PAEDIATRIC ANAESTHESIA

AIRWAY MANAGEMENT

Describe the anatomy of the neonatal airway, how this changes with growth and development and the implications for airway management

Compare and contrast the neonatal respiratory system with the adult: PAST QUESTION 36%

- Neonatal period = 0-28 days

Differences between neonatal and adult resp system

- Anatomy
- Lung volumes
- Ventilation/ gas exchange
- Control of ventilation
- Hb

	Neonate	**Adult**
Anatomy		
Upper airways	Large head, short neck, prominent occiput Narrow nasal passages → 50% airway resistance Large tongue Obligate nose breathers → 2o cephalad position of larynx/ large tongue Neutral position required	Sniffing position optimal
Larynx	Larynx high + anterior: C3-4 → straight blade Glottis is cephalad → C3-4 position (cf adult C5-6) Funnel shaped → narrowest point cricoid	Larynx C3-6 Narrowest at oesophageal opening
Lower airways	Short trachea: 4-5cm→ endobronch intubation common Steeper angle R)main bronchus Less bronchial muscles → ↓response to bronchodilators; bronchospasm less common	Bronchospasm more common
Lungs	diaphragm less oxidative fibres → ↑prone to fatigue 1o diaphragmatic breathing More horizontal ribs (prevent bucket handle → limits ↑VT) Chest wall compliance +++ Muscles of ventilation subject to fatigue	Bucket handle movement ↑type 1 muscle fibres ↑alveoli
Lung volumes		
Dead space VD	2.2 mL/kg	2.2 mL/kg
Tidal volume VT	7 mL/kg	7 mL/kg
FRC	30 mL/kg - less stable; tendancy to atelectasis - FRC < CC → gas trapping	30 mL/kg
VD/VT	0.3	0.3
FVC	35ml/kg	
Ventilation/ gas exchange		
Alveolar ventilation	120 - 140 mL/kg/min ↑A-a gradient (30mmHg cf 5mmHg in adults) due to ↑venous admixture	60 - 70 mL/kg/min
Respiratory rate	30 - 40 breaths/min shorter time constants; ↑effective to ↑RR than VT	10 - 15 breaths / min
I:E ratio	1:1	1:1.5
Specific compliance	0.05 cmsH2O-1	0.05 cmsH2O-1
Oxygen consumption	6 - 7 mL O2 / kg / min	3 - 3.5 mL O2 / kg / min
Physiological dead space	30%	
Control of ventilation	Immature resp control centre at birth Blunted hypercapnic response Apnoea episodes post op Limited resp reserve	
Hb	¾ of total Hb is HbF($\alpha 2\gamma 2$) HbF OHDC LEFT shifted HbA ↑ from birth → becomes main type of Hb in 1st few months	HbA

PERIOPERATIVE MEDICINE – PHYSIOLOGY

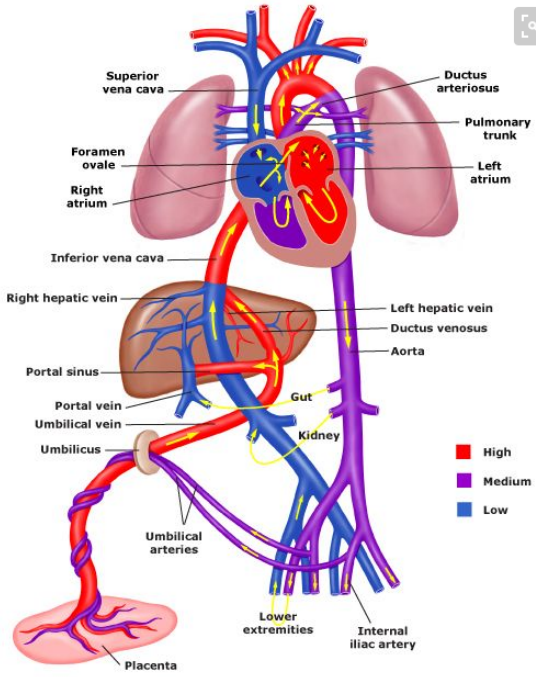
Describe the foetal circulation

Key points:

- foetal circulation supplies foetal tissues with O2 + nutritents from the placenta; bypasses the foetal lungs
- foetal Hb (OHDC L shifted) ensures DO2 maintained despite low PaO2

***Foetal circulation* - <u>Structure</u>**

- 2 umbilical arteries
  - arise from internal iliac a
  - return deoxygenated foetal blood to placenta
  - PaO2 18mmHg; SpO2 45%
- 1 umbilical vein
  - supplies oxygenated blood from placenta to foetus
  - PaO2 28mmHg; SpO2 70%
  - 60% of blood from umbi vein enters IVC; 40% enters liver
- 2 ducts
  - ductus venosus: shunts blood from umbi vein to IVC
  - ductus arteriosus: shunts blood from pulmonary trunk to descending aorta
- Foramen ovale
  - Shunts blood from RA to LA
- Immature myocardium
  - Does not obey Starlings Law
  - Does not adjust contractility for any given preload
  - SV is fixed; CO is HR dependent
  - Normal HR at term = 110-160



***Foetal circulation* – <u>circulation:</u>**

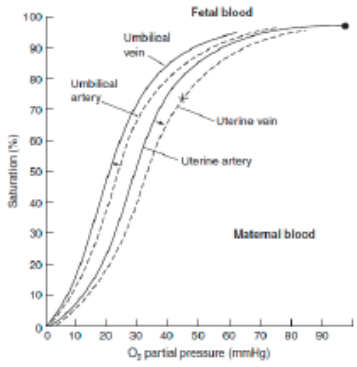
- Oxygenated blood returns via umbi vein:
  - 40% flows to liver via portal vein → hepatic vein → IVC
  - 60% bypasses liver via ductus venosus → directly to IVC
- Blood reaches the heart → divided into 2 streams by interatrial septum:
  - 1. Oxygenated blood from IVC directed via Eustachian valve through foramen ovale → LA → LV → ascending aorta → O2 rich blood to head + upper body
  - 2. Blood returning from SVC (drains myocardium + upper body; ↓PaO2) → directed into RV → descending aorta by ductus arteriosus + ↑PVR
  - arrangement has several features:
    - Patency of ductus arteriosus maintained by low PaO2 + vasodilating effects of prostaglandin E2
    - NB: ~10% CO passes through lungs → low O2 in lungs → vasoconstriction → ↑PVR
    - Blood with most O2 delivered to brain
    - Blood with least O2 delivered to umbi arteries for gas exchange
    - Both RV + LV eject to systemic circulations; similar size + wall thickness

Mechanisms whereby O2 transfer is facilitated at placenta

- placenta = large vol, low pressure, low resistance A-V shunt responsible for transfer of O2 and nutrients to meet ↑demands of growing foetus
- 1. ↑blood supply to placenta: uterine flow ↑x20 during pregnancy; not autoregulated and is pressure dependent
- 2. ↑foetal blood supply to placenta: umbilical arteries supply foetal deoxygenated blood to placenta; foetal CO is 1L/min (25055% goes to placenta)
- 3. HbF: ↑affinity for O2 than HbA; HbF = 2a2y; lower affinity for 2,3,DPG → shifts HbF OHDC to L → means that HbF has ↑affinity for O2 and assists it to load O2 in placenta; ↑saturation at given pO2 than adult Hb
- 4. Hb concentration: ↑concentration HbF → ↑O2 carrying capacity
- 5. Double Bohr effect: Bohr effect operative in both maternal and foetal circulations

Physiological principles

- Bohr effect: describes how changes in pCO2 and pH affect O2 transport
  - ↑pCO2 and ↓pH stabilises deoxy-Hb facilitating release of O2 → R shift in OHDC
  - ↓pCO2 and ↑pH → L shift OHDC
- Double Bohr effect: describes both effects happening on either side of placental gas exchange in mother + f
  - ↑pCO2 in maternal intervillous sinuses assists O2 unloading → ↓pCO2 on foetal side assists O2
  - Foetal blood flows from umbilical artery to umbilical vein → releases CO2 to mother and ↑O2 f
- Haldane effect
  - Describes how changes in O2 saturation of Hb affect CO2 transport.
  - DeoxyHb is able to bind H+ improving carriage of CO2 as HCO3 and carbamino compounds
- Double Haldane effect:
  - As maternal blood unloads O2, it is able to take up more CO2 for a given change in pCO2
  - As foetal blood takes up more O2 it releases more CO2 for a given change in pCO2



Approximate values:

	Umbilical vein	Umbilical artery	Maternal arterial
PO2	30mmHg	15	~100mmHg
pCO2	45	52	30
pH	7.2	7.3	7.4
%saturation Hb	30	70	100

Describe the circulatory and respiratory changes that occur at birth

Circulatory changes that occur after birth

Describe the cardiovascular changes that occur in the foetus at birth: PAST QUESTION 35%

Indicate the sequence of the physiological changes to the foetal circulation at birth and briefly describe the mechanisms that account for these changes: PAST QUESTION 46%

- Birth is associated with significant cardiovascular changes as gas exchange is transferred from placenta to lungs
- Results in the change from foetal circulation to adult circulation

Foetal circulation

- 2 circulations in parallel
- blood is oxygenated at the placenta → single umbilical vein → IVC (50%) + ductus venosus (50%)
- RA → blood through foramen ovale → LV → aorta → head, neck, and upper limbs
- RA → RB → pulmonary artery → ductus arteriosus → lower limbs
- Foetal pulmonary circulation = ↑pressure, ↓flow

Adult circulation

- 2 circulations in series
- RA → RV → pulmonary → LA → LV → aorta
- Adult pulmonary circulation = ↓pressure, ↑flow

The sequence of changes is:

1. **Removal of low resistance placenta**
   a. clamping of umbilical cord → removal of low resistance placenta → ↑SVR, ↑LVEDP, flow + ↓RAP
2. **Closure of ductus venosum:** over 3-10 days
3. **Inflation of the lungs**
   a. Relative asphyxia → central/peripheral chemoR + sensory stimulation → resp centre +
   b. ↑lung vol + ↓resistance of extra-alveolar vessels + ↑alveolar pO2 → ↓HPV
   c. **end result:** ↓↓PVR + ↑pulmonary blood flow
4. **Closure of PDA**
   a. ↑PaO2 + ↓circulating + locally produced PGs (PGE1, PGE2) → constriction of ductus flow
   b. Permanent closure: 2-3weeks
   c. COX inhibitors can prevent complete closure in CHD who rely on shunt from PDA for
   d. Hypoxia in neonatal anaesthesia can trigger re-opening of PDA
5. **Closure of foramen ovale**
   a. ↓PVR, ↑pulmonary blood flow, ↑LAP → **LAP>RAP** → closure of foramen ovale
   b. permanent closure 4-6weeks

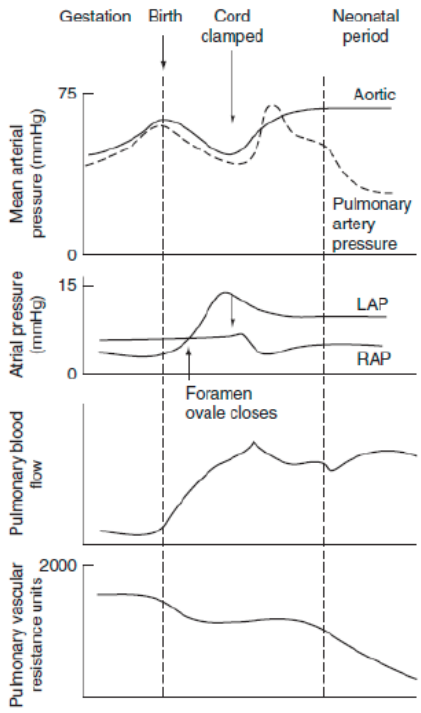


Figure 14.16 *Haemodynamic changes at birth. LAP, left atrial pressure; RAP, right atrial pressure.*

Factors that can modify above changes

- ↑RAP → persistence of foramen ovale
- ↓PVR → persistence of ductus arteriosus
- PGs and hypoxia → inhibit closure of ductus arteriosus

Respiratory changes that occur with birth

Discuss neonatal respiration including the first breath and response to increased oxygen demand: PAST QUESTION

- During birth, the neonate has to transition from obtaining O2 supply from maternal circulation via placenta (parallel circuit bypassing the lungs) to obtaining its own O2 from gas exchange in lungs (blood flowing in series circuit)

First breath:

- **trigger**:
  - Relative asphyxia → central + peripheral chemoreceptor stimulation + sensory bombardment → stimulates resp centre and lung ventilation
- **↓lung compliance**
  - 1st breath requires a very large –ve intrathoracic pressure (~-60cmH2O – due to poor compliance of lungs)
  - subsequent breaths are easier due to establishment of air-liquid interface + surfactant ↓surface tension
- **foetal lung fluid**
  - before delivery: foetal lung contains 20ml/kg fluid
  - some fluid expelled during thoracic compression associated with vaginal delivery
  - rest absorbed due to ↓pulmonary vascular resistance facouring fluid shift into pulmonary vasculature → fluid rapidly replaced by air after delivery + initiation of ventilation
- **↑chest wall compliance**
  - chest wall is very compliant → allows compression of chest to facilitate passage through birth canal
- **↑in FRC**
  - FRC rises rapidly after 1st breath
  - By 10mins the FRC is 17ml/kg, and by 30-60mins it is almost the same value as adults at 30ml/kg

Neonatal lungs

- not viable before 24 weeks: inadequate surface area, inadequate surfactant, immature control
- Airway: jaw angle 140 degrees, high larynx (C3-4); long epiglottis; narrow cricoid; short trachea (4cm); large nasal airway
- Control:
  - High rate minimises WOB
  - ↑ response to ↑PCO2
  - unreliable response to hypoxia
  - Transient apnoea is normal
  - true apnoea: >15sec, ↓d PO2, ↓HR

Responses to ↑neonatal O2 demand

- O2 consumption in neonate = 6-7ml/kg/min = 2x adult per kg basis
  - dependent on environmental temp (↓T by 2oC → doubling of neonatal O2 consumption): minimised in thermoneutral zone
- Neonatal alveolar ventilation = 120-140ml/kg/min (2x that of adult on per kg basis)
  - Achieved by ↑RR to 30-40min rather than ↑VT
  - This pattern of ventilation ↓WOB and hence O2 cost of ventilation

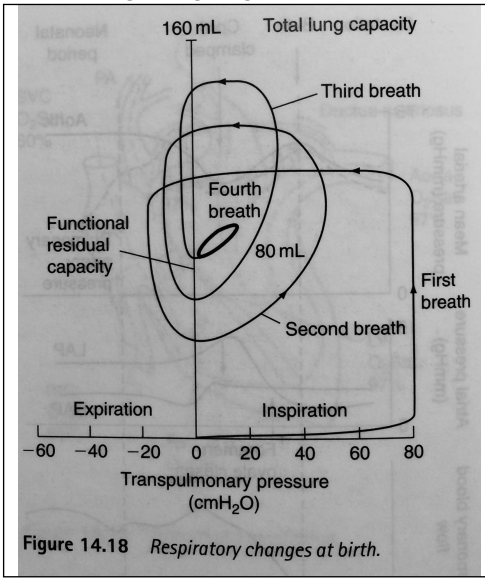


Figure 14.18 *Respiratory changes at birth.*

Define the thermoneutral zone, describe temperature regulation in the neonate and the physiological responses to lowered and raised environmental temperature, the effects of anaesthesia on these responses and how this changes with growth and development

Thermoneutral zone

- Temperature = measure of average kinetic energy of a substance per degree of freedom of its constituent molecules
- body temperature is tightly controlled to maintain optimal conditions for enzyme activity; 35-41°C

Thermoneutral zone

- Range of environmental temperature in which the metabolic rate (and O2 consumption) is minimal and steady
- Heat production is balanced by heat loss
- Adults = 27-31°; neonates 32-34°
- Deviations from threshold temp → thermoregulatory responses → ↑heat production, ↓heat production, or ↑heat loss

Interthreshold range

- range of core body temp where no autonomic thermoregulatory responses occur:
- Approx 0.2° at normal temp (37°) in nonanaesthetised state
- Influenced by circadian rhythms, food intake, thyroid function, drugs

Temperature sensation + regulation

- *Sensors*: central + peripheral
  - temperature gated ion channels: transient receptor potential (TRP) channels
  - Peripheral
    - Cold Rs: dermis; excited by cooling → signals to hypothalamus via Adelta fibres; regular + periodic discharges at constant temp; ↑discharge <25°
    - Warm Rs: bulbs of Ruffini; deep to dermis; excited by warming; active from 30-40°; max 44°C; signals via unmyelinated C fibres
  - Ascending thermal info → travels along lateral spinothalamic tract in anterior spinal cord → synapse at reticular system of medulla → posterolateral + venteromedial nuclei of medulla
- regulation: hypothalamus
  - Hypothalamus = main body temp regulatory centre; establishes set point
  - Integrates afferent inputs → initiates physiological + behavioural response
  - Anterior hypothalamus:
    - Sensitive to warming of blood → ↑firing rate → sweating + vasodilation
    - Neutotransmitter: norepinephrine, dopamine, prostaglandins
  - Posterior hypothalamus:
    - responds to cold afferent impulses → ↑shivering thermogenesis
    - neurotransmitter: acetylcholine
  - Interthreshold range = range of core body temp where no autonomic thermoregulatory responses occur:
- Effector responses
  - CNS
  - Cardiovascular
  - Musculocutaneous: shivering
  - Metabolic: BMR; non shivering thermogenesis

Physiological response to hypo- and hyper-thermia

Hypothermia

- Hypothermia = core temp <35°C
- Sensory → regulator → effector: behavioural + physiological responses → ↑heat production or ↓heat loss
  - ↑heat production: voluntary + involuntary muscle activity (shivering); non-shivering thermogenesis
  - ↓heat loss: behavioural changes; piloerection; cutaneous vasoconstriction
- temp <34°C: confusion
- temp 30-32°C: loss of consciousness
- temp <28°C: arrhythmias (VF)
- frost bite: severe form of cold injury due to freezing of peripheral tissues; damage due to cell dehydration + mechanical effects of ice crystals

Hyperthermia

- Occurs when heat loss mehcanisms fail
- Hyperthermia → sensor → regulator → ↓heat production or ↑heat loss
  - ↓heat production: behavioural (↓activity, ↓feeding, appropriate clothing)
  - ↑heat loss: sweating (evaporation); cutaneous vasodilation
- Extreme heat: thermoregulatory mechanim can fail → head stroke, heat exhaustion, heat collapse
- Temp >42: unconscious; cellular damage, coagulation of proteins; cerebral oedema; irreversible neuronal damage
-

Summary of effects:

	↑heat loss	**↓heat loss/ ↑heat production**
CNS	Remove clothing; ↓activity	Huddle; add clothing
Cardiovasc	↑peripheral vasodilation + ↑CO	Vasoconstriction
Musculocutaneous	Sweating	Piloerection; Shivering: ↑BMR
Metabolic		↑BMR Non shivering thermogenesis : hormonal (thyroid, adrenaline); brown fat (uncoupled oxidative phosphorylation → ETC to produce heat rather than ATP. Vital in neonate)

- Cutaneous response to heat
  - Control of cutaneous blood flow = important in regulating heat loss by convection, radiation, and conduction
  - Skin circulation receives 8% of CO
  - Superficial network of arterioles, capillaries, venules, plexus are innervated by alpha-adrenergic SY fibres
  - If body temp >30 → ↓SY activity to skin → vasodilation → ↓PVR → triggers ↑CO → prodives large area for heat transfer between skin + environment

Temperature regulation in the neonate, physiological responses to lowered and raised environmental temperature, the effects of anaesthesia on these responses and how this changes with growth and development

- Thermoneutral zone = range of ambient temperature in which body temp can be maintained without ↑heat production (metabolic rate) > resting level → within this ideal zone, the person is in thermal equilibrium with their environment

<u>Temperature regulation in the neonate</u>

- Thermoneutral zone: higher and more narrow in neonates cf adults
  - Adults: 25-30°C
  - Term neonates: 32-34°C
  - Pre-term infant: 35-36°C due to ↑evaporative heat loss
  - Within thermoneutral zone, body temp is controlled by Δposition and Δskin blood flow
- Shivering poorly developed
- Non-shivering thermogenesis:
  - ↑metabolism of brown fat
  - brown fat has ↑mitochondrial content and SY input
  - SY stimulation via thermoRs release NAd → acts on β3 adrenoceptors → ↑effect of lipase
- Sweat glands
  - ↑sweat gland density cf adult, however ↓ability to sweat
- behavioural response ↓/ absent

<u>Physiological responses to lowered and raised environmental temperature</u>

Reasons neonates are more prone to heat stress:

- immature shivering response
- large surface area to volume ratio
- thin subcut tissue
- limited sweating capacity
- limited ability to control personal environment
- heat loss due to evaporation from wet skin

Response to cold

- behavioural changes
- skin vasoconstriction
- non-shivering thermogenesis (brown fat metabolism: can ↑metabolic rate 2x > resting)
- ↑muscular activity

Response to heat

- behavioural changes
- skin vasodilation
- sweating

Brown fat

- located: interscapular areas, perinephric fat, around intra-abdominal vessels
- highly vascular + abundant mitochrondria + richly innervated by adrenergic fibres
- produces heat through uncoupled oxidative phosphorylation which uses ETC to produce heat rather than ATP
- Proposed mechanisms:
  - 1. Presence of large amounts of non-esterified FAs uncouple mitochondrial phosphorylation from respiration → energy directly lost as heat
  - 2. Recycling of TGs and FAs by lipolysis and re-esterification → ↑ATP hydrolysis + heat production

Effects of anaesthesia on thermoregulation

- GA = absence of awareness + LOC/ hypnosis +/- muscle relaxant
- Degree of hypothermia depends on: dose of anaesthesia, neuraxial anaesthesia, surg exposure, ambient temp, patient factors
- Effect of GA:
  - Widened interthreshold range
  - Heat redistribution + heat loss: 1° radiation in infants
  - Inability to effect response: infants have

Role of anaesthetist to maintain body temp of child in theatre

- warming blankets (forced air convection blankets)
- wrap non-operative sites in insulating materials
- ↑theatre temp
- warm humidification of inspired gases
- warm IV fluids and wash solutions
- use of radiant heaters after delivery in LUSCS
- short operating times
- ↓exposure time to wet surfaces (↓evaporation)
- monitor body temp

Changes with growth and development

- ↓brown fat
- maturity of shivering response
- ↓surface area to volume ratio
- thicker subcut tissue
- ↑sweating capacity
- ↑ability to control personal environment

Describe the physiology of the cardiovascular, respiratory, renal and neurological systems in the neonate and the changes that occur with growth and development and the implications of this for anaesthetic care

Definitions

- premature: <37 weeks
- neonate: birth to 28d
- infant: <1 year
- toddler: 1-3years
- child: 3-puberty
- adolescence: puberty to 18yrs

Cardiovascular	Implications

Cardiovascular function
- Cardiac muscle immature at birth
- Behave as fixed CO state
  ○ HR = important determinant of CO
  ○ SV relatively fixed
  ○ Myocardium less contractile: ventricles less compliant + less able to generate tension during contraction → limits SV → CO therefore rate dependent
- ↑VA + PSY tone → ↑prone to bradycardias
- neonatal heart ↑↑sensitive to systemic or PVR → ↓CO
- ↓SVR → ↓SBP
- O2 transport
  ○ ↑metabolic requirement
  ○ ↑CO, ↑HR, ↑RR
  ○ do not tolerate bradycardia or interruption in ventilation
  ○ HbF 70-80% total Hb → HbA
Transitional circulation
- foramen ovale closure by 6 weeks; patent FO in 30% adults
- PPHN
- PDA: 50% extreme prems; contracts few days; closure 2-4weeks
- Congenital heart disease
- persistence of foetal circulation with hypoxia and acidosis
	- Do not tolerate fluid overload
	- Hypoxia and laryngoscopy → profound bradycardia
	- ↑sensitivity to –ve inotropic effects of anaesthetic agents cf older children → avoid deep anaesthesia, esp. ↑conc volatiles
	- maintain normal HR → excessive tachycardia → inadequate ventricular filling in diastole
	- bradycardia associated with ↓CO
	- atropine may counteract ↓CO seen with volatiles and will protect against VA mediated reflexes

Respiratory	**Implications**

Anatomical
- Dentition
- Large tongue; prominent occiput
- narrow airway: ↑airway resistance + easily blocked by secretions/ oedema
- funnel shaped; narrowest point at cricoid
- epiglottis long and floppy
- trachea short
- diaphragmatic breathing
Ventilation
- Immature control of ventilation
  ○ Blunted response to hypercapnoia in 1st few weeks
  ○ Respond to hypoxia by ↑ventilation followed by apnoea
  ○ Control of respiration matures by 3 weeks of age
- ↓alveoli → ↓SA for gas exchange
- ↑O2 consumption and rate dependent MV → faster desat
- ↓FRC cf adult
- CC occurs in tidal ventilations
- ↑lung + chest wall compliance
	Anatomical
	- Sniffing position does not help BVM or visualisation of glottis → need to be in neutral position
	- Easily obstructed
	- Endobronchial intubation common
	- Straight Magill blade used in neonates + infants
	- Un-cuffed tubes to avoid oedema until age 8-10
	- Small leak should be present
	- Tube size = age/4 + 4
	Ventilation
	- WOB up to 15% O2 consumption
	- Low distending pressures of lung + prone to collapse → use CPAP/ PEEP
	- Gastric distension common after BVM
	- Anaesthetic agents → ↓pharyngela dilators → upper airway obstruction.
	- ETT have ↑resistance which ↑WOB: all neonates

- Volumes same as adult by 1 week ***Other*** - Surfactant produced from 24-26 weeks - ↑VA tone upper airway → predisposes to bradycardia + laryngospasm - ↑onset and emergence with volatiles due to ↑alveolar vent	should be intubated and PPV used - post op apnoeas esp. if prem, anaemic, opiates - Limited resp reserve; prone to fatigue
Renal	**Implications**
- ↓RBF and ↓GFR during <2years due to ↑renal vascular resistance - tubular function matures over 1st few weeks of life - fluid and electrolytes: ECF compartment is expanded; TBW 85% body weight in prem, 75% in term, cf 60% adult - UO 1-2ml/kg/hr	- dehydration poorly tolerated - does not handle fluid or Na+ overload - ↑ECF → ↑VD → ↑dose requirements, despite ↑sensitivity
Neuro	**Implications**
- well developed responses to painful stimuli - neuronal fine tuning of pain pathways - BBB poorly formed - Cerebral vessels thin walled + fragile - Cerebral autoregulation present + functional from birth	- Pain → ↑HR, BP, neuroendocrine response - Narcotics depress vent response to ↑PaCO2 - Drugs e.g. barbiturates, opioids, abx, Br cross BBB easily → prolonged + variable DoA - Prone to intraventricular haemorrhages: risk ↑with hypoxia, hypercarbia, hypernatraemia, low HCt, airway manipulations, fluctuations in BP - Inhalational induction excellent technique

Other:

Hepatic function

- newborn liver: 20% of hepatocytes in adults + grows until early adulthood
- liver = principle site of drug metabolism
    - phase I processes sig ↓at birth
    - phase II (conjugation): well developed (sulfation) or limited (glururonidation)
    - In general: drug effects are prolonged
    - Maturation of enzymatic processes ↑over 1st few weeks
- ↓plasma protein binding → ↑toxicity
- ↓hepatic stores of glycogen + immature gluconeogenic enzyme systems
- Implications
    - Drugs should be given in boluses + titrated rather than by infusions
    - Susceptible to hypoglycaemia → should not be starved excessively + glucose should be added to fluids

Haematology

- 70-90% Hb = HbF
    - HbF combines more readily with O2; released less readily as there is less 2,3DPG
    - age 3 months: HbF ↓ to 5% and HbA predominates → OHDH shifts to right as levels of HbA and 2,3DPG ↑
- ↑Hb and ↑Hct at birth
- vit K dependent clotting factors (II, VII, IX< X) and platelet function are deficient in 1st few months

Temperature control

- large surface area to weight ratio with minimal subcut fat
- thermoregulation limited → become cold easily
    - heat production limited
        - poorly developed shivering, sweating, vasoconstriction mechanisms
        - ↑risk of heat loss; ↑body surface area, ↑thermal conductance, ↑evaporative heat loss
    - brown fat
        - located around scapulae, mediastinum, kidneys, adrenals
        - non shivering thermogenesis
        - ↑O2 requirement
- hypothermia: associated with hypoxia, ↓wound healing, prolonged coagulation, ↓platelet function, ↓drug metabolism, cerebral depression, myocardial depression, acidosis, ↓immunity
- implications:
    - vulnerable to heat + evaporative losses
    - heat loss during anaesthesia mostly via radiation
    - optimal ambient temp to prevent ehat loss: 34oC for premature infant, 32oC neonate, 28oC adolescent/ adult

Describe the composition of body fluids in the neonate and explain the changes that occur with growth and development

Neonates

- ↑TBW (preterm > term 75% > 2yr > children > adults 60%
- ↓fat, ↓muscle content
- ↑ECF component in term neonates (60% cf adults 30%)

Implications

- water soluble drugs: ↑VD → require ↑initial doses to achieve desired blood level (e.g. abx, sux)
- less fat: drugs that depend on redistribution into fat for offset of action will have ↑DoA (e.g. thio)
- drugs that redistribute into muscle may have ↑clinical effect e.g. fent
- thermoregulation: ↓subcut fat = prone to heat loss, less insulation)

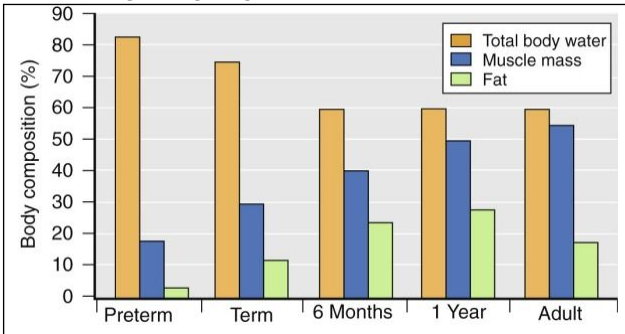


Table 81-3 -- Variation of Body Fluid Distribution by Age Group

Distribution of Body Fluids	Preterm Neonates	Full-Term Neonates	Infants	Children	Adults
Total body fluids	80-85%	70-75%	65%	55-60%	50-55%
Intracellular	20-25%	30-35%	35%	35-40%	40-45%
Extracellular	55-60%	45%	30%	20-25%	20%

Describe glucose homeostasis in the neonate and explain the changes that occur with growth and development

Foetus

- constant supply of glucose across placenta: diffusion according to uptake + Transplacental gradient
- energy from: glucose, amino acids, lactate, FFA, ketones
- Foetal blood glucose = 70% maternal
- insulin secretion by foetus:
  - does not cross placenta
  - secretion regulated by plasma [glucose] + [aminoacids]
  - ↑β cells in 3rd trimester
- utilises amino acids from mother → gluconeogenesis
- foetal liver = 3x glycogen cf adult

Neonate

Glucose homeostasis after birth:

- Reference ranges:
  - Normal BSL range: 2.8-5.6mmol/L
  - Neonate: BSL >2mmol acceptable for 1st 24hrs then >2.5mmol/L
- glucose = main energy source for newborn
  - only glucose: kidneys, erythrocytes, heart
  - ketones + glucose: brain
  - foetal brain uses ↑glucose cf adult: 10-12% total body weight
- At birth
  - ↑glycogen: mins to hours → prevents hypoglycaemia
  - ↑Ad, NAd, GH → minor role
  - ↓insulin over days
- BSL post delivery depends on:
  - Substrate: glycogen store, fats, amino acids
  - Enzymes: functioning liver + metabolic pathways
  - Hormones: pancreas, hypothalamus, pituitary
- Hypoglycaemia
  - Physiological hypoglycaemia
    - 1st 4-6hrs post birth: physiological ↓glucose to ~2.5mmol/L
    - → lipolysis + ketosis
  - Pathological hypoglycaemia
    - ↑insulin
    - altered endocrine function
    - inadequate glycogen/ fat: SGA, IUGR
    - metabolic disorder
    - sepsis/ infection/ resp distress → ↑demand
  - Clinical signs: cyanosis, seizure, apnoeic episodures, ↑RR, weak/ high pitched cry, floppiness, lethargy, poor feeding
- 1st few weeks: adaptation due to regular feeding + maturation of metabolic system (+GIT)

Infants and older children

- children: poorer tolerance to fasting state: hypo at 24hrs cf adult days
- poorer glucose production + ↑demand
  - ↑BMR + ↑weight of brain
  - poorer liver + metabolic systems
  - ↓substrates e.g. amino acids from muscles
- early childhood characterised by predisposition to produce ketones
  - faster + ↑rapid ↑ketones
- Hypoglycaemia: BSL<2.2mmol/L

Describe vital signs for children of different ages

Age	RR	HR	SBP
<1	30-40	110-160	70-90
1-2	25-35	100-150	80-95
2-5	25-30	95-140	80-100
5-12	20-25	80-120	90-110
> 12	15-20	60-100	100-120

GENERAL ANAESTHESIA AND SEDATION – CLINICAL AND APPLIED PHARMACOLOGY

Describe how the pharmacokinetics of drugs commonly used in anaesthesia in neonates and children differ from adults and the implications for anaesthesia

Pharmacokinetics

Absorption	Distribution	Metabolism	Excretion
PO - ↑pH → ↓absorption acidic drugs, ↑absorption basic drugs - ↓gastric emptying → variable absorption - ↓bile: ↓absorption lipid soluble ***IM*** - ↓muscle mass → variable absorp ***transdermal*** - thin skin + variable blood flow - ↑absorption with fever ***Rectal*** - variable absorption ***Lung*** - ↓FRC cf adult (similar by end of 1st week) - ↓FRC, ↑MV, ↑alveolar vent → ↑uptake volatiles → faster onset and offset	***VD*** - ↑TBW + ↑ECF → ↑VD water soluble drugs e.g. sux - ↓fat, ↓muscle: ↓ditribution to peripheral compartments → ↑[plasma] e.g. thio - ↑CO to brain → ↑effects of induction agents - poor BBB → ↑effects of water soluble drugs e.g. morphine ***PB*** - ↑PB → ↑free drug, ↑toxicity, ↑excretion e.g. LA, diaz, barbiturates, phenytoin	***Phase I reactions (ox, red, hydrolysis)*** - ↓activity p450 enzymes → ↑T ½ - variability of CYP450 systems ***Phase II reactions (conjugation)*** - sulfonation mature at birth - glucuronidation matures 12 months ***Hepatic blood flow*** - ↓neonate - ↑child ***↓plasmacholinesterase activity***	***Neonate*** - RBF 5% CO (cf adult 25%) - GFR 10% adult at birth: ↓excretion - Tubular function immature - Most affected is drugs dependent on renal excretion e.g. aminoglycosides, cephalosporins ***Child*** - ↑CO → ↑excretion

Describe the changes in the pharmacodynamics of volatile agents, analgesics, opioids and neuromuscular blocking agents in the neonate and the changes that occur with growth and development and the implications for anaesthesia

Inhalational
- ↓MAC in neonate → peaks 6-12months → ↓to adult value over few years. Mechanism unknown
- des good in neonates: rapid wake up; ↓post op apnoeas
- R to L shunt will ↓onset due to ↓blood exposure to volatile
- ↑emergence delirium → ↑with sevo/ des due to faster offset

IV anaesthetic agents
- Generally neonates have ↑sensitivity to induction drugs, ↑permeability of BBB and immaturity of resp centre (↑apnoea)
- Propofol
  - ↑induction dose (3-4mg/kg) cf adult (1-2mg/kg) and ↑maintenance dose due to rapid distribution and metabolism (↑CO)
  - not licensed for sedation in children due to propfol infusion syndrome
  - 60% pain on injection
  - SE: bradycardia
- Thiopentone
  - Neonate: ↓PB + ↓cortical maturity + ↓distribution due to ↓fat/ muscle mass → ↓dose
  - Infant: ↑dose due to ↑CO
- Ketamine
  - ↑dose due to ↑metabolism in child (neonate ↓metabolism → ↓dose)
  - less hallucinations and dreams in younger cf older children
  - SE: ↑PONV 30%, salivation, ↑ICP
- Benzos
  - ↑↑T ½ in neonates: ↓enzymes and blood flow
  - ↓T ½ in child
  - diaz: ↑T 1/2 : not good for short procedures
  - midaz = less fat soluble → slower onset

Analgesics
- morphine: ↑sensitivity due to ↓receptors, ↑resp depression, ↑penetration BBB
- fent: similar PD in neonate / child / adult

NMBDs
- ↓maturity of NMJ → ↓dose
- sux: beware bradycardia
- pan: delayed excretion due to ↓renal function

LAs
- ↓block duration and require 4x weight scaled dose than adult due to:
  - differences in myelination, nodes of ranvier
  - issues with fast absorption (↑CO, thin skin), poor metabolism
- so neonates need more LA, but ↑risk of toxicity

Describe the pharmacology of agents used for premedication in children, including midazolam, clonidine, and ketamine

	Ketamine	Midazolam	Clonidine
Chem	phencyclidine derivative Racemix mix: 2 enantiomers 2° chiral centre cyclo-hexanone ring S+R	Imidazobenzodiazepine	Aniline derivative
Uses	Induction, sedation Dissociative anaesthesia; analgesia	induction, sedation, hypnotic, anti-seizure	Premedicaion/ anxiolysis / analgesia / sedation / HTN Intraoperative haemodynamic stability: ↓SNS outflow; blunt response to stimuli Migraine/ menopausal flushing/ chronic pain/ opiate or etoh withdrawal
Pres	CCS 10/50/100mg/ml racemic ketamine hydrochloride	CCS midazolam hydrochloride for injection	Tablets: 100-300microg/ CCS 150microg/ml clonidine hydrochloride
Action	non-competitive NMDA R antagonist → ↓pre-synaptic release of glutamate ?antagonist at monoaminergic, muscarinic, and nicotinic receptors	Acts on BZD Rs in CNS (midbrain + cortex) Facilitate action of GABA Rs → open Cl ion channels → hyperpolarize synaptic membrane	Antihypertensive + analgesia + sedative + anxiolytic **MoA**: Partial agonist at α-adrenoceptor; α2:α1 selectivity 200:1 α2 adrenoceptors: - on target tissues: presynaptic on SY nerve fibres (peripheral); post synaptic within CNS/ SC (central); platelets - GPCR Gi coupled adenylyl cyclase inhibition → ↓cAMP α2 presynaptic adrenoceptor agonist → ↓NAd release from SY nerve terminals → ↓SY tone + ↑VA tone Analgesic: ↓NAd transmission at dorsal horn + ↑inhibitory descending pathway
CNS	Dissociative state Sedation + analgesia ↑CBF, ↑ICP, ↑IOP ↑CMR	hypnosis, sedation, anterograde amnesia	Sedation + analgesia: central α2 agonism → inactivation of locus ceruleus + activation of descending inhibitory pain pathways Spinal: spinal α2 Rs in dorsal horn → depress wide dynamic range neurons involved in peripheral nociceptive input ↓adrenergic transmission in CNS ↓CBF ↓IOP SY depressant
CVS	↑SNS tone → ↑circulating Ad + NAd → ↑HR, ↑BP, ↑CVP, ↑CO mild direct myocardial depressant	↓SVR, ↓BP; ↑HR	α2 agonist → ↓SNS outflow from BS vasomotor centre → ↓SVR ↓HR ↓MAP initial ↑MAP 2° peripheral vasoconstriction 2° α1 R stimulation sustained ↓MAP with 2° central α2 activation (↓NAd release) NB prolonged use: upregulate α-adrenoceptors → rebound HTN NB no direct effect on heart, but ↓circulating catecholamines
Resp	Bronchodilation ↑pulmonary compliance ↑secretions	↓VT but ↓RR so MV unaffected; apnoea; ↓hypercarbic drive	↓gastric + small bowel motility Antiemetic: ↓sensitivity of CTZ
Toxicity/ SE	Emergence delirium, dreams, hallucinations; N+V; rash	Paradoxical agitation Unpleasant taste	Drowsiness + dry mouth 50% CNS disturbance, fluid retention, constipation Rapid withdrawal → rebound HTN + ↑HR
Route/ dose	IM: 5mg/kg Nasal: 5mg/kg PO 5mg/kg	IM: 0.05mg/kg PO/Buccal: 0.5mg/kg Nasal: 0.2mg/kg	IM: 4µg/kg Nasal: 4µg/kg PO: 4µg/kg
pKa	7.5	6.5	
Onset	IV: 30sec; IM: 3-5mins;	IV: 3-5min; PO 15-20min	IV: 10mins
Duration	IV: 5-10mins; IM: 10-20mins	20-60mins	IV: 3-7hrs
A	PO 25%; Nasal 25-50%; IM 95%	bioavailability PO 40%; IM 80%	Bioavailability 100%
D	20-50% protein bound Vd 3L/min	96% protein bound Vd1L/kg	Very lipid soluble: penetrates BBB / 20% protein bound Vd 2L/kg
M	**Liver** **N-demethylation + hydroxylation** via CYP450 Norketamine (30% potent) → glucuronide (inactive)	**liver** via CYP3A4; active metabolites 1-hydroxymethylmidazolam → conjugated to glucuronide.	50% liver to inactive metabolites
E	**Urine** Clearance 17ml/kg/min Elimination ½ life 3hrs	**urine** (90%); **faeces** (2%) Clearance 7ml/kg/min Elimination ½ life 1-4hrs	65% unchanged in urine 20% faeces elimination ½ life 6-23hrs
Special points		Little effect from renal impairment Short DoA due to high lipophilicity, high metabolic clearance, and rapid rate of elimination	↓MAC coadministered volatiles prolongs duration of LA when coadministered for neural blockade

Outline how the pharmacokinetics of morphine, bupivacaine and suxamethonium differ in the neonate compared to the adult. Briefly describe the clinical implications of these differences: PAST QUESTION 73%
Outline the pharmacological differences between neonates and adults with reference to sevoflurane, vecuronium, and morphine: PAST QUESTION 42%

Background

- neonate = first 28 days of life
- morphine = naturally occurring opiate analgesic
- bupivacaine = long actin amide LA
- suxamehtonium = depolarising NMBD
- sevoflurane = volatile anaesthetic (fluorinated ether)
- vecuronium = NDNMBD (benzylisoquinolone)

Pharmacokinetic differences: neonate vs. adult

- Absorption
  - Poor compliance with PO intake + ↓gastric emptying → unreliable PO/ GI absorption
  - Unpredictable skin blood supply → less reliable transdermal, subcut, intramuscular absorption kinetics
  - ↑RR → ↑Mv → ↑absorption of volatiles
- Distribution
  - Porportionally ↑ECF → ↑Vd (esp. for hydrophilic drugs)
  - ↓plasma protein (albumin and α1 acid glycoprotein) → ↑fraciton unbound
  - ↓plasma pH → alter ionised fraction
  - immature BBB → ↑penetration of lipid soluble drugs
- Metabolism
  - Immature liver enzyme system → ↓hepatic phase I and II metabolism
  - ↓plasma cholinesterase levels
- Excretion
  - Immature kidneys → ↓GFR (10% of adult) → ↓renal clearance of drugs
  - ↓tubular secretion mechanisms

Pharmacokinetic differences of above drugs

	Morphine	**Bupivacaine**	**Sux**	**Sevo**	**Vec**
A	↓PO absorption unreliable IM/ SC	Unreliable cutaneous absorption → safe dose ?<3mg/kg	IV therefore absorption unaffected	↑MV → ↑absorption of volatiles → faster induction	Unchanged
D	↓[protein] ↑unbound fraction immature BBB → ↑CNS availability	↓α1-acid glycoprotein → ↑free drug ↓pH (pKa 8.1) → ↑ionised fraction → slower onset	↑Vd → ↓availability at NMJ → need ↑dose	↑cardiac index → slightly ↓ rise of FA/FI ↓blood:gas solubility	↑CI → faster onset ↑Vd → ↓availability at NMJ → may need ↑dose
M	↓hepatic glucuronidation → ↑DoA	↓hepatic metabolism → ↑DoA → ↑risk toxicity	↓plasma cholinesterases → ↑DoA		↓hepatic metabolism → ↑DoA
E	↓renal function → ↓renal clearance → ↑DoA	↓renal excretion → ↑DoA	↓renal excretion → ↑DoA		↓renal excretion → ↑DoA
	↑resp depression and apnoea			More rapid induction ↑MAC	Net effect dose per kg similar to adult

NB re sux:

- opposite forces at work
  - ↑ECF volume → ↑Vd → ↓activity
  - countered by ↓pseudocholinesterase levels in neonate
  - end result clinically is little change in duration of action

Pharmacodynamics

- What the drug does to the body
- Different sensitivities to drugs; permeability of BBB; sensitivity of resp centre

REGIONAL ANAESTHESIA

Describe the difference in pharmacokinetics of local anaesthetic agents in neonates and children from adults and the implications for regional blockade

Absorption

- Can be given IV, epidural, spinal, compartment block, peripheral nerve blocks, mucoud membranes, topical
- ↑CO neonates/ children cf adults = ↑uptake LA from high blood-flow regions → ↑absorption of LA on mucous memebranes in infants
- absorption from neuraxial space ↑due to ↑CO → ↑initial plasma concentrations + ↓DoA

Distribution

- ↓α-1 acid glycoprotein = ↓PB → ↑free fraction of LAs → ↑risk toxicity
  - neonates have 20-40% adult levels → reach normal levels at 12 months
  - ↓max dose of amides in neonates
- ↑VD of LAs
  - due to ↑ECF content
  - ↓peak plasma conc after bolus → ↓toxicity after single dose
  - ↑risk of drug accumulation with infusion → ↑plasma conc → ↑T ½ and ↓clearance
  - loose fascial attachments around nerves → ↑spread + ↓length of block
  - red cell storage:
    - once in circulation, LAs distribute to RBC (20-30% total dose) = minor impact in adults; ↑significance in neonates/ infant
    - neonates: ↑Hct + large RBCs (physiological macrocytosis) → entrapping ↑LA in RBCs → ↓Cmax after single bolus dose but ↑secondary release thereby ↑1/2 life
    - infants: physiological anaemia → ↓RBC storage of LA thereby ↓systemic toxicity of LA after single shot injection

Metabolism

- immaturity of hepatic enzyme systems until ~3 months (CYP3A4 for lignocaine + bupivacaine, and CYP1A2 for ropiv and levobupiv)
- potential for toxicity from accumulation of lignocaine metabolite MEGX in neonates
- infusion rate in infants should be ↓after 24hrs to prevent accumulation

Elimination

- T1/2 elimination depends on metabolism + distribution
- Longer elimination ½ life due to ↓metabolism + clearance
  - E.g. bupivacaine t1/2 elimination 3.5hrs in adults cf 8-12hrs in neonates/ young infants
  - T1/2 elimin is same in 12mo and adults 2o to ↑CO + ↑liver blood flow (↑Vd compensated by ↑plasma clearance)

Implications for regional anaesthesia

- caudal + lumbar epidural analgesia common
- continuous infusions
  - prolonged elimination = concern for continuous infusions
  - seizures associated with high bupivi infusion rates
  - Bupivi: max infusion dose of: children + adults: 0.4mg/kg/hr; neonates + infants: 0.2mg/kg/hr
  - Lignocaine max infusion dose of: 0.8mg/kg/hr neonates
- Max safe dose for single shot peripheral nerve blockade similar for adults
  - Bupiv: 3mg/kg
  - Lignocaine 3mg/kg without adrenaline; 7mg/kg with adrenaline
  - Ropivacaine 2mg/kg

	Lignocaine		**Bupivacaine**		**Levobupivacaine**		**Ropivacaine**	
	Neonate	Adult	Neonate	Adult	Neonate	Adult	Neonate	Adult
Protein binding %	25%	55-65%	50-70	95%	50-70%	95%	94%	94%
Vd L/kg	1.5-5L/kg	0.2-1L/kg	4L/kg	0.8-1.5L/kg	2.7	0.7-1.4L/kg	2.4	1.1L/kg
Clearance ml/kg/min	5-20	10-15	7	7-9	14	30-40	6	4-6
Elimination ½ life (hr)	3	1-2	6-22	1-3	4	1	4	1

Describe the maximum safe doses of local anaesthetic agents in different age groups

- **continuous infusions**
  - prolonged elimination = concern for continuous infusions
  - seizures associated with high bupivi infusion rates
  - **Bupivi**: max infusion dose of:
    - children + adults: 0.4mg/kg/hr
    - neonates + infants: 0.2mg/kg/hr
  - **Lignocaine** max infusion dose of:
    - 0.8mg/kg/hr neonates
- Max safe dose for **single shot peripheral nerve blockade** similar for adults
  - **Bupiv**: 3mg/kg
  - **Lignocaine** 3mg/kg without adrenaline; 7mg/kg with adrenaline
  - **Ropivacaine** 2mg/kg