EFFECTS OF GENERAL ANESTHESIA ON RESPIRATORY SYSTEM

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Respiratory system dysfunction during general anesthesia is one of the major causes of morbidity and mortality during the operative and postoperative period in human, pediatric and veterinary anesthesia. Significant hypercapnea or hypoxia during anesthesia can delay postoperative recovery and lead to postanesthetic myopathies in large animals or post anesthetic renal, hepatic, cardiac failure due to compromised respiratory system function during general anesthesia in companion animals (1).

Respiratory system function can be influenced by postural changes, premedication and anesthetic drugs, inspired oxygen concentrations, ventilation maneuvers, obesity and previous respiratory or cardiovascular pathology. Respiratory system deterioration during anesthesia is caused by disruption of physiological factors and, in larger animals especially, also by anatomical and mechanical factors (1, 2,). Most of the current knowledge regarding changes of respiratory function during anesthesia originates from human studies. This information is applicable to veterinary medicine, especially with regard to the influence of anesthesia on neurological control of breathing, hypoxemic vasoconstriction, drive and role of high inspired oxygen concentration on the development of absorption atelectasis. Mechanical properties of the chest wall, diaphragm and lungs also follow the basic principles, but can be further influenced by body conformation and size of the animal or by the differences in the physiology of the respiratory system found in wild and exotic animals (fishes, reptiles, marine mammals and insects). In this review we will examine the mechanics and physiology of respiration during general anesthesia in companion animal veterinary medicine.

Mechanical changes of chest wall properties during anesthesia

Anesthesia has a pronounced effect on the elastic properties of the respiratory system and its components, the lung and chest wall (3, 4, 5, 6, 7). Moreover, general anesthesia induces atelectasis formation, a reduction in lung volume, and respiratory mechanical impairment that may be combined with gas exchange abnormalities (8). The most significant findings are reductions in functional residual capacity (FRC) in recumbent subjects after induction of anesthesia.

FRC refers to the volume of air remaining in the lungs after a normal, passive exhalation. It is determined by the balance between the forces of the lung and chest wall and it is the lung's physiological reserve. Loss of chest wall or lung compliance causes reduced FRC so anything that reduces movement of the chest wall and diaphragm or reduces the volume of the lungs will reduce their compliance and FRC. Several mechanisms may be responsible or contribute to the reduction in FRC and lung compliance. Anesthesia and both open and closed abdominal surgery causes a progressive cranial displacement of the diaphragm .A cephalad shift of the diaphragm may be explained by loss of respiratory muscle tone, allowing the abdominal content to push the diaphragm cranially(10). A few studies describe impairment in diaphragmatic function due to use of volatile anesthetics in dogs and rats (11,12,13). This may be associated with the failure of neuromuscular transmission and/or impaired membrane excitation, resulting in decreased FRC and development of intraoperative atelectasis, intrapulmonary shunting, and hypoxemia. The patient's position (head-down) or type of surgery (abdominal surgery or laparoscopy with insufflation) or concurrent use of muscle relaxant (rarely seen in veterinary medicine compared with humans) will further influence the degree of the diaphragmatic shift and increase of intra-abdominal pressure (IAP) followed by decreased chest compliance and lung volumes. As a result of peak airway pressure increases and the expansion of the bronchial tree, the anatomical dead space will increase (5).

As the size of the animal increases there is a decrease in chest wall and diaphragm function during anesthesia which is more pronounced in smaller animals. Therefore in all animals, from mice to elephant we will see the changes these which will become progressively more significant in larger animals. McDonell *et al.* (1) compared changes in FRC non-anesthetized and anesthetized horses. FRC of the awake horse in lateral or dorsal recumbency was reduced by approximately 20% from that in the standing horse. In contrast, FRC in the anesthetized laterally recumbent horse was reduced by almost 50% from the awake standing horse (14). In a study performed in dogs, there was a significant mean anesthetic-induced reduction in FRC of 16.9% in dorsal recumbency compared with awake dogs in same position. Thus similar changes in mechanical properties of the respiratory system are induced by general anesthesia, and the amplitude of those changes increases with the size of the animal (15).

Anesthesia reduces respiratory system compliance and increases airflow resistance, mainly because of the reduction in lung volume. In obese patients in dorsal recumbency, the

increased mass loading of the ventilatory system, particularly on the thoracic and abdominal component of the chest wall modifies lung volume and gas exchange to a greater extent. Anesthesia may thus produce more adverse effects on respiratory function in obese subjects than in normal patients (6).This information is obtained mainly from human studies. Anesthetic risk is reportedly increased in obese companion animals, most likely due to recognized problems with anesthetic dose, catheter placement, and prolonged operating time (16). At present, there are no studies observing respiratory system dysfunction during general anesthesia in the obese veterinary patient. However, we could expect similar changes in mechanical properties of the respiratory system in veterinary and human obese patients. Body mass is an important determinant of lung volume, oxygenation and respiratory mechanics. Pelosi *et al.* found a linear relationship between the increase in body mass index (BMI) and the reduction in FRC (6). The magnitude of reduction of FRC with consequent atelectasis has been found to be related to age, weight, and size (8). In other studies it has been observed that airway resistance was approximately twice as high in patients with severe obesity compared with those with minimal obesity (17). One hypothesis explaining the increase in airway resistance with BMI is the intrinsic narrowing of the airways in obesity. Moderate to severe hypoxemia has been reported in supine obese subjects during spontaneous breathing, anesthesia and paralysis (18, 6). Moreover ventilation-perfusion mismatch has been reported even in awake, seated and obese subjects (19). If FRC is reduced below closing capacity, airway closure will occur. In this case, the lung bases are well perfused, but they are underventilated because of airway closure and alveolar collapse. This phenomena increases ventilation-perfusion mismatch and favors formation of compression and absorption atelectasis, leading to hypoxemia. Most human medicine studies agree that the BMI is an important determinant of lung volume, respiratory mechanics, and oxygenation in anesthetized patients.

Inspired oxygen concentration influence on respiratory system

High inspired oxygen concentrations have been shown to cause pronounced atelectasis (3). In a study by Mead and Collier, a progressive reduction in lung compliance was seen during anesthesia in either spontaneous breathing or mechanically ventilated dogs (20). Another study made similar observations in anesthetized man and found that the decreasing compliance was accompanied by decreasing alveolar oxygen tensions (21). They suggested these changes were due to an increased formation of atelectasis. Atelectasis during anesthesia is caused by three basic mechanisms (22, 23): compression atelectasis, loss of surfactant atelectasis, or absorption atelectasis. It was first thought that compression atelectasis was the major mechanism (24), but other studies have shown that very little atelectasis develops during anesthesia if preoxygenation is avoided and the fraction of inspired oxygen FIO_2 of 0.3 is used after induction (25). This argues strongly for gas absorption being the main mechanism of atelectasis due to high inspired oxygen concentrations.

The mechanism of absorption atelectasis is better understood today. The atmosphere is composed of 78% nitrogen and 21% oxygen. Since oxygen is exchanged at the alveoli-capillary membrane, nitrogen is a major component for the alveoli's state of inflation. If a large volume of nitrogen in the lungs is replaced with oxygen, like in patients breathing 100% oxygen, the oxygen may subsequently be absorbed into the blood reducing the volume of the alveoli, resulting in a form of alveolar collapse known as absorption atelectasis.

Pulmonary atelectasis develops in the most dependent part of the lungs during general anesthesia in 90% of humans with normal lung function, and is considered the major cause of impairment of gas exchange and lung compliance (26, 27). It is independent of age and is only loosely related to body configuration, in both IV and inhalation anesthesia (3). Compression of lung tissue and absorption of alveolar gas (absorption atelectasis) contribute to the development of atelectasis during anesthesia as a result of high inspired oxygen concentrations (26). Atelectasis also plays an important role in the postoperative period. In humans, the formation of pulmonary atelectasis during anesthesia is an important factor for the onset of postoperative hypoxemia as atelectasis resolves only within 24 hours after surgery (26 , 28). Results of few studies (29, 30) have indicated that hypoxemia during the postoperative period could be a major morbidity factor in dogs that have undergone abdominal surgery during anesthesia with volatile agents delivered in 100% oxygen, even in dogs without preexisting lung disease. A recent study in dogs undergoing inhalation anesthesia showed that ventilation with 40% of inspired oxygen maintained significantly better lung aeration and gas exchange than ventilation with 100% oxygen (31). During general anesthesia and in some cases of sedation, oxygen support therapy is absolutely obligate. In most clinical settings, there are two choices: room air or 100% oxygen. Regardless to the limitations described above, 100% oxygen is superior in supporting the anesthetized animal than using the room air of only 21% oxygen.

Anesthetic drugs influences on respiratory system

Several inhalational anesthetics have been found to inhibit hypoxic pulmonary vasoconstriction (HPV) in isolated lung preparations (3). Hypoxic pulmonary vasoconstriction is a physiological phenomenon in which pulmonary arteries constrict in the presence of hypoxia without hypercapnia redirecting blood flow to alveoli with a higher oxygen content.

Inhibition of HPV has not been demonstrated with intravenous anesthetics (32). Results from different studies can vary, because of the complexity of the changes during anesthesia, which causes several variables to change simultaneously. The HPV response may thus be obscured by concurrent changes in cardiac output, myocardial contractility, vascular tone, blood volume distribution, blood pH and CO_2 tension, and lung mechanics (33). In studies with no gross changes in cardiac output, the inhalational anesthetics isoflurane and halothane depress the HPV response by 50% at two times minimum alveolar concentration (MAC).

Study of Dueck *et al.* compared intravenous (pentobarbitone) and inhalational (halothane and nitrous oxide) anesthesia in a sheep model and found no significant changes during intravenous anesthesia in the shunt formation (34). However, inhalational anesthesia increased shunt from 1% when awake to 11% and 14% during anesthesia with spontaneous and mechanical ventilation, respectively. In the sheep, therefore, inhalation anesthesia produced ventilation perfusion mismatch and shunt, whereas intravenous anesthesia produced no changes. In dogs, similar results are observed when using 2.5 MAC (35). When using 0.5 MAC and up to 1 MAC, changes were still present but to a much lesser extend which could be considered to be clinically insignificant.

As mentioned, volatile inhalant anesthetics are connected with impairment of diaphragmatic function (11,12,13). This mechanism may be associated with the failure of neuromuscular transmission and/or impaired membrane excitation.

All of the drugs used for general anesthesia produce dose dependent decreases in response to increasing carbon dioxide tensions (36). In ruminants, the degree of hypercapnea is greater with equipotent inhalant anesthetic doses than for horses and in horses greater than in dogs. Swine, ferrets and rabbits are also more prone to hypercapnia and deep diving seals can become totally apneic during light levels of anesthesia or sedation (37). Injectable drugs (barbiturates, propofol and ketamine) also produce similar dose dependent respiratory depression. Hypoxic ventilatory drive is influenced by general anesthesia in the same manner as described above. Other drugs commonly used in veterinary and human anesthesia can change breathing drastically (38). It is well known that morphine and other opioids influence ventilatory control. Arterial carbon dioxide tension increases and the ventilatory response to inspired carbon dioxide is reduced or shifted to higher end-tidal carbon dioxide tension values (39, 40). That means that, in therapeutic doses, resting carbon dioxide levels can be higher, but response to further challenge will be intact (1). At routine doses of opioids in veterinary practice, respiratory depression is not commonly recorded, and can actually improve alveolar ventilation in painful cases (41).

The phenotiazine and benzodiazepine sedatives can reduce respiratory rate, but they do not change blood gas values (42, 43). Furthermore, they have synergistic effect with other anesthetic drugs, decreasing the anesthetics drugs dose required and therefore reducing respiratory depression caused by general anesthesia (1).

The α-2 adrenoceptor agonists interfere with respiratory system function during sedation and anesthesia. In horses, administration of those drugs can lead to laryngeal relaxation that can influence compliance and resistance of respiratory system (44, 45). In sheep, sedative doses of this group of drugs can lead to significant hypoxemia, without producing hypoventilation that can last longer than the sedation period (46). Other ruminants, domestic and wild have the same reaction to this group of drugs.

A recent study by Lerche and Muir documented that medetomidine decreases respiratory center sensitivity and neurorespiratory drive in response to increases in inspired CO_2 in conscious healthy dogs (47). Care should be taken to closely monitor breathing and pulmonary gas exchange in dogs that have been administered medetomidine, especially when given concurrently with drugs known to depress respiration like opioids which is a common procedure during the perianesthetic period. Veterinarians should always remember that all anesthetic and analgesic drugs have a synergistic effect, with all the positive and negative aspects of their action.

Control of ventilation

All general anesthetic agents and the action of anesthesia by itself have a fundamental effect on the chemical and behavioral regulation of ventilation (48, 49). Firstly, anesthetic drugs depress central and peripheral chemoreceptor response to carbon dioxide and oxygen in a dose-depended manner (50, 51). This will diminish external signs of respiratory distress in anesthetized animals. They cause ventilation to be totally dependent upon chemical stimulation so reduction of stimuli below a critical threshold with passive hyperventilation results in apnea. Secondly, they reduce ventilatory responses to added chemical stimuli.

Control of respiration in conscious animals is achieved through complex neural regulatory mechanisms (1). There are certain similarities in the mechanisms between the species, with various components having greater importance in the different species. Central chemoreceptors, located on the ventral surface of the medulla and reacting to arterial tension of carbon dioxide are the primary factors responsible for control and adjustment of ventilation in conscious animals. Peripheral chemoreceptors located on carotid and aortic bodies are activated when arterial tension of oxygen falls below 60 mm Hg. Result of the study by Knill and Gelb (49) indicated that modern halogenated anesthetics are powerful depressants of several peripheral chemoreceptor mediated ventilatory reflexes in humans.

Control of ventilation is also influenced by the level of central nervous system activity through the reticular activating system (RAS).This is evidenced by decrease in ventilation and increase in carbon dioxide tension during sleep. This mechanism is called behavior control and it is severely influenced by general anesthesia. Behavioral control adjusts breathing in specific situations such as barking, exercise, pain, arousal and stress (38). Chemical, metabolic and behavioral control of breathing interacts in a very complex manner varying from inhibitory to excitatory connections depending on the nature of the drive involved. A study in humans compared increase of ventilatory response to hypoxia during reading to decreased response in a control group that was in a relaxed state with closed eyes (52). The study showed that during physiological sleep or general anesthesia, the respiratory system lacks behavioral control of breathing and is in a state of decreased response to chemical stimuli like changes of arterial carbon dioxide or oxygen tensions.

Conclusions

During general anesthesia, the respiratory system faces major changes. Compliance of the chest wall and lung is decreased and resistance increased. The diaphragm is shifted cranially, even more reducing lung volume and FRC. High inspired concentrations of oxygen usually used during maintenance of general anesthesia contribute to significant aletectasis formation. Sedation and analgesic drugs can negatively influencing breathing and volatile anesthetics diminish hypoxic pulmonary vasoconstriction. Even more, control of the breathing is depressed during anesthesia and shows a decreased response to ongoing metabolic changes.

Any additional load on the respiratory system during general anesthesia can have dramatic effects. This includes obesity, drug overdose, preexisted respiratory or cardiovascular pathology, any postural changes and others. It takes at least 24 hours from the anesthetic episode for the respiratory system to regain its full control, to resolve atelectasis and restore normal FRC values.

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