Review Article

Effects of anaesthesia techniques and drugs on pulmonary function

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ABSTRACT

The primary task of the lungs is to maintain oxygenation of the blood and eliminate carbon dioxide through the network of capillaries alongside alveoli. This is maintained by utilising ventilatory reserve capacity and by changes in lung mechanics. Induction of anaesthesia impairs pulmonary functions by the loss of consciousness, depression of reflexes, changes in rib cage and haemodynamics. All drugs used during anaesthesia, including inhalational agents, affect pulmonary functions directly by acting on respiratory system or indirectly through their actions on other systems. Volatile anaesthetic agents have more pronounced effects on pulmonary functions compared to intravenous induction agents, leading to hypercarbia and hypoxia. The posture of the patient also leads to major changes in pulmonary functions. Anticholinergics and neuromuscular blocking agents have little effect. Analgesics and sedatives in combination with volatile anaesthetics and induction agents may exacerbate their effects. Since multiple agents are used during anaesthesia, ultimate effect may be different from when used in isolation. Literature search was done using MeSH key words 'anesthesia', 'pulmonary function', 'respiratory system' and 'anesthesia drugs and lungs' in combination in PubMed, Science Direct and Google Scholar filtered by review and research articles sorted by relevance.

Key words: Anticholinergic agents, benzodiazepines, compliance, dead space, functional residual capacity, general anaesthesia, induction agents, neuromuscular blocking agents, ventilation perfusion ratio, volatile anaesthetic agents

INTRODUCTION

The primary function of the lungs is to provide an adequate gas exchange for maintaining normal oxygen content in blood and eliminate carbon dioxide. This is achieved by optimising lung volumes to meet higher metabolic demand during the peri-operative period. General anaesthesia (GA) *per se* causes respiratory impairment and both oxygenation and elimination of carbon dioxide are affected. The factors affecting pulmonary function include loss of consciousness, mode of ventilation (spontaneous or mechanical), posture of patient, actions of anaesthetic agents and drugs, used during anaesthesia on respiratory smooth muscles and secretions. Literature search was done using MeSH key words in PubMed, Science Direct and Google Scholar filtered by review and research articles sorted by relevance.

EFFECT OF GENERAL ANAESTHESIA

Effect on upper airway

GA causes relaxation of jaw and pharyngeal muscles and leads to posterior displacement of tongue. Loss of cough reflex along with increased secretions results in airway obstruction, laryngospasm and bronchospasm. Patients with hyperreactive airways are more prone to complications.[1] Tracheal intubation protects airway

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but increases the dead space, and delivery of dry gases may affect pulmonary function, especially in younger patients.

Effect on volumes

Anaesthesia causes respiratory impairment by mismatch in alveolar ventilation (Va) and perfusion (Q). GA abolishes the sigh reflex with rapid onset of atelectasis in the majority of the patients. Irrespective of mode of ventilation (spontaneous or mechanical), there is loss of muscle tone and dose-dependent decrease in minute ventilation (MV) as a result of decrease in respiratory rate or tidal volume (VT) or both.[2] Simultaneously, there is fall in functional residual capacity (FRC) and forced expiratory volume in 1 s (FEV1) leading to alveolar collapse and increase in shunts. Alveolar recruitment manoeuvres, followed by positive end-expiratory pressure (PEEP) which limits the shunts, may reduce post-operative pulmonary complications and improve patient outcomes.[3]

Effects on functional residual capacity

Anaesthesia leads to fall in FRC despite maintaining spontaneous breathing and irrespective of anaesthetic used (intravenous [IV] or inhalational).[4,5] FRC (approximately 3L in normal person) falls by 0.8–1.0 L by a change in position from upright to supine due to upward pressure from abdominal contents and more cephalad position of the diaphragm. Induction of GA further decreases it by 0.4–0.5 L due to relaxation of diaphragm and intercostal muscles, which further moves the diaphragm up. The resultant volume is close to residual volume. The muscle paralysis and mechanical ventilation does not cause any further reduction in FRC. As FRC approaches closing capacity, small airways collapse resulting in atelectasis and consequently hypoxia. Atelectasis occurs in approximately 90% of the patients undergoing anaesthesia. FRC increases significantly in the 30° head-up position in comparison with supine.[6] PEEP applied during anaesthesia may increase FRC; however, patients with high intra-abdominal pressure (IAP) may require PEEP higher than IAP.[7]

FRC is also reduced in neonates, elderly, obesity, smokers, pregnancy, abdominal distension and patients with respiratory diseases even before induction of anaesthesia. Total static compliance (both lung and chest walls) is also reduced, which may be due to decrease in FRC. FRC remains unaffected during ketamine anaesthesia as muscle tone is maintained.[8]

Effects of pre-oxygenation

The higher oxygen concentration, used during pre-oxygenation, leads to faster gas adsorption and consequently collapse of alveoli and atelectasis. As alveolar ventilation decreases, $PaCO_2$ increases and displaces oxygen from the alveoli, consequently, increasing shunt fraction and hypoxia. Ventilation with PEEP reduces the atelectasis, but oxygenation need not improve, because blood flow may shift to remaining atelectatic tissue. Application of PEEP of 40 cm H_2O recruits almost all collapsed lung and the lung remains open if ventilation is with moderate oxygen concentration (<40%) but recollapses within a few minutes if ventilation is with 100% oxygen.[8] However, recent study has found no significant difference in oxygenation index or FRC between patients given 80% and 30% oxygen for approximately 5 h.[9]

Effect on dead space

The distribution of pulmonary blood flow is altered during anaesthesia due to increased mismatch of ventilation to perfusion ratios (Va/Q ratio). Pulmonary blood flow distribution is primarily determined by gravity. Although anatomical dead space remains unchanged, alveolar dead space increases as a result of perfusion of non-ventilated and poorly ventilated lung areas. Pulmonary perfusion alters during change from upright to supine, sitting and lateral decubitus positions, which are not matched by altered ventilation. Hence, an increased mismatching of ventilation to perfusion develops. This includes the lung regions with high Va/Q ratio (ventilation of non-perfused or poorly perfused areas) or 'dead space ventilation' and regions with low Va/Q ratios (poor ventilation in highly perfused areas) or 'shunt' (due to atelectasis). Dead space ventilation impairs CO_2 elimination whereas shunt impairs oxygenation. The shunt may increase about 5%, which has a profound effect on arterial oxygenation. The increase in inspired oxygen concentration (FiO_2) may improve oxygenation to a small degree.

Effect on ventilatory response

Anaesthesia depresses movements of intercostal muscles, alters the shape and motion of chest wall and diminish rib cage excursion affecting lung mechanics and consequent decrease in FRC and ventilatory response to CO_2. $PaCO_2$ is the predominant factor controlling ventilation. Any rise in $PaCO_2$ is detected by peripheral (carotid bodies) and central (medullary) chemoreceptor with resultant increase in ventilation. Acidosis also stimulates ventilation via the peripheral

chemoreceptors. This ventilatory response to carbon dioxide is blunted by all anaesthetic drugs (except ether) resulting in hypercarbia. Anaesthesia also reduces the sensitivity of carotid and aortic body chemoreceptors to hypoxia, which increases MV by sympathetic nervous system stimulation. However, at low concentrations of anaesthetic agents (≤0.2), hypercapnic ventilatory response is not significant. It is probable that it is more resistant to the effects of anaesthetics than the hypoxic ventilatory response.[10]

EFFECT ON HYPOXIC PULMONARY VASOCONSTRICTION

Hypoxic pulmonary vasoconstriction (HPV) is the response of pulmonary capillaries in poorly ventilated areas to divert the blood flow to better-ventilated areas to improve oxygenation. There is some dependence on FiO_2 as an increase in FiO_2 causes attenuation of HPV. All volatile anaesthetic agents suppress HPV in a dose-dependent manner. Isoflurane and halothane may depress HPV by 50% at 2 minimum alveolar concentration (MAC). IV induction agents do not seem to have any such effect.[11] Sodium nitroprusside and nitroglycerin-induced hypotension increases pulmonary shunting and decrease pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) in a patient with normal lung function. In patients with chronic obstructive pulmonary disease (COPD), pulmonary gas exchange is not affected after deliberate hypotension as destructive vascular changes increase PAP, preventing vasodilators from decreasing PVR.[12]

Effect of position

Normal ventilation is determined by the degree of movement of the diaphragm, lung compliance and movement of the chest wall. The diaphragm is the major muscle of inspiration, responsible for two-thirds of the vital capacity. The movement of the diaphragm is the greatest close to most dependent portion of lungs, thereby increasing well-perfused areas during inspiration. In the supine position, the contribution of the chest wall is reduced from 30% to 10% and diaphragmatic movements close to most dependent portions of lung are significantly restricted. Hence, spontaneously breathing anaesthetised patients have reduced VT, FRC and increased closing volume. After induction of anaesthesia and muscle paralysis in the supine position, the shape and motion of rib cage is altered resulting in further decrease in FRC and impaired Va/Q ratio. Mechanical ventilation improves Va/Q ratio by delivering adequate MV and limiting atelectasis.

Naitoh *et al*. reported a significant decrease in FEV1 upon changing position from sitting to six recumbent positions. Rib cage motion was restricted in all recumbent positions (left retroversion at a 45° tilt, right retroversion at a 45° tilt and right anteversion at a 45° tilt), but not in supine, left anteversion at a 45° tilt and prone. There was no change in the maximum inspiratory pressure or maximal expiratory pressure in any recumbent positions.[13]

Semi-recumbent or upright position compared to supine does not offer any advantage in improving oxygenation due to decrease in cardiac output and uneven distribution of pulmonary blood flow as well-perfused dependent areas of the lung may remain poorly ventilated or non-ventilated.[14]

In lateral decubitus position, dependent lung is often the healthy one, which may become compromised due to weight of the mediastinum and cephalad position of diaphragm due to pressure of abdominal contents leading to decrease in lung compliance. This favours preferential ventilation of non-dependant poorly perfused lung while, pulmonary blood flow is diverted to dependent under-ventilated lung due to gravity. During one lung ventilation, non-dependant lung is collapsed, which necessitates higher MV to dependent and poorly compliant lung, resulting in maintaining high airway pressures to achieve adequate ventilation. Head-down tilt or reverse Trendelenburg position may further increase shunts. In case, flexion, which is required to spread the ribs to improve surgical exposure, may result in further compression of dependent lung.

Pulmonary functions in prone position are better than supine or lateral position, provided abdominal pressure is avoided, and legs are at same level as chest. Pressure on abdominal wall pushes the diaphragm cephalad, decreasing FRC and lung compliance along with increase in airway pressure. It may also compress inferior vena cava and decrease venous return. When abdominal pressure is eliminated by proper positioning, there is a significant improvement in Va/Q ratio. The distribution of perfusion is more homogeneous possibly due to regional vascular configuration that favours dorsal lung regions, irrespective of dependent or non-dependent position. The distribution of ventilation is also more uniform in prone position.

Prone position improves PaO_2 by an increase in FRC without any change in respiratory system compliance while, in obese subjects, FRC and the lung compliance increase and the chest wall compliance decreases.[15] Certain surgical manoeuvres such as abdominal wall lift, sternal splitting and sternum lift manoeuvre are physiologically superior to supine position for normal weight patients and avoid derangement of pulmonary functions by changes in the respiratory compliance.[16]

Effect of mechanical ventilation

Mechanical ventilation with high VT may directly damage lung parenchyma by shearing stress in alveoli, which results in interstitial oedema, decreased lung compliance and gas transfer. Higher VT cause more severe oxidative stress and increased antioxidant responses.[17] It may be avoided by low VT ventilation technique (lung-protective ventilation), which reduces shear stress. It is uncertain whether higher levels of PEEP have lung-protective properties as well. There are indications that too high FiO_2 or PaO_2 targets are harmful.[18] Variable ventilation with PEEP adjusted at the level of the PEEP of minimal elastance seems to prevent anaesthesia-induced atelectasis and might improve lung protection throughout GA.[19,20] PEEP at 10 cm H_2O is necessary to maintain lung function if low VT ventilation is used.[21,22]

EFFECTS OF REGIONAL ANAESTHESIA

In healthy patients, the central neuraxial blockade has no effect on pulmonary functions. During high spinal anaesthesia, owing to paralysis of abdominal muscles, there is a decrease in expiratory reserve volume and consequently the vital capacity, which may impair forced exhalation and ability to cough. Decrease in FEV1, forced vital capacity (FVC) and forced expiratory flow 25–75 is significant in old patients and patients with poor respiratory reserve in whom spinal anaesthesia is above T6.[23] VT is usually not affected unless phrenic nerve is blocked. In patients with debilitating respiratory disease, inspiratory muscles are adequate to maintain ventilation, but paralysis of expiratory muscles may impair effective coughing and clearing of pulmonary secretions. However, compared with post-operative lung function following abdominal or thoracic surgery without epidural anaesthesia, these effects are so small that the beneficial effects still lead to an improvement in post-operative lung function. Even, in patients with severe asthma, thoracic epidural anaesthesia leads to a decrease of about 10% in VC and FEV1 and no increase in bronchial reactivity.[24]

Cervical epidural anaesthesia can reduce lung volumes and capacities, resulting from partially paralytic intercostal muscles and diaphragm. Without inadvertant total spinal or IV anaesthesia or pre-existing pulmonary dysfunction, the patients with normal lungs could tolerate these changes well with the procedure.[25] In case of high or total spinal anaesthesia, severe respiratory dysfunction or apnoea may occur without loss of consciousness. Regional blocks such as supraclavicular and interscalene blocks do not have a significant effect on pulmonary functions in healthy young adults.

Local anaesthetics do not affect pulmonary functions; however, in the presence of hypoxia and acidosis, they potentiate the cardiac depressant effects of lignocaine and bupivacaine.

EFFECTS OF DRUGS USED DURING ANAESTHESIA

Induction agents

Barbiturates

Barbiturates cause dose-dependent respiratory depression due to central depression. Following IV administration, there is transient apnoea, which co-relates well with electroencephalography suppression and MV. The peak depression of MV occurs typically after 1–1.5 min after induction dose of 3.5 mg/kg and returns to pre-drug level after 15 min.[26] The ventilatory pattern with thiopentone is described as 'dual apnoea'. The initial apnoea lasts for few seconds followed by few breaths of normal breathing (VT) and then again followed by prolonged apnoea, hence need to provide respiratory assistance by jaw holding and bag-mask ventilation during barbiturate anaesthesia. During induction, barbiturates, more often methohexitone than thiopentone, cause excitatory symptoms such as cough, hiccough, tremors and twitching due to increase in muscle tone.

Methohexitone also produces central respiratory depression similar in duration to thiopentone. The peak reduction in ventilatory response to CO_2 and VT occurred after 30 and 60 s after induction dose that returns to base line after 15 min, but patients are awake in about 5 min.

Propofol

Induction dose of propofol produces profound respiratory depression by decreasing VT and respiratory rate and consequently MV. The subsequent doses may not have such profound effects. Deeper

level of anaesthesia led to a significant decrease in the FRC and increased lung clearance index, an index for ventilation distribution.[27] Ventilatory response to CO_2 and hypoxia are also decreased. Following an induction dose, there is an increase in $PaCO_2$ and fall in pH, similar to thiopental. Propofol produces apnoea, which is more frequent than thiopental and other anaesthetics and may last more than 30 s. The apnoea is usually preceded by reduction in VT and tachypnoea. The incidence and duration of apnoea depend on dose, speed of injection and premedication. It has bronchodilatory effect in patients with COPD and attenuates HPV.[28]

Ketamine

Ketamine has minimal effect on the central respiratory drive. Higher doses of ketamine do not affect FRC, ventilation distribution or MV suggesting that the depth of ketamine anaesthesia has a minimal effect on pulmonary function.[29,30] Following a rapid bolus dose, there can be transient decrease in MV and may produce apnoea more so in children. When combined with other sedatives, especially opioids used during premedication or anaesthetic agents, it may cause respiratory depression. Ketamine is a potent bronchial smooth muscle relaxant by its sympathomimetic effects. It produces bronchodilation and improves pulmonary compliance in patients with reactive airway and bronchospasm. In children, it causes increased salivation and increase in tracheobronchial secretions, which may lead to airway obstruction and laryngospasm. Although, upper airway reflexes are preserved, silent aspiration may occur.[31]

Etomidate

Compared to other anaesthetics, etomidate causes less effect on ventilation. Ventilatory response to CO_2 is depressed, but the drive is more than other agents. There is slight increase in $PaCO_2$ but no effect on PaO_2. Similar to methohexitol, hiccup and coughing may be present.

Dexmedetomidine

Dexmedetomidine reduces MV, but slope of ventilatory response to CO_2 is maintained similar to natural sleep. Dexmedetomidine sedation causes slight increase in $PaCO_2$ but, in response, the respiratory rate also increases. There is no effect on oxygenation and pH. It also exhibits hypercarbic arousal phenomenon, seen in normal sleep.

Inhalational agents

All volatile anaesthetic agents exhibit dose-dependent respiratory depression by decreasing VT and MV, which may be partially compensated by an increase in respiratory rate. The concomitant increase in respiratory rate is more pronounced with halothane, desflurane and sevoflurane than with isoflurane. Compensatory tachypnoea maintains MV with desflurane up to alveolar concentrations of 1.6 MAC. Individual anaesthetic agents vary in their effect on the extent of changes. The degree of respiratory depression is indicated by resting $PaCO_2$. The relative effect of volatile agent in increasing $PaCO_2$ is enflurane > desflurane = isoflurane > sevoflurane = halothane > nitrous oxide. The addition of nitrous oxide to volatile agents reduces MAC of volatile agents and respiratory depression. Xenon also causes decrease in MV and increase in $PaCO_2$. However, the effect is primarily on respiratory rate, which is compensated by increase in VT. This effect is unique and opposite to volatile agents.

Bronchial smooth muscles

All volatile anaesthetic agents are potent bronchodilators and reduce bronchomotor tone. Enflurane, isoflurane, sevoflurane, nitrous oxide and especially halothane produce a dose-dependent decrease in airway resistance. At equivalent MAC, halothane and sevoflurane cause greater bronchodilation than isoflurane. Halothane, isoflurane and desflurane relax distal airways (bronchioles) more than proximal (bronchi) whereas sevoflurane has greater effect on bronchial than tracheal smooth muscles.

Mucocilliary function

All volatile anaesthetic agents and nitrous oxide reduce the rate of mucus clearance by decreasing ciliary beat frequency, disrupting metachronism and altering physical characteristics and quantity of mucus. This effect is highest with halothane and isoflurane and less with sevoflurane. Halothane and isoflurane also decrease the synthesis of surfactant in a dose-dependent manner. These two effects together may cause decreased mucus clearance, mucus pooling, atelectasis and infection.

Desflurane and isofurane when used for induction cause respiratory irritation due to their pungent smell leading to breath holding and coughing. Halothane and sevoflurane do not cause such effects.[32] Nitrous oxide is known to increase PVR, especially in patients

with pre-existing pulmonary hypertension. All other inhalation agents may decrease PVR and blunt the HPV.[33]

Anticholinergic agents

Atropine and glycopyrrolate are the most commonly used anticholinergic agents used during anaesthesia, primarily to reduce bronchial secretions as premedication drug. They act by blocking muscarinic receptors. Both drugs cause decrease in airway resistance by dilatation of large and small airways, increase in specific airway conductance and maximum expiratory flow rates, but effect is more sustained by glycopyrrolate. Lung elastic recoil is decreased over full range of lung volume.[34] As a result of bronchodilation, there is increase in anatomical and physiological (anatomical > physiological) dead space, FEV1, FVC, FEV1/FVC ratio and peak expiratory flow.[35] When used in combination with anticholinesterases for reversal of neuromuscular blocking agents (NMBAs), both drugs effectively block the muscarinic actions.

Analgesics

Opioids cause dose dependent respiratory depression by direct action on brain stem respiratory centre and decreasing sensitivity of peripheral chemoreceptors to carbon dioxide. Respiratory rate is reduced by prolongation of expiratory time (gasping respiration) and spontaneous respiration can be eliminated by high doses; however, patient may be aroused when directed and can breathe on verbal command. Ventilatory response to CO_2 and hypoxic drive is reduced. Delayed respiratory depression may occur due to release of opioids (like morphine) from skeletal muscles, as repeated or high doses can be deposited being highly lipophilic. Buprenorphine also causes depression of MV, which has a ceiling effect on higher doses (more than 3.0 μg/kg).[36]

Opioids depress upper airway, tracheal and lower airway reflexes which allow patient to tolerate endotracheal tube without coughing. It also blunts autonomic responses to tracheal intubation. Morphine causes depression of respiratory mucus transport which is important to prevent respiratory infections; however, there is no effect on beating frequency of nasal cilia.

Opioids cause histamine release leading to bronchospasm, vasoconstriction and hypersensitivity reactions. However, fentanyl has antihistaminic, antimuscarinic and antiserotonic actions and may be better suited than morphine in bronchial asthma. Opioids can increase muscle tone and may cause muscle rigidity, which may lead to difficulty in mask ventilation. Chest wall rigidity may limit pulmonary functions. It is more common with synthetic opioids with large doses, rapid administration and perhaps in younger patients (neonates and infants).[37] Morphine also causes decrease in PVR. Opioids administered via intrathecal or epidural route, with or without local anaesthetics, improve lung functions by reducing diaphragmatic dysfunction and pain.[38] Non-steroidal anti-inflammatory drugs do not have a significant effect on pulmonary functions.

Benzodiazepines

Both diazepam and midazolam decrease VT and increase respiratory rate with no change in MV. Higher doses lead to dose-related central respiratory depression leading to decrease in VT and MV and may lead to apnoea. Ventilatory response to carbon dioxide is decreased. These alterations in breathing pattern are associated with CO_2 retention. Respiratory changes are not cumulative after subsequent doses.[39] Both drugs, when combined with pethidine, cause increase in expiratory time, but no change in inspiratory time and VT. However, profound decrease in diaphragmatic performance due to abdominal wall relaxation leads to decrease in VT.[40] Benzodiazepines and opioids produce additive or synergistic respiratory depression by acting on different receptor sites.

NEUROMUSCULAR BLOCKING AGENTS

NMBAs exhibit their clinical effects on pulmonary functions indirectly by acting on autonomic nervous system. Succinylcholine stimulates autonomic ganglia whereas D-tubocurarine blocks it. D-tubocurarine, succinylcholine, atracurium and mivacurium are associated with histamine release that may cause increased airway resistance and bronchoconstriction in patients with hyperactive airway. Pancuronium, vecuronium and rocuronium do not have any effect on pulmonary functions. The allergic reactions are most common in NMBAs amongst all drugs used in anaesthesia. Cross-reactions with other NMBAs are also common; hence, allergy test must be done if found allergic to one of them.[41,42] Anticholinesterases do not have direct effect on pulmonary functions but when used alone cause increased tracheal secretions and consequent bronchoconstriction.

SUMMARY

Anaesthesia effects on pulmonary functions may continue well into post-operative period. GA exhibits its effects by changes in respiratory mechanics brought about by loss of consciousness and changes in body position, mandated by requirement of surgery. Pulmonary functions are also affected by actions of agents and drugs used during anaesthesia, and the effects are manifested by changes in lung volumes, airway resistance and respiratory compliances, which alter V/Q ratio. Newer agents and drugs have better safety profile and fewer side effects, still all adverse effects of GA cannot be eliminated. A good understanding of pulmonary functions can prevent potential complications during anaesthesia and post-operative period.

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Conflicts of interest

There are no conflicts of interest.

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Announcement

Dr. TN Jha and Dr. KP Chansoriya Travel Grants

For the year 2015 the Dr. TN Jha and Dr. KP Chansoriya travel grant will be awarded to the participants from 15 states. All the states can select their candidate during their annual conference and send them with the recommendation of the Secretary. Only one candidate is allowed from each state. In case if two states have a combined annual meet but separate as per the records, have to select one candidate from each state. If more than 15 states recommend the candidates for the award, selection will be made on first come first served basis.

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