the fetus still unaware. Given this, it is remarkable that so many infants are normal. Neither is it surprising that the major reason for fetal death remains placental causes and very severe congenital malformations.

However, as soon as the baby is born, all of the basic organs must become functional.

Lung Physiology

Parents wait for the sound of their baby's first cry, knowing this is the key event of birth. And they are right - the most dramatic change at the moment of birth is the transition from placental gas exchange to air breathing. In the lung this requires the removal of fetal lung liquid, expansion of airspaces and tidal gas exchange. Together these processes bring oxygen close to blood vessels. Before the first breath, the lung must be prepared structurally and physiologically for this changes.

Fetal lung liquid

The fetal lung is filled with fetal lung liquid (FLL), formed continuously by the active transport of chloride ions into the lung lumen from early pregnancy, at a rate ($3 \text{ ml.kg}^{-1}.\text{hr}^{-1}$) similar to that of fetal urine. FLL makes up about a half of amniotic fluid. It is thought to act as a template around which the fetal lung can grow.

At birth the neonate must stop production and absorb the FLL, so that the lungs do not remain full of liquid. This also concentrates the surfactant. The maturation of the FLL absorptive mechanism is controlled by fetal corticosteroids, thyroid hormones and adrenaline. The thyroid hormones and corticosteroids lead to the synthesis of sodium

channels, β -adrenoceptors and Na^+/K^+ ATPase ion pumps. A surge of adrenaline in response to the stress of birth is sensed by the β -adrenoceptors and increases the activity of membrane-associated adenylate cyclase, in turn increasing the levels of cAMP in the pneumocytes. This leads to incorporation of the pre-formed Na^+ channels into the apical membrane and absorption of the FLL from the lung lumen. This keeps the airspaces dry, allowing air to get near to blood vessels.

Surfactant

Surfactant is a mixture of phospholipids and proteins, made by the alveolar type II cells. The most abundant lipid, dipalmitoylphosphatidylcholine (DPPC) itself is thought to be mainly responsible for lowering the surface tension of the air-liquid interface in alveoli. The proteins, surfactant protein (SP) -A, SP-B, SP-C and SP-D are involved in the translocation and organisation of the phospholipids sheets, and in immune defence.

Surfactant is synthesised from 20 weeks, and has reached 35% of adult values by 24 weeks, however levels of SP's are very low. After 30 weeks, the levels of phospholipids and SP's gradually increases to term. Many hormones affect surfactant production and prepare the lung *in vivo* for air breathing. Like FLL, thyroid hormones, glucocorticoids and agents with β -adrenoceptor activity act independently to increase synthesis of all elements of surfactant.

Because it lowers surface tension of an air-liquid interface, it promotes expansion of alveoli surfactant and opposes their collapse, apparently acting as a rigid cage. Its effects can be seen in the pressure-volume loops (figure 1). The premature lungs, deficient in surfactant, require more pressure to inflate, inflate less for a given pressure and collapse entirely in expiration, failing to maintain a functional residual capacity (FRC).

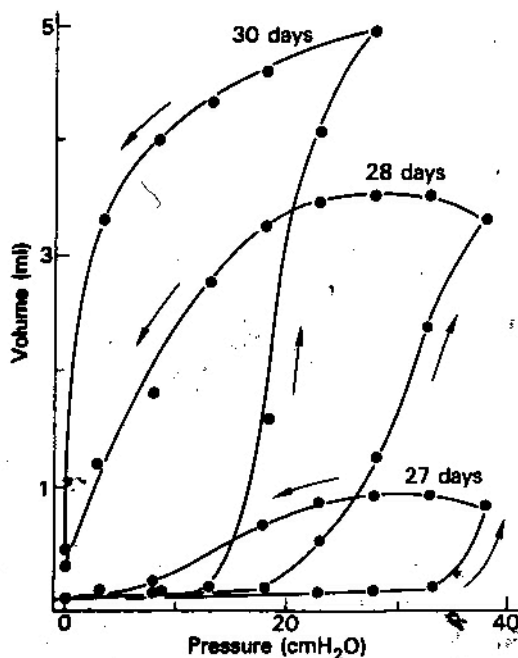


Figure 1 - Pressure volume loops from fetal rabbits lungs at different gestations. Term is 30 days for a rabbit. From Humphreys PW, Strang LB. 1967 Effects of gestation and prenatal asphyxia on pulmonary surface properties of the foetal rabbit. *J physiol* 192 53-62

The first breath

At the first breath, the neonate must overcome the surface tension of the FLL with an enormous respiratory exertion (up to - 70 cmH₂O) to create an air-liquid interface, a gas exchange surface within the lung. Then, by exhaling against a resistance, other air spaces not opened initially will be forced open and FLL forced into the interstitium. This process and the reabsorption of the FLL will concentrate the surfactant present and establish the FRC.

All just for the first cry.

Cardiovascular physiology

These physiological processes enable the lungs to expand with air. But this would be useless unless the fetus could direct more blood to the lung.

Changes in pulmonary vascular resistance

In the fetus, only 7% of the biventricular output enters the lung, but this increases to around 100% after birth mainly due to a dramatic fall in the pulmonary vascular resistance. This is caused by simple mechanical expansion of the lung, a fall in blood CO₂, and a rise in pO₂.

The mechanisms that lead to this fall in response to changes in gas concentrations are still not completely understood. Flow of blood through the pulmonary vascular bed is controlled by vascular smooth muscle tone, itself dependent of intracellular calcium [Ca_i]. A high [Ca_i] maintains contraction and a low blood flow and vice versa. The [Ca_i] is maintained by voltage dependent calcium channels in the cell membrane. Increasing oxygen tension in the smooth muscle cell activates potassium ion channels in the membrane. This causes membrane hyperpolarisation and closes the voltage sensitive calcium channels, in turn reducing [Ca_i] and relaxing the smooth muscle cell.

Nitric oxide (NO) too has an important role in the modulation of pulmonary vascular tone. Made by the nitric oxide synthetase in pulmonary vascular endothelium in response to increased levels of oxygen, NO diffuses into the adjacent smooth muscle cells. There it induces the enzyme guanylate cyclase, increasing intracellular cyclic GMP. This activates a specific cGMP-dependent kinase enzyme that activates a potassium channel in the membrane. Again this hyperpolarises the cell and closes voltage dependent calcium channels, reducing [Ca_i] and relaxing muscle cell.

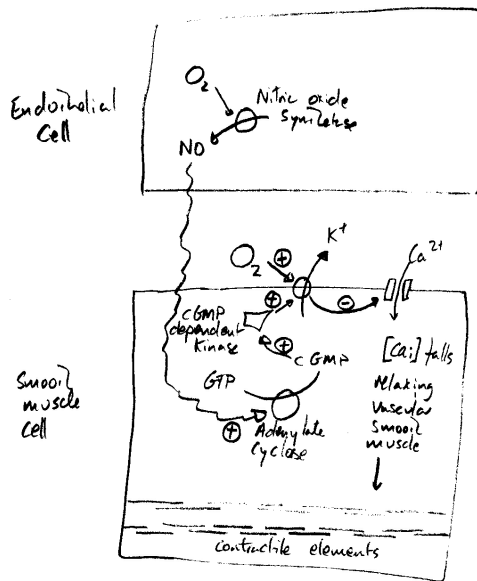
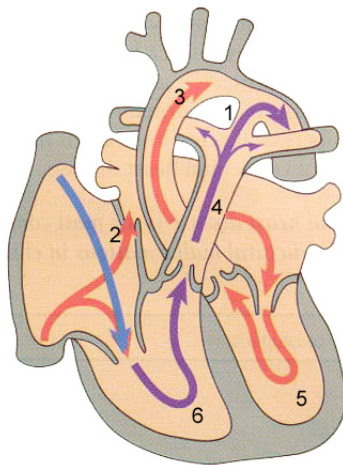


Figure - mechanisms in pulmonary vasodilatation

Right to left shunts

When pulmonary resistance is high, as in the fetus, blood bypasses the lungs at two levels - the ductus arteriosus and at the foramen ovale.



- 1 Ductus arteriosus
- 2 Foramen Ovale
- 3 Aorta
- 4 Pulmonary artery
- 5 Left ventricle
- 6 Right ventricle

At birth, two events occur. Firstly, pulmonary vascular resistance falls dramatically. Also, umbilical artery flow stops. These changes together have the effect of reducing afterload on the right side of the heart and raising it on the left side. The foramen ovale flap valve shuts and the ductal shunt become left-to-right.

Over the next three days the ductus physically closes, in response to biochemical signals, such as pH and pO_2 . These signals are sensed by in the mitochondria of ductal smooth muscle cells. Increased oxygen tension leads to production of H_2O_2 which closes potassium channels in the cell membrane. This lowers the membrane potential and brings more calcium

into the muscle cells through voltage gated calcium channels, raising $[Ca_i]$ and constricting the ductus. Eventually both ductus and foramen ovale become fibrotic so cannot reopen.

Adaptation of Fluid balance mechanisms.

The fetus need not worry about its fluid balance. Water and electrolytes equilibrate across the placenta in response to growth and metabolic demands. The fetal kidneys make urine that passes into the amniotic cavity to make up half the amniotic fluid which is then swallowed and absorbed in the gut.

After birth, the neonate needs to control its own fluid balance or it will rapidly become dehydrated, particularly as it has a high surface area/body weight ratio. The gut must develop ways to absorb fluid, solutes and digest protein and fat.

Neonates, and preterm infants in particular, have structurally and physiologically different kidneys from those of older children and adults. Nephrons are still being formed up to 35 weeks gestation. Consequently the glomerular filtration rate is much lower in a 28 weeker ($0.55 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) than a term baby (up to $1.6 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) or a two year old child ($2 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$). The renal medulla has a lower tonicity than older children, reducing the potential effect of anti-diuretic hormone on urine volume. However, all of the hormones that affect the kidney are active even in very immature infant, albeit with reduced potency.

The renin-angiotensin-aldosterone system acts to reduce sodium loss from the distal tubule, but it is less effective in the very immature. Overall, the neonate has a tendency to accumulate sodium, as this is essential for growth. Atrial natriuretic peptide (ANP) too is present, but its effects are blunted.

In effect, the neonatal kidney is able to excrete water and sodium well, but cannot conserve these like an older child.

Adaptation of neural mechanisms

By contrast with children, neonates are very limited in their neural capabilities. The process of myelination that enables complex and rapid neurological function begins in the second trimester and is far from complete at a year of age. Despite this, even fetuses can suck, swallow, move their limbs, have primitive reflexes and can breathe, albeit in short bursts. At birth, these functions need to be sufficiently efficient to maintain homeostasis.

Development of neonatal breathing

The control of respiration has been extensively investigated, but the exact mechanisms that are working in a particular species or age are still unknown. Clearly a network of neurones in the medulla and cervical cord exists, making up the respiratory centre. This controls stimuli to phrenic and intercostals muscles. In a part of the rostral ventrolateral medulla, there is the equivalent of a respiratory pacemaker.

One of the most important changes at birth is the onset of regular respiration, but the mechanisms behind this also are unclear. It is thought that a local increase of 5-HT acts on the respiratory centre to effect this change.

The respiratory centre is controlled by a number of afferent nerves. The vagus nerve conveys information from, amongst other receptors, stretch receptors in the intrathoracic trachea, which inhibits inspiratory signals from the respiratory centre. Because of the "on-off" nature of the respiratory centre's output, this produces respiratory cycling. Other afferent nerves modify the respiratory centre's output. The trigeminal nerve, carrying information from the nose, stimulates sneezing, and cutaneous afferents cause a prolonged inspiration, hence the value of vigorous skin stimulation in neonatal resuscitation. Afferents also come from other parts of the brain, and alter breathing to reflect changes in emotion, wakefulness, CO₂ and acidosis.

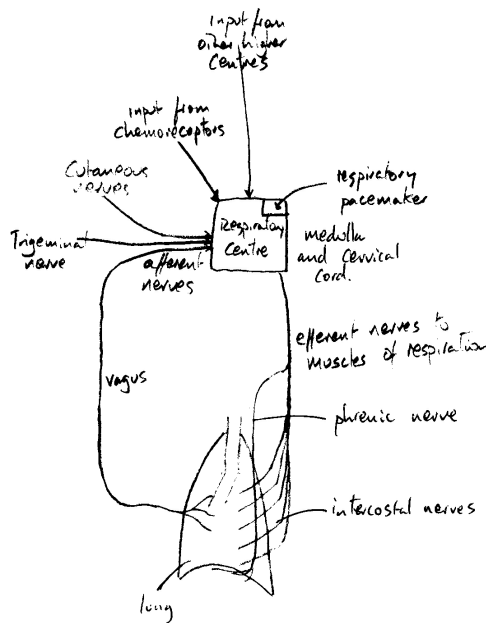


Figure - elements of ~~the~~ respiratory control

Figure - elements of respiratory control

Those working with term and preterm infants will notice several unusual features in their respiratory drive. Firstly, breathing is irregular, with spontaneous periods of tachypnoea, bradypnoea and even apnoea within a few seconds of each other. This is more noticeable in more premature infants and more pronounced in awake rather than lightly asleep babies. The reason for this "periodic" breathing is not known, although immaturity of the respiratory centre or afferents is doubtless the cause. It always resolves with time and is often treated with theophyllines such as caffeine if symptomatic.

Neonates also demonstrate a very different response to hypoxia from older children. In contrast to a pattern of sustained tachypnoea, neonates show transient tachypnoea and then bradypnoeic or even apnoeic. Acidosis may eventually lead to gasping.

Adaptation of the gut

In contrast to other systems, relatively little changes structurally in the gut at birth. The fetus swallows and absorbs amniotic fluid in the small intestine. After birth, peristalsis pushes meconium out of the gut, stimulated in part by feeding. Preterm infants, even under 25 weeks gestation are able to absorb feed, although swallowing is not usually efficient enough until around 36 weeks gestation to meet nutritional requirements.

In the first section, we have seen that in order for the neonate to survive, elaborate mechanisms exist in many systems, primed for the moment of birth. However for infants born affected by complications of pregnancy or labour, congenital anomalies or simply too early, these mechanisms may not work. The next section looks at common neonatal problems and their management from a physiological perspective.

A physiological approach to resuscitation

Due to events in pregnancy or labour, or because of drugs given to the mother, some infants may need resuscitation. This presents as apnoea, bradycardia or both. Hypoxia and acidosis, occasionally with sepsis are usually present. The priority is prompt expansion of the lungs with oxygen. The baby may take a breath itself, perhaps in response to vigorous drying, but bag and mask ventilation will be required if this does not work. Expansion of the lung with oxygen will form a gas exchange surface, create a FRC, lead to pulmonary vasodilatation and reverse the reflex apnoea and bradycardia. In surfactant deficient babies, higher pressures will be needed to inflate the lung to overcome the higher surface tension found in their airspaces. Clinically this is seen as chest movement and signs of improved cardiac output. Occasionally, if there is cardiac arrest, cardiac massage and adrenaline are needed to move oxygen out of the lung and into the circulation.

A Physiological approach to neonatal management

Overview

Almost all chronic morbidity arising from neonatal illnesses results from brain damage, chronic lung disease or congenital anomalies. The brain damage is haemorrhagic (particularly intraventricular haemorrhage) or ischaemic. Hence management aims to provide a stable environment for the brain, free of swings in blood pressure, pH, blood gases, temperature or electrolytes. Ventilation attempts to provide such an environment, but avoid mechanical damage or oxygen toxicity. For congenital defects a multidisciplinary approach is needed, of which surgery is often an important part, and withdrawal of care sometimes the most appropriate option. Neonatal problems caused by immaturity usually improve with time, so much neonatal intensive care is supportive, with a strong emphasis on normal growth.

Respiratory distress syndrome (RDS)

This illness, called "hyaline membrane disease" by pathologists, results from immaturity of the lungs. It affects under 1% at 40 weeks, 50% at 32 weeks and over 90% at 28 weeks without antenatal steroid treatment. It is caused by alveolar collapse, (caused by surfactant deficiency), excessive lung water, a persistently high pulmonary vascular resistance and poor

approximation of pulmonary capillaries to airspaces, and a deformable chest wall. As discussed earlier, surfactant reduces the surface tension of air-liquid interfaces. Without it, airspaces fail to open at the first breath and collapse with each expiration, greatly increasing the work of breathing. Also, gas exchange cannot occur and pulmonary vasodilatation is impaired

Clinically the baby will be desaturated with tachypnoea and chest recession. Chest radiograph shows poorly expanded lungs, air bronchograms and the "ground glass" appearance, which is caused by clumps of unexpanded acini next to expanded units (see figure).

{insert CXR here}

figure - RDS in a premature infant. In addition to RDS features, an umbilical arterial catheter, NG tube, endotracheal tube and monitoring wires are seen. The baby also has a small pneumomediastinum.

Management first aims to prevent the condition. Administration of Betamethasone for 48 hours antenatally reduces the incidence of RDS by a half to two thirds, as steroids promote surfactant synthesis and FLL clearance. This intervention has also been shown to reduce intraventricular haemorrhage, necrotising enterocolitis and persistent ductus arteriosus.

After birth, strategies to inflate airspaces can be used, such as continuous positive airway pressure (CPAP) at around 5cmH₂O via nasal prongs, as shown in the figure.



Figure - an infant breathing with nasal CPAP

For more severe RDS, intubation and mechanical ventilation is required. This still aims to expand airspaces and take over the work of breathing. Typical starting pressures of 18/4 can be increased to meet desired blood gas goals. However, mechanical ventilation may cause damage to the lung.

Damage is thought to be caused by oxygen toxicity or overexpansion of acini, which occurs most in acini that are already well expanded, as predicted by the Laplace equation (internal pressure = $2 \times \text{surface tension}/\text{radius}$). This "volutrauma" manifests as pulmonary interstitial emphysema and pneumothorax. Premature lungs are also particularly susceptible to oxygen toxicity from oxygen free radicals because of low levels of superoxide dismutase. Over weeks, lung damage sets up an inflammatory response, leading to pulmonary infiltrates and a condition called chronic lung disease.

To avoid this, a lung protective strategy is used, maintaining open airspaces but limiting peak pressures and tolerating mildly abnormal blood gases. High frequency oscillatory ventilation (HFOV) enables gas exchange and lung expansion but minimising the peak pressure. Limiting inspired oxygen to $<85\%$ may reduce oxygen toxicity.

Intubation allows administration of exogenous surfactant. This is synthetic ("Exosurf" or "ALEC") or animal (Curosurf or Survanta). This begins to corrects the physical properties of the lung, encouraging expansion and reducing pulmonary vascular resistance. Surfactant reduces the incidence of pneumothorax and mortality, especially due to chronic lung disease. For many infants with RDS, ventilation and CPAP are weaned over several days. Others require longer periods of ventilation, some dying of lung disease and others developing chronic lung disease, requiring months of oxygen therapy.

Fluid balance

Neonates have a high fluid turnover. After the first week, a baby requires $150 \text{ ml.kg}^{-1}.\text{day}^{-1}$ of fluid, equivalent to 20 pints a day for an adult. This is because milk has a low concentration of energy compared to solid food, and because neonates cannot physiologically reduce urine output below $1 \text{ ml.kg}^{-1}.\text{hr}^{-1}$. They also have high insensible losses, particularly from evaporation, owing to their high surface area to body weight ratios, 4 times an adult, and immature skin. These problems are accentuated for the preterm. A 26 week gestation baby on day 1 can lose over 100 ml.kg^{-1} of fluid by evaporation, although this improves with time after birth and gestational age at birth. Hence humidified incubators are integral to the management of pretermers, reducing water and heat loss. Thirst mechanisms are poorly developed and are affected by other problems, such as sepsis or RDS. Also, a surge of antidiuretic hormone at birth causes oliguria over the first few days.

Unit protocols for fluid requirements aim to match needs resulting from these physiological processes. Those caring for sick or preterm neonates must pay close attention to indicators of fluid balance and act accordingly.

- serum sodium should be $133\text{-}144 \text{ mmol.L}^{-1}$
- body weight should fall by up to 10% below birth by 1 week, then increase
- haematocrit rises (without transfusion) suggest dehydration
- creatinine should fall from maternal levels to $<50 \text{ }\mu\text{mol.L}^{-1}$ after 5 days

Hypotension

Hypotension results from poor cardiac output and/or inappropriate vasodilatation. In neonates, cardiac output may be sufficient, but large shunts removing blood from the systemic circulation might lower systemic blood pressure. Examples include patent ductus

arteriosus, ventricular septal defect and a vein of Galen aneurysm, the condition diagnosed head auscultation! Poor cardiac output may be caused by dehydration, sepsis or prematurity, as neither ventricle in the preterm's heart is prepared to pump the entire cardiac output. Inappropriate vasodilatation is commonly seen in the extremely preterm, but can also found in sepsis.

The initial approach is of careful assessment, looking for fluid depletion and end organ hypoperfusion (oliguria, altered activity, gastric stasis, prolonged capillary filling, raised serum lactate).

The neonatal heart, unlike an older child's, is working near maximum contractility and stroke volume, mainly due to the large increase in left ventricular afterload with cord clamping. So cardiac output is altered by changing heart rate. Agents causing vasoconstriction will reduce cardiac output even if the blood pressure improves.

Therefore, hypotension can be managed with crystalloid volume boluses ($10-20 \text{ ml.kg}^{-1}$) to increase preload. If cardiac output is still insufficient, dobutamine can be used, producing a tachycardia and vasodilatation. If blood pressure is too low to perfuse vital organs, dopamine is used that increases heart rate and vasoconstricts at higher doses.

Patent ductus arteriosus

The ductus allows blood to bypass the lungs in the fetus. After birth it closes to prevent blood passing from aorta to the low resistance pulmonary circulation.

In some infants, especially those with RDS, it does not close. There is a left to right shunt, increasing pulmonary artery blood flow. This increase may be small, but larger volumes may result in left ventricular overload, pulmonary hypertension, pulmonary oedema, and systemic hypoperfusion. The baby may be tachypnoeic, tachycardic and desaturated.

Management first attempts to reduce pulmonary oedema with fluid restriction and diuretics. If the baby is still symptomatic, cyclo-oxygenase inhibitors, such as indomethacin or ibuprofen are used to close the duct, presumably by reducing prostaglandin synthesis. However, these drugs also affect other vessels, including those supplying the kidney, gut and brain. If medical treatment is unsuccessful, the duct is ligated through a left subscapular incision.

Necrotizing enterocolitis (NEC)

NEC is characterised by ischaemic necrosis in the bowel wall. It is strongly linked with prematurity and intrauterine growth retardation (IUGR), hypotension and both the presence of, and the treatment of, a patent ductus. It almost never occurs before enteral feeding and is less common in those receiving breast milk. Certain bacteria are commonly, but not always, cultured from affected infants.

It is postulated infants cannot fully digest and absorb enteral feeds. Bacteria use that not absorbed as substrate, producing fatty acids. The fatty acid produced depends on the feed and bacteria present, and some are toxic, causing local necrosis. Conditions that reduce

splanchnic blood flow allow the accumulation of these toxins, extending the necrosis. Butyrate, produced by bacteria from formula feed leads to the release of inflammatory mediators such as IL-8, in turn increasing gut wall permeability and causing vasoconstriction, further reducing toxin clearance.

Clinically, some infants demonstrate only increased naso-gastric aspirates, but some develop multiorgan failure. More commonly, abdominal distension, bilious aspirates, malaena and features of systemic infection are seen. Radiography may show simply distension (grade I), gas in the intestinal wall (II) or evidence of perforation, or gas in the biliary tree (III).

Management comprises broad spectrum antibiotics with anaerobic cover (typically benzylpenicillin, gentamicin and metronidazole), supportive treatment, including fluid resuscitation, inotropes, ventilation and blood products, and surgery. Surgery aims to preserve the most normal gut, but remove necrotic bowel as early as can be tolerated.

Diaphragmatic hernia

A diaphragmatic hernia in the fetus, especially on the left, allows intestines into the left hemithorax. The lack of space for the lung causes pulmonary hypoplasia, with a number of airway divisions and reduced vasculature. Affected infants may not "pink up" at birth, and the problems may be exacerbated by feeding.

Although tempting to simply pull the intestines out of the chest and patch the hole, this approach has been superseded by prior stabilisation of the respiratory system, with adequate expansion using high frequency oscillatory ventilation and nitric oxide. Once pulmonary vasodilatation is established, surgery is safer.

Summary

Physiological changes are dramatic and essential at birth. However they are only part of a more gradual controlled development from embryo to adult. Those with congenital defects, prematurely born infants, and some term infants are often unprepared for these changes and so develop diseases characteristic of this period. A clear understanding of the underlying physiology allows rational and effective treatment.

Further Reading and References

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