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REVIEW ARTICLE

# The neonatal lung – physiology and ventilation

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## Summary

This review article focuses on neonatal respiratory physiology, mechanical ventilation of the neonate and changes induced by anesthesia and surgery. Optimal ventilation techniques for preterm and term neonates are discussed. In summary, neonates are at high risk for respiratory complications during anesthesia, which can be explained by their characteristic respiratory physiology. Especially the delicate balance between closing volume and functional residual capacity can be easily disturbed by anesthetic and surgical interventions resulting in respiratory deterioration. Ventilatory strategies should ideally include application of an 'open lung strategy' as well avoidance of inappropriately high $V_T$ and excessive oxygen administration. In critically ill and unstable neonates, for example, extremely low-birthweight infants surgery in the neonatal intensive care unit might be an appropriate alternative to the operating theater. Best respiratory management of neonates during anesthesia is a team effort that should involve a joint multidisciplinary approach of anesthetists, pediatric surgeons, cardiologists, and neonatologists to reduce complications and optimize outcomes in this vulnerable population.

## Introduction

Three quarters of all critical incidents and one-third of all perioperative cardiac arrests in pediatric anesthesia are related to the respiratory system (1,2). Preterm and term infants are at even higher risk of anesthesia-related critical incidents than older children, which can be explained by the differences in respiratory physiology in this vulnerable population. This review article focuses on neonatal respiratory physiology, mechanical ventilation of the neonate and changes induced by anesthesia and surgery. Optimal ventilation techniques for preterm and term neonates are discussed.

## Respiratory physiology in neonates

Lung physiology and pulmonary mechanics in neonates, especially if born preterm, are considerably different compared to older children and adults. The special characteristics of neonatal respiratory physiology need to be appreciated to ensure safe respiratory management during pediatric anesthesia.

### Respiratory control

The development of respiratory control starts early in gestation but continues to mature for weeks or months after term birth (3). The breathing pattern of preterm and term infants is often irregular and periodic and can be associated with severe and life-threatening apneas, which reflects the immaturity of the respiratory control system (4). All levels of the respiratory control system are immature including brainstem respiratory rhythmogenesis, peripheral and central chemoreceptor responses, and other parts of the network (3). The ventilatory response to hypercapnia and hypoxia is impaired in neonates. Whereas hypercapnia increases tidal volume and respiratory rate in term infants, children, and adults, the response seems to be attenuated in preterm neonates (5,6). Preterm infants show a biphasic response under hypoxic conditions. After an initial increase

in ventilation for approximately 1 min, ventilation subsequently decreases with the potential for apneas (7). Anesthetic drugs can further blunt the respiratory control to both hypoxia and hypercapnia (8). Another important mechanism contributing to apneas in neonates is an exaggerated inhibitory response to either an afferent laryngeal stimulation (9,10) or an excessive inflation of the lung (11). The latter is also known as Hering–Breuer inflation reflex, which is more pronounced in preterm and term neonates (12) compared with older children.

Apneic episodes are defined as absent airflow for more than 20 s and classified as either central apneas in absence of breathing efforts or obstructive apneas in the presence of breathing efforts (13). Clinically, most apneas occur as mixed apneas (14), that is, a combination of poor respiratory drive (central apnea) and failure to maintain a patent airway (obstructive apnea). Central apneas result from a decreased respiratory center output due to the immaturity of the respiratory control system. Obstructive apneas most often occur during active sleep (i.e., rapid eye movement phase); the predominant site of airway obstruction is the pharynx, which shows reduced muscle tone during this period (4). Poor respiratory control, especially in very preterm infants, might require the use of methylxanthines (such as theophylline of caffeine), continuous positive airway pressure, or even intubation and mechanical ventilation (4).

### Upper and lower respiratory tract

Compared to older children and adults, there are considerable differences of respiratory physiology of upper and lower airways in the neonate. Due to the anatomy and relatively large head size of infants, the anatomical dead space in infants is greater than in older children and adults (15). The epiglottis in neonates is relatively large and positioned high in the pharynx and in very close proximity to the soft palate. This results in a lower airflow resistance in the nasal passage and explains why neonates breathe preferentially through their nose (16). Pharynx, larynx, trachea, and the bronchial tree are more compliant in the neonate compared with older children. This can lead to dynamic airway collapse of the upper airways during forceful inspiration. Airway diameters are much smaller in the neonate than in older children or adults resulting in higher airflow resistance in infants (17) as the resistance is inversely proportional to the fourth power of the airway radius. Airway resistance decreases continuously in the first year of life (18). Narrowing of the airways due to luminal blood, secretions, or an endotracheal tube have a much greater impact on the work of breathing (WOB) in preterm and term infants compared with older patients. Additionally, conditions such as laryngomalacia, tracheobronchomalacia, subglottic or tracheal stenosis are more common in neonates and (ex-premature) babies and are associated with reduced airway diameter, which can substantially increase WOB in infants (19). Highly compliant and compressible intrathoracic airways in conditions such as tracheobronchomalacia may result in expiratory airway collapse due to the high intrathoracic pressure, which can further increase airway resistance and WOB. Positive end-expiratory pressure (PEEP) is an important measure to stent collapsed airways open (20).

### Lung and thorax

Newborn infants, especially if born premature, have fewer and larger alveoli than older children and adults (17). Alveolarization, that is, the growth and development of alveoli, continues into childhood and adolescence (21). Collateral connections between alveoli (pores of Kohn and bronchoalveolar canals of Lambert) are not present until the first years of life (22). The absence of accessory interalveolar communications in neonates increases the risk of atelectasis in dependent lung areas.

Production of pulmonary surfactant begins by 23 to 24 weeks gestational age and reaches sufficient levels after about 35 weeks of gestation (23). However, surfactant production can be delayed under certain conditions such as maternal gestational diabetes or perinatal asphyxia (24). Administration of antenatal corticosteroids to mothers in preterm labor stimulates lung maturation and endogenous surfactant production (25). Surfactant-deficient lungs are characterized by poor compliance, reduced volume and widespread atelectasis, ventilation-perfusion mismatching and hypoxia (24). Endotracheal administration of exogenous surfactant as well as application of PEEP significantly improves respiratory physiology and clinically relevant outcomes of preterm infants with respiratory distress syndrome (24,26).

Term infants and especially preterm infants have immature antioxidative systems and are at risk of oxygen toxicity (27). High inspired oxygen ($F_iO_2$) concentrations not only cause retinopathy (28) but also contribute to the development of bronchopulmonary dysplasia in preterm infants (29).

In the mature lung, collapse of airways is being prevented by the elastic tissue of the surrounding alveolar septa. In neonates, due to fewer alveoli, there is

less elastic recoil and therefore an increased risk of airway collapse mainly on expiration (30). The thorax of neonates is highly compliant and deformable (31). In respiratory distress, there can be pronounced inspiratory intercostal, sternal, and supraclavicular recessions as well as a paradox inspiratory inward movement of the chest wall due to the high compliance of the thorax. Under these circumstances, a significant part of the energy generated by diaphragmatic contraction is wasted on thorax distortion. Chest wall compliance decreases rapidly in the first few years of life (31).

As in older children and adults, the diaphragm is the most important muscle during inspiration. However, in neonates, the efficiency of the intercostal muscles is reduced as the ribs are aligned more horizontally (32). Additionally, the diaphragm of preterm and term infants as well as the intercostal muscles contains less type 1 muscle fibers (slow endurance) compared with children or adults, which explains why respiratory muscles of neonates are more susceptible to fatigue (33). Resting lung volume or functional residual capacity (FRC) is determined by the static balance between the outward and inward recoil pressure of the chest wall and lung, respectively, and is lower in neonates than in older subjects (30). Due to the poor elastic properties of infants lungs, their closing volume is greater than their FRC, with terminal airway closure occurring during normal tidal ventilation (30). Infants apply several mechanisms to maintain and dynamically increase their FRC: (i) postinspiratory activity of intercostal and diaphragmatic muscles (self-recruitment maneuver) (ii) high respiratory rates with short expiratory times (auto-PEEP or dynamic hyperinflation) (iii) laryngeal adduction in expiration to increase expiratory airway resistance (functional PEEP) (34–36). Main differences between respiratory physiology in infants and adults are summarized in Table 1.

**Table 1** Main differences between respiratory physiology in infants and adults

| Difference in infants | Physiological background |
|---|---|
| Rapid desaturations | Higher oxygen consumption rate<br>Smaller oxygen reserve relative to body size |
| Increased risk of apneas | Immature respiratory control |
| Increased airway resistance | Smaller airway size<br>Increased tendency for airway collapse due to increased airway compliance |
| Increased risk of FRC loss | Reduced pulmonary elastic recoil<br>Closing pressure near or below FRC<br>Dynamic, active FRC elevation |
| Reduced efficiency of respiratory muscles | Less type I (slow endurance) muscle fibers<br>Higher chest wall compliance<br>Ribs aligned more horizontally |

FRC, functional residual capacity.

## Neonatal ventilation

In the past decades, significant advances in neonatal ventilation were introduced in clinical practice, such as lung-protective ventilation strategies to avoid ventilator-induced lung injury (VILI). VILI is an important risk factor for the development of bronchopulmonary dysplasia (BPD) (37). Mechanical ventilation can inflict lung trauma by several mechanisms: (i) Excessively high tidal volumes ($V_T$) result in alveolar overdistension and injury of the lung periphery (volutrauma); (ii) High pressures during ventilation have an injurious effect to the lung (barotrauma); (iii) Insufficiently opened lung areas may be damaged by shear forces occurring during the respiratory cycle by repetitive opening and closing of alveoli (atelectotrauma); (iv) Mechanical injury of the lung (volutrauma, barotrauma, and atelectotrauma) leads to the release of proinflammatory cytokines and an inflammatory cascade, which contributes to VILI and the development of BPD (biotrauma); and (v) High levels of inspired $O_2$ cause oxidative stress and inflammation ($O_2$ toxicity) (38).

Consequently, lung-protective ventilation strategies should include (i) avoiding excessively high $V_T$ (volutrauma), (ii) excessively high airway pressures (barotrauma), (iii) applying recruitment maneuvers, if required, (iv) preventing repetitive opening and closing of alveoli (atelectotrauma) by applying appropriate PEEP, and (v) avoiding high fractions of inspired $O_2$ ($F_iO_2$) (39,40).

## Oxygen toxicity

High levels of inspired $O_2$ should be avoided in an attempt to reduce $O_2$ toxicity. In addition to $O_2$ toxicity, high $F_iO_2$ can promote atelectasis and decrease of FRC through absorption of $O_2$ (41) as well as contribute to the development of BPD and retinopathy of prematurity (42). $FiO_2$ needs to be adjusted to achieve the desired to the oxygen saturation ($SaO_2$) or partial arterial oxygen pressure ($P_aO_2$). Results from recent large randomized trials suggest that a preductal $SaO_2$ target range of 90–95% compared to 85–89% increases survival and reduces the risk of necrotizing enterocolitis in preterm

 

infants up to 36 weeks postconceptional age albeit at the expense of an increased rate of retinopathy of prematurity (43,44). However, the negative impact of high levels of $FiO_2$ on lung volumes can be counteracted by recruitment maneuvers and sufficient levels of PEEP (45).

## Permissive hypercapnia

Retrospective observations in preterm infants showed that low levels of carbon dioxide ($CO_2$) <30 mmHg before the first dose of surfactant are associated with an increased risk of BPD (46). These findings led to a ventilation strategy allowing for mild hypercapnia of 45–55 mmHg (i.e., permissive hypercapnia) in preterm and term neonates (47,48). Animal data (49) as well as data from randomized controlled trials (50) and observational studies (47) in very low-birthweight infants suggest that permissive hypercapnia is safe and may be effective to reduce pulmonary morbidity in mechanically ventilated infants (48). However, there is not enough evidence to currently support the routine use of permissive hypercapnia in infants (51). On the contrary, hypocapnia due to hyperventilation should definitely be avoided in neonates as it is associated with the development of periventricular leukomalacia (52). In a retrospective study, both hypocapnia and hypercapnia (<39 and >60 mmHg) as well as great fluctuations of $P_aCO_2$ in the first 4 days of life were associated with severe intraventricular hemorrhage in preterm infants (53).

## Ventilation modes

### Time-cycled pressure-limited ventilation

The most widely used mechanical ventilation mode in neonatal intensive care is the time-cycled, pressure-limited ventilation mode (TCPL), which is also known as intermittent positive pressure ventilation (IPPV). In this mode, inspiratory ($T_i$) and expiratory time ($T_e$) is being set and a limited pressure applied under conditions of continuous baseline flow throughout the respiratory cycle. Disadvantages of TCPL are that the applied $V_T$ may vary from breath to breath due to variable spontaneous breathing efforts, endotracheal tube leaks, secretions, or changes in lung compliance and/or resistance. Depending on the time constant of the lung, $T_i$ and $T_e$ might not be appropriate to achieve optimal $V_T$ and a peak pressure plateau allowing for even ventilation distribution within the lungs. Pressure-controlled ventilation (PCV) differs from TCPL as the inspiratory flow is variable and decreases when the set peak pressure is being approached.

### Flow-cycled ventilation

In flow-cycled ventilation, modes such as pressure-support ventilation (PSV) inspiratory flow supports every inspiratory effort and terminates inspiration once the flow drops below a certain threshold in proportion of the peak inspiratory flow. This enables the patient to breathe with variable inspiratory times instead of synchronizing only the onset of the inspiration. PSV may improve patient–ventilator synchrony, reduce VILI, and facilitate weaning (54). However, evidence of clinically relevant benefits of flow-cycled vs time-cycled ventilation and particularly of any long-term effects is lacking (55).

### Synchronized ventilation

Synchronized ventilation modes also known as patient-triggered modes are standard care in industrialized countries. Synchronized ventilation delivers positive pressure inflations after triggering by the patient's own spontaneous inspiratory breathing efforts. Asynchrony between the patient and ventilator may result in large changes in $V_T$. Furthermore, it can result in air trapping, blood pressure fluctuations, and poor oxygenation (56,57). A recent meta-analysis showed that synchronized ventilation in neonates is associated with a reduced risk of air leak and a shorter duration of mechanical ventilation (58). The most commonly used modes of synchronized ventilation in infants are synchronized intermittent mandatory ventilation (SIMV) and assist–control ventilation [ACV, equivalent to synchronized intermittent positive pressure ventilation, (SIPPV)]. In SIMV, only a predetermined respiratory rate is synchronized and supported by the ventilator but additional spontaneous breaths are unsupported, whereas in ACV, every spontaneous effort of the infant is supported (59). ACV compared to SIMV showed a trend to a shorter duration of weaning of the ventilator (58).

### Volume-targeted ventilation

The recognition that volutrauma rather than barotrauma contributes to VILI in neonates has shifted the focus of interest toward the control of $V_T$ to avoid alveolar overdistension (60). Traditional volume-controlled ventilation in neonates was abandoned due to technical difficulties in reliably monitoring and administering small $V_T$ in the presence of leaks around uncuffed endotracheal tubes, compliant ventilator tubing, and physiological changes in lung compliance and resistance.

Technological advances have led to the development of volume-targeted ventilation (VTV). Many current neonatal ventilators have a flow sensor placed between the Y-piece of the ventilator circuit and the endotracheal tube, whereas older designs used a flow sensor that was built into the ventilator. In VTV, inspiratory peak pressure of any current breath is chosen based on pressure requirements over the last couple of breaths to approach a preset target $V_T$. Provided there is only little endotracheal leak and an acceptable amount of tracheal secretions, such computationally intense breath-to-breath adjustment of peak inspiratory pressure leads to $V_T$ slightly undulating around preset target $V_T$, allowing for an automated ventilator response to changes in respiratory mechanics. Some ventilators additionally adjust inspiratory flow or $T_i$ to achieve target $V_T$. The use of VTV enables to reduce $V_T$ variability as compared to conventional TCPL (61). VTV modes can be combined with current TCPL and flow-cycled modes. In a recent meta-analysis, the use of VTV compared to pressure-limited ventilation modes resulted in a reduction in the combined outcome of death or BPD, pneumothorax, severe cranial ultrasound abnormalities, and hypocarbia (60). Currently, VTV seems to be the only modern neonatal ventilation mode with evidence of superiority over other ventilation modes regarding the composite outcome of death or BPD. The initial $V_T$ setting in VTV largely depends on the type of ventilator and the individual patient (e.g., commonly recommended $V_T$ target for Draeger Babylog 8000 plus$^R$ in preterm neonates with respiratory distress: 4.0–5.0 ml·kg$^{-1}$); subsequently, $V_T$ needs to be adjusted to maintain normocapnia or mild hypercapnia (48,62).

### High-frequency ventilation

High-frequency ventilation uses a low $V_T$ (smaller or close to respiratory dead space) and a frequency faster than normal respiratory rates (63). Modes of high-frequency ventilation include high-frequency oscillatory ventilation (HFOV), high-frequency jet ventilation (HFJV), and high-frequency flow interrupter ventilation (HFFI). The most commonly used high-frequency mode in neonatal intensive care is high-frequency oscillatory ventilation (HFOV), which is discussed in the following. HFOV allows applying a higher mean airway pressure (MAP) than under conventional mechanical ventilation, which prevents atelectasis and optimizes lung volume. Additionally, the risk of volutrauma is reduced by application of a very small $V_T$ making it theoretically an optimal lung-protective ventilation mode. Unlike conventional ventilation, HFJV or HFFI, in HFOV not only the inspiratory but also the expiratory phase is active. As HFOV is very effective even in severe respiratory failure, it is often used as a rescue therapy although there is evidence that it might have advantages using it as primary ventilation mode (64). In a recent meta-analysis, HFOV seemed equally effective to conventional ventilation in preterm infants with no differences in the outcomes BPD or death, oxygen dependency, and severe neurological sequelae (65). Observational studies suggest that the use of HFOV in term or near-term infants might be more effective than conventional mechanical ventilation (66,67). However, there are no randomized controlled trials supporting the use of HFOV in term or near-term infants with severe respiratory failure (68).

### Neurally adjusted ventilatory assist ventilation

Neurally adjusted ventilatory assist (NAVA) is a new ventilation mode, which uses the electrical activity of the diaphragm to trigger and proportionally assist mechanical ventilation (69). NAVA was associated with higher patient-ventilator synchronization and lower peak airway pressures compared to pressure-support ventilation (PSV) in preterm infants (70). However, there is insufficient data to recommend routine use of NAVA in neonatal intensive care, especially in neonates with unstable respiratory control.

## Cuffed versus noncuffed endotracheal tubes

Controversy exists on the use of cuffed endotracheal tubes in term and preterm infants. It has been standard practice for many years to use uncuffed endotracheal tubes in children aged below 8 years following standard textbook advice as conventional cuffed endotracheal tubes were thought to cause subglottic trauma. However, with the development of improved cuffed tubes, this concern is no longer valid. A disadvantage of uncuffed endotracheal tubes is the potential ventilatory leak around the tube leading to inaccurate monitoring of $V_T$ and capnographic measurements (71,72). Additionally, in the anesthesia setting, uncuffed tubes have been linked to a significantly increased risk for perioperative respiratory complications including postoperative stridor even when corrected for age (73,74). Recently developed high-volume, low-pressure cuffed tubes are appropriate and safe for infants ≥3 kg body weight and children and do not seem to be associated with an increased risk of airway injury also during longer periods of intubation of several weeks (72,75). However, it is vital to closely monitor cuff pressure (<20 cm $H_2O$) to avoid cuff hyperinflation and therefore the potential for mucosal damage due to hypoperfusion (74,76).

## Inhalative nitric oxide

Inhaled nitric oxide (iNO) is a therapeutic option in the treatment of both term and preterm infants with hypoxic respiratory failure. It seems to improve outcome of hypoxemic term or near-term infants with persistent pulmonary hypertension of the newborn (PPHN) in terms of reduced oxygenation indices and a decreased incidence of the combined endpoint of death or need for extra-corporal membrane oxygenation (77). A recent meta-analysis did not show a beneficial effect of iNO as a rescue therapy on clinically important outcomes in hypoxemic preterm infants (78). iNO does not seem to improve outcome in infants with respiratory failure due to congenital diaphragmatic hernia although its use is recommended by many experts in the presence of PPHN (77,79).

## Respiratory problems induced by anesthesia and surgery

### Choice of operating site

Intrahospital transport of ventilated infants from the neonatal intensive care unit (NICU), for example, to the operating theater is associated with an increased risk of respiratory complications (80). Typical respiratory complications include accidental extubation, ventilatory circuit disconnection, or other equipment failure during transport associated with potential loss of FRC, respiratory decline, hypoxemia, and cardiac arrest. Surgery of critically ill neonates in the NICU is feasible and might therefore be the preferred option in selected cases to reduce transfer-associated complications (81,82). The relative risks of surgery in the NICU need to be balanced with those of transporting a sick neonate to the operating theater (83). Especially preterm infants weighing <1500 g are at increased risk of deterioration of physiological parameters associated with the transfer to the operating theater for laparotomy compared to surgical intervention in the NICU (84). Beneficial effects of surgery in the NICU versus operating theater may include better temperature control, maintenance of fluid and inotropic therapy and optimized mechanical ventilation. Especially in preterm infant or small term infants, adequate minute ventilation might be better maintained by use of the established NICU ventilator reducing the risk of VILI by excessive $V_T$ application (85). Additionally, disconnection from mechanical ventilation on NICU, manual ventilation on transfer, and reconnection to an anesthesia ventilator may lead to derecruitment episodes which might have associated complications, for example higher $FiO_2$ requirements, escalation of ventilatory support. HFOV, extra-corporeal membrane oxygenation (ECMO) or iNO-administration to critically ill neonates might preclude patients from transport to the operating theater (83). There are several disadvantages of surgery on NICU. Firstly, lack of space to fit the surgical and anesthesia team including all their equipment in a full NICU cubicle is a major issue in many hospitals. Additionally, surgeons and anesthetists have to work outside their comfort zone in an environment, which is not their usual work place. It is not as well equipped for their particular needs and extra equipment required in the event of an unanticipated emergency, for example, for difficult intubation is often not as readily available as it is in the theater setting. In theater, the anesthetist, the anesthetic nurses/technicians, the surgeon, and the operating room nurses are a team, which is used to work closely together and which uses in general a common terminology. Working outside the theater environment particularly on complex cases involving other hospital teams (e.g., neonatologists and neonatal nurses) might therefore also be complicated by lack of experience of the NICU team with the theater environment resulting in problems such as communication issues, sterility, and equipment. When operating on NICU, it is often beneficial to include the neonatal team closely with the procedure to avoid issues with equipment, which the team might not be as familiar with (e.g., HFOV or neonatal ventilators).

### Influence of anesthetic drugs on neonatal lung function

Based on age-dependant differences of lung physiology, anesthetic drugs have different effects in neonates compared to older children or adults. Various anesthetic drugs have shown to affect FRC and ventilation homogeneity in neonates. Neuromuscular blocking agents decrease FRC and ventilation homogeneity in infants and preschool children (86). This effect is more pronounced in infants and can be restored by application of PEEP (87). Similarly, propofol given for procedural sedation in preschool children caused a dose-dependent decrease in FRC (88). Alike, the administration of midazolam as a premedication resulted in a mild decrease in FRC and ventilation homogeneity (89). This decrease in FRC can be attributed to the muscle relaxing properties of propofol and midazolam (90,91). Inhaled anesthetics such as halothane, isoflurane, or sevoflurane are associated with changes of $V_T$, minute ventilation and respiratory rate in spontaneously breathing infants and young children (92,93). Ventilatory drive is suppressed which leads to a dose-dependent decrease in $V_T$ and blunted response to $CO_2$ (93). Inhaled anesthetics have an inhibitory effect on respiratory muscle activity

(94). The inhibitory effect of halothane seems to preferentially affect the intercostal muscles and less the diaphragm resulting in paradoxical respiratory movements of chest and abdomen during induction of anesthesia (94,95). Desflurane can increase airway resistance and is associated with an increased risk for respiratory complications (e.g., laryngospasm, bronchospasm) in children (96). Opioids such as morphine and fentanyl increase the risk of respiratory depression in infants similarly as in children and adults with reduced $V_T$ and respiratory rate (97,98). Another potential side effect of fentanyl and other opioids can be a short term chest wall rigidity even when administered at low doses, which can severely compromise respiratory function and might require the administration of neuromuscular blocking agents (99).

## Abdominal surgery

### Laparoscopic surgery

Technical advances as well as growing surgical and anesthesiologic experience have led to an increased use of laparoscopic surgery also in neonates (100). Laparoscopic surgery confers several advantages for the patients including smaller incision sites, shortened hospital stay, reduced postoperative pain, and shorter time to full oral intake after surgery (101,102). However, it is associated with certain physiological changes of the cardiorespiratory system during anesthesia. $CO_2$ insufflation during laparoscopic surgery affects respiratory function and pulmonary mechanics due to increased intraabdominal pressure. The diaphragmatic muscle is being pushed cephalad, which reduces respiratory system compliance (mainly due to a reduction of chest wall compliance) and FRC (103,104). This can lead to atelectasis potentially resulting in hypoxemia with neonates being particularly prone to these complications due to their specific lung physiology (e.g., low closing volume). The loss of FRC is aggravated by head-down tilt positioning of the patient during a surgical intervention (105). $CO_2$ has become the routine gas in laparoscopic surgery, as it is noncombustible, inexpensive and highly soluble. Due to its high solubility, $CO_2$ is absorbed by the peritoneum and leads to an increased $P_aCO_2$ and endtidal $CO_2$, which is proportionally higher than in older children (106). Laparoscopy is also associated with decreased cardiac function as well as changes in pulmonary and systemic vascular resistance (107) which might further deteriorate V/Q mismatch in unstable patients. Strategies to attenuate physiological changes induced by laparoscopy include the limitation of the applied pressures for the laparoscopy [ideally not exceeding 6 mmHg in neonates (100)], application of an appropriate PEEP to prevent FRC loss, atelectasis, and V/Q mismatch. Endtidal $CO_2$ should be closely observed and minute ventilation increased if required to off-load any increased $CO_2$ load. Volume-targeted ventilation modes can be useful as they adjust ventilatory requirements automatically, resulting in stable minute ventilation and tidal volumes ($V_T$).

### Laparotomy

Necrotizing enterocolitis (NEC) affects almost exclusively premature infants, and its clinical presentation is often associated with multiorgan dysfunction including cardiovascular and respiratory failure due to increased intraabdominal pressure (108). Although NEC can be treated medically, advanced stages of disease (i.e., intestinal perforation) often require surgery. Primary peritoneal drainage has been shown to considerably improve respiratory function and reduce ventilatory requirements (109). After surgical closure of abdominal wall defects such as gastroschisis and omphalocele, respiratory insufficiency due to increased intraabdominal pressure may occur (110). Delayed closure and the use of silo bag can improve outcome and respiratory function (111). Monitoring of the intraabdominal pressure can be helpful in the surgical management to avoid abdominal compartment syndrome and respiratory failure after closure of abdominal wall defects (112–114). Sufficient levels of PEEP are of particular importance in these children. If ventilation is an issue due to raised intraabdominal pressure, it is prudent to observe the patient for a while in theater before taking the patient back to NICU. Additionally, neuromuscular blocking agents are often used in the immediate postoperative period to improve ventilation particularly while there is intraabdominal edema further increasing the intraabdominal pressure.

## Thoracic surgery

Common indications for thoracic surgery in neonates are tracheal, esophageal, and pulmonary malformations, vascular rings, patent ductus arteriosus, and congenital diaphragmatic hernia. Anesthetic techniques for thoracic surgery in neonates include conventional anesthesia and single lung ventilation (SLV), the latter optimizing often surgical access (115,116). FRC seems to rise after change from supine to lateral decubitus position but decreases markedly during thoracic surgery (117). Loss of FRC induced by anesthesia, surgical retraction, and SLV as well as the higher oxygen consumption of neonates compared to older children or adults increases the risk of desaturations during the

 

procedure. Contrary to improved V/Q matching of adults in the lateral decubitus position, oxygenation is worse in infants in the lateral decubitus position compared to supine position (118). Double-lumen tubes and Univent™ tubes are not appropriate for neonates due to their small airway size. Different techniques in neonatal anesthesia to selectively intubate a single lung or to insert an endotracheal blocker under fiberoptic guidance have been described (116,119). Equipment dead space can be significantly increased by the use of a specific setup such as multiport adapters resulting in the need of increased minute ventilation for maintenance of normocapnia. High-frequency ventilation might be useful to optimize oxygenation and to control $P_aCO_2$. HFJV has been reported in term infants undergoing thoracotomy for Blalock–Taussig shunt placement to improve oxygenation and to lower $P_aCO_2$ compared to conventional ventilation (120). Impact of anesthesia and surgery on neonatal lung function is summarized in Table 2.

## Ventilatory strategies during neonatal anesthesia

In contrast to older children, neonates are critically dependent on dynamically elevated FRC to maintain their lung volume above closing volume during tidal breathing (30). Thus, general anesthesia and surgery impose a considerable risk of atelectasis and V/Q mismatch as several active mechanisms of FRC preservation are blocked and/or unavailable. The above outlined principles of lung-protective ventilation on the basis of the open lung strategy are therefore of special importance during neonatal anesthesia and not only for ventilatory management in the NICU. Diligent and continuous PEEP application of a minimum of 5 $cmH_2O$ is recommended to maintain FRC and prevent atelectasis during anesthesia (87) although higher PEEP levels might be necessary under special circumstances. The use of a noninvasive airway with a laryngeal mask airway is recommended in neonates for minor cases as it has been shown to be associated with fewer respiratory complications than the use of an endotracheal tube and a reduced risk of postoperative ventilation in the NICU (73). As neuromuscular blocking agents are administered less and less during pediatric anesthesia, synchronized ventilation modes have gained more widespread use in the intraoperative care and are beneficial to counteract the detrimental effects of anesthesia on lung function as the child is breathing spontaneously. Synchronized ventila-

**Table 2** Impact of anesthesia and surgery on neonatal lung function

| Component of anesthesia/surgery | Impact on neonatal lung function |
|---|---|
| Opioid | High risk for apneas, thorax rigidity |
| Sedation | Reduced FRC, risk for apneas |
| Inhaled anesthetics | Reduced FRC, $V_T$ and minute ventilation, risk for apneas<br>Increased airway resistance and increased risk for respiratory complications (e.g., laryngospasm, bronchospasm) with desflurane |
| Muscle relaxation | Reduced FRC, apneas |
| Raised intraabdominal pressure (e.g., by laparoscopy, abdominal surgery) Pneumoperitoneum | Reduced 'chest wall' compliance<br>Loss of FRC<br>Hypercarbia and need for higher minute volume |
| Airway management (endotracheal tube, laryngeal mask airway) | Increased airway resistance<br>Potential for airway damage and mucosal swelling<br>Increased risk for respiratory complications (e.g., bronchospasm, laryngospasm) |

FRC, functional residual capacity; $V_T$, tidal volume.

**Table 3** One approach to optimize neonatal ventilator settings

| Aim | Means |
|---|---|
| 1. Maintain normal FRC | • Use positive end-expiratory pressure of 4–6 $cmH_2O$ and adjust as needed |
| 2. Optimize $V_T$ | • Ideally use VTV mode to avoid overdistension or underinflation of alveoli (set target $V_T$ as recommended by ventilator manufacturer)<br>• Otherwise adjust $V_T$ by adjusting PIP |
| 3. Maintain normocapnia to mild hypercapnia (35–55 mmHg) | • Adjust $V_T$ within recommended limits<br>• Adjust respiratory rate between 30 and 60 breaths/min<br>• Control $T_i$ and $T_e$ to avoid underinflation and inadvertent PEEP |
| 4. Optimize oxygenation | • Use $SaO_2$ monitoring to adjust $F_iO_2$ (avoid hypoxemia and hyperoxemia) (Preterm infants: target 90–95% with $O_2$ supplementation, 90–100% without $O_2$ supplementation; Term infants: 94–98% with $O_2$ supplementation, 94–100% without $O_2$ supplementation) |

$V_T$, tidal volume; PIP, peak inspiratory pressure; VTV, volume-targeted ventilation; $T_i$, inspiratory time; $T_e$, expiratory time; PEEP, positive end-expiratory pressure; $SaO_2$, saturation of arterial oxygen; $F_iO_2$, fraction of inspired oxygen.

tion modes in neonates have been shown to reduce the risk of air leak and to facilitate weaning from mechanical ventilation (58). Although PSV has become popular in pediatric anesthesia and offers various theoretical advantages, there is currently no evidence showing that it is superior to other synchronized ventilation modes such as SIMV or ACV in neonates (55). Currently, VTV seems to be the only modern ventilation mode in neonates with evidence of superiority over other ventilation modes regarding the composite outcome of death or BPD, and its use is therefore strongly recommended (60). For infants, who are already ventilated prior to the surgical intervention, NICU ventilator settings can be used as guidance for ventilatory management during anesthesia. Use of a NICU ventilator in the operating theater might be extremely useful in very low-birthweight infants, and other critically ill neonates as NICU ventilators might be more appropriate in delivering and monitoring required $V_T$ and minute ventilation.

To illustrate an approach to neonatal ventilatory settings during anesthesia, please refer to the following example and Table 3: a preterm infant of 28 weeks gestational age, 1.1 kg body weight would be continued on similar settings as in the NICU. Initially ventilated on ACV mode, target $V_T$ 5 ml·kg$^{-1}$ that is, 5.5 ml, respiratory rate 30 min$^{-1}$, PEEP 5 cm$H_2O$, $P_{max}$ 20 cm$H_2O$. After induction and due to lack of spontaneous breathing efforts, it is often necessary to increase the back-up rate to about 40–60 min$^{-1}$ to maintain adequate minute ventilation and achieve normocapnia/mild permissive hypercapnia. Adjust $F_iO_2$ to achieve target $SaO_2$ during maintenance of anesthesia. Higher $F_iO_2$ might be required during induction and toward the end of anesthesia. The goal is to balance perioperative safety and avoid severe oxygen desaturations on the one side and potential oxygen toxicity on the other (121). Recruitment maneuvers appear to be useful in infants and children to prevent atelectasis, but currently no general recommendations for safe application of recruitment maneuvers in neonates can be given (122). Depending on the preanesthetic requirements, early extubation for minor cases of surgery is aspired. CPAP or nasal intermittent positive pressure ventilation might be postoperatively helpful to overcome obstructive apneas and respiratory distress by decreasing WOB, stenting airways open and maintaining FRC. Slightly delayed extubation on NICU might be beneficial in other cases allowing safe transport from the operating theater to the NICU.

## Conclusion

Neonates are at high risk for respiratory complications during anesthesia, which can be explained by their characteristic respiratory physiology. Especially the delicate balance between closing volume and FRC can be easily disturbed by anesthetic and surgical interventions resulting in respiratory deterioration. Ventilatory strategies should ideally include application of an 'open lung strategy' as well avoidance of inappropriately high $V_T$ and excessive oxygen administration. In critically ill and unstable neonates, for example, extremely low-birthweight infants surgery in the NICU might be an appropriate alternative to the operating theater. Best respiratory management of neonates during anesthesia is a team effort that should involve a joint multidisciplinary approach of anesthetists, pediatric surgeons, cardiologists, and neonatologists to reduce complications and optimize outcomes in this vulnerable population.

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## Conflict of interest

The authors have no conflicts of interest to declare.

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