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Potential long-term complications of general anesthesia in small animals

Literature review

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Budapest, 2023

1. Abstract

This thesis explores the potentially damaging effect general anesthesia can have on small animals beyond the immediate perioperative period. The thesis investigates the influence of anesthetic drugs on various systems, including the cardiovascular-, respiratory-, nervous-, urinary-, gastrointestinal-, endocrine-, reproductive-, and musculoskeletal systems. By going through available data, this thesis aims to contribute to a comprehensive understanding of the potential risks associated with general anesthesia in small animals.

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2. List of abbreviations

ADH: Antidiuretic hormone

ALP: Alkaline phosphatase

ALT: Alanine transaminase

AST: Aspartate aminotransferase

ATP: Adenosine triphosphate

CNS: Central nervous system

ECG: Electrocardiogram

$ETCO_2$: End-tidal carbon dioxide

GABA receptor: Gamma-aminobutyric acid receptor

GGT: Gamma-glutamyl transferase

IM: Intramuscular

IRIS: International Renal Interest Society

IV: Intravenous

LDH: Lactate dehydrogenase

MAC: Minimum alveolar concentration

MAP: Mean arterial blood pressure

NMDA receptor: N-methyl-D-aspartate receptor

PaO_2: Partial pressure of oxygen

PNS: Peripheral nervous system

WBC: White blood cells

3. Introduction

General anesthesia is the induced state of unconsciousness through controlled and reversible intoxication of the CNS. In this state, the patient is unresponsive to stimuli. Three requirements should be present in the case of general anesthesia: analgesia, unconsciousness, and inhibition of reflexes. Because there is no single drug that can fulfill all of the three criteria, we have to use a combination of several drugs, and this is referred to as "balanced anesthesia" [1] (chapter 1.1-1.2).

3.1 General anesthesia in small animal medicine

Anesthesia is considered a specialty within the field of veterinary medicine, however administration of anesthetic drugs and monitoring of animals is very frequently performed by veterinarians without specialization and veterinary nurses. Insufficient knowledge, inexperience, and additional responsibilities at the clinic could potentially result in intraoperative complications, which can lead to death or long-term complications [2].

3.2 Importance of understanding long-term complications of general anesthesia

Conditions such as hypovolemia, circulatory problems, or respiratory problems can lead to insufficient oxygen delivery throughout the body. The visual cortex in the CNS, myocardium, kidneys, and liver are especially at risk of being damaged in case of insufficient delivery of oxygen [1] (chapter 2.2.1.1). These are problems that often arise due to a lack of sufficient monitoring and knowledge of the physiological effects of the drugs. Understanding the potential long-term complications of general anesthesia is important for patient safety, minimizing risk, and providing more informed decision-making. Perioperative complications and the immediate effect anesthetic drugs can have are better known compared to long-term complications.

3.3 Aims and objective

This thesis investigates the potential harm general anesthesia can cause in dogs and cats beyond the perioperative period. The effects of general anesthesia during the perioperative period are much better documented than the long-term effects. In this thesis, long-term complications after general anesthesia refer to adverse health effects or conditions that persist beyond the immediate perioperative period.

4. Literature review and method

The search engines on VIN.com (veterinary information network) and Google Scholar were used throughout 2022 and 2023 to find relevant articles. VIN.com was preferred as it provided the opportunity to make species-specific searches. The thesis is also based on several published books in the field of veterinary medicine. The articles included in the thesis were both from studies and literature reviews.

I aimed to find the most recent literature on dogs and cats. Although certain subjects only had research from over 30 years ago, I included them in this thesis because the studies seemed just as relevant today. I also included some articles and studies from the field of human medicine when it was the only available source of information or when other articles referenced research from this field. I tried, however, to stay within research based on dogs and cats. The drug halothane is briefly mentioned in the thesis despite its widely documented long-term adverse effects due to its absence in veterinary medicine today in Europe.

5. Common anesthetic agents

5.1 Premedication and sedation

The aim of premedication is to sedate, reduce the anesthetic dose, and provide analgesia. The choice of drugs used during premedication can significantly influence the overall anesthesia experience. Proper selection of premedication can greatly enhance analgesia, maintain cardiovascular stability during anesthesia, and improve the recovery period. There are numerous protocols about the type of drug and dose that can be used to reach general anesthesia, but individual needs should always be considered [3] (chapter 13, page 170-172).

Phenothiazines, alpha-2 adrenoreceptor agonists, benzodiazepines, and opioids are commonly used as premedication [3] (chapter 13, page 172).

5.1.1 Phenothiazines

Acepromazine is in the group of phenothiazines. It provides tranquilization and sedation [4] (chapter 6, page 125). However, It is important to remember that the drug does not provide any analgesic effect [5] (page 4).

Mechanism of action: The mechanism of action is not fully understood, but phenothiazines are dopamine receptor antagonists, causing a sedative effect. Acepromazine is also an alpha-1 adrenoreceptor antagonist, which potentially can cause hypothermia and hypotension due to peripheral vasodilation. The hypotension can in worst case lead to cardiovascular collapse. Acepromazine cannot be antagonized and has a long duration of action (about 6 hours). This should be kept in mind, especially when hypotension and cardiovascular compromise are risk factors [3] (chapter 13, page 174).

Contraindication and caution: Acepromazine should not be used in animals with hypovolemia or shock because of the hypotensive effect. The drug should be used with caution in animals with liver problems and heart diseases. It should also be used cautiously in breeds with the MDR-1 gene mutation, as these animals can experience a more pronounced and longer sedative effect [5] (page 3-4).

5.1.2 Alpha-2 adrenoreceptor agonists

Xylazine, medetomidine, and dexmedetomidine are commonly used alpha-2 adrenoreceptor agonists. They all provide sedation and analgesia, but the use of xylazine has decreased as both medetomidine and dexmedetomidine are proven more selective for the alpha-2 adrenoreceptor [3] (chapter 13, page 175).

Mechanism of action: Alpha-2 adrenoreceptor agonists exert their effects in CNS and PNS. In CNS, activation of alpha-2 adrenoreceptors decreases the activity of the sympathetic nervous system, and the release of norepinephrine responsible for the "fight or flight" response decreases. Consequently, the body experiences a calming and sedative effect [3] (chapter 13, page 175-176). The drugs produce a bi-phasic effect on arterial blood pressure with initial hypertension followed by hypotension. The arterial baroreceptors will decrease the heart rate and cardiac output as a response to the hypertension. The drugs also reduce central sympathetic outflow, decreasing heart rate. Consequently, bradycardia occurs, and the next phase with hypotension begins [4] (chapter 6, page 131).

Contraindication and caution: The drugs are contraindicated in animals with decreased cardiovascular reserve as they might reduce the oxygen delivery to organs like the heart, kidneys, liver, and brain in these animals [3] (chapter 13, page 176). Nausea and vomiting can occur, especially after IM administration, as the onset of sedation is slower than when given IV. Therefore, the drugs are contraindicated in animals with esophageal foreign bodies, and it should also be noted that vomiting can increase intracranial and intraocular pressure. The drugs reduce the blood flow in the liver, so they should also be avoided in animals with liver problems [3] (chapter 13, page 177).

5.1.3 Benzodiazepines

Diazepam and midazolam are commonly used in dogs and cats and can be used during both pre-medication and induction. It is important to keep in mind that these drugs don't provide analgesia. The drugs are often given in combination with opioids as the drug only produces minimal or no sedation. The drugs can also cause excitation when given alone [3] chapter 13, page 179.

Mechanism of action: Their mechanism of action is exerted through the activation of GABA-receptors, which leads to inhibition of acetylcholine in the CNS [3, 5] (reference 3: chapter 13, page 179, reference 5: page 275).

Contraindications and caution: There are no absolute contraindications of benzodiazepines [4] (chapter 6, page 130), however the drugs should be used with caution in patients with liver or kidney problems [5] (page 616).

5.1.4 Opioids

Morphine, methadone, and buprenorphine are often used in combination with other drugs during premedication. They are potent analgesic agents and enhance the sedative effect of other sedative drugs, such as benzodiazepines [3] (chapter 13, page 179-180).

Mechanism of action: Opioids acts on different type of opioid receptors (mu, delta, and kappa receptors) depending on which opiate is used. Opiates are either agonists, partial agonists, mixed agonist-antagonists, or antagonists of these receptors. Mu agonists, like morphine and methadone are considered the most potent analgesics and are often indicated in painful procedures. Partial mu agonists like buprenorphine are recommended in less painful procedures [3] (chapter 10, page 124-125).

Contraindications and caution: Opiates should not be used, or with caution in animals with head injuries and/or increased intracranial pressure, animals with hypothyroidism, kidney problems, and Addison's disease. Morphine should be used cautiously in animals with uremia as the drug increases the release of vasopressin [5] (page 633).

5.2 Induction and maintenance

Injectable and inhalational anesthetics can be used for both induction and maintenance of general anesthesia. Thiopental, propofol, etomidate, and ketamine are examples of injectable anesthetics. Isoflurane and sevoflurane are examples of inhalational anesthetics [3] (chapter 14 page 190-192, chapter 15 page 207-208).

5.2.1 Thiopental

Thiopental is in the group of short-acting barbiturates. The drug causes CNS depression, providing hypnosis. It should only be used during induction, not maintenance, as repeated administration can cause drug accumulation. Drug accumulation can lead to depression of the cardiovascular and respiratory system [3] (chapter 14, page 193).

Mechanism of action: The exact mechanism of action of barbiturates is unknown. However, the drugs are proven to inhibit the release of acetylcholine, norepinephrine, and glutamate [5] (page 95). Barbiturates act as agonists on the $GABA_A$-channels. Upon their activation, these channels allow the entry of chloride ions into the brain, inducing neuron hyperpolarization [6] (chapter 4.2).

Contraindications and caution: Thiopental should only be used in case of endotracheal intubation as the drug can cause respiratory depression and apnea [4] (chapter 6, page 136).

Cardiovascular depression, hypotension, and tachyarrhythmias can also occur [3] (chapter 14, page 193).

5.2.2 Propofol

Propofol provides hypnosis and has a short onset and duration of action. Propofol has minimal accumulation, making it an excellent drug to use during maintenance [3] (chapter 14, page 194-195).

Mechanism of action: Propofol acts on the same receptor as thiopental, exerting its effect by activating $GABA_A$-receptors [6] (chapter 6.4).

Contraindications and caution: The drug should be used with caution in case of shock, stress, or trauma due to its potential to induce respiratory depression [5] (page 778).

5.2.3 Etomidate

Etomidate is an imidazole derivative and provides hypnosis but lacks analgesic effects. It should not be used during maintenance due to its potential to cause acute hemolysis from continuous infusion. The drug has minimal cardiovascular changes, which makes it suitable for patients with cardiovascular problems [3] (chapter 14, page 196).

Mechanism of action: Etomidate acts on the $GABA_A$-receptors [3] (chapter 14, page 196).

Contraindications and caution: Addison crisis can occur as it inhibits adrenocortical function [3] (chapter 14, page 196). The drug should therefore not be used in animals with impaired adrenocortical function [5] (page 369).

5.2.4 Ketamine

Ketamine is a dissociative anesthetic. It provides analgesia and amnesia. The animal goes into a state of catalepsy, meaning that the muscle tone increases and certain reflexes, like the ocular, are intact [3] (chapter 14, page 197).

Mechanism of action: The state of catalepsy occurs due to stimulation of the limbic system and inhibition of thalamocortical pathways. Ketamine acts on several receptors but is mainly an NMDA-antagonist [3] (chapter 14, page 197).

Contraindications and caution: As the drug increases intracranial pressure, it should not be used after head trauma. Ketamine should also be avoided in patients with seizure disorders. It is important to remember that the drug can cause increased salivation, which can cause obstruction of the upper airways [3] (chapter 14, page 197-198).

5.2.5 Inhalational anesthetics

Inhalational anesthetics can be used during induction and maintenance [1] (chapter 8.1). The two most often used inhalational anesthetics in veterinary medicine are the volatile agents isoflurane and sevoflurane. They are not considered analgesics as they do not prevent noxious stimuli from reaching the CNS. The potency of inhalational anesthetics is expressed as minimum alveolar concentration (MAC). MAC describes the minimum drug concentration in the alveoli that prevents movements in 50% of patients when exposed to a standardized noxious stimulus at sea level. This means that 1 MAC causes movement in 50% of animals, however the measurement of MAC does not take into consideration the use of other sedatives in combination, which in turn decreases the dose requirement of inhalational anesthetics [3] (chapter 15, page 207-211).

Mechanism of action: The mechanism of action of the volatile agents isoflurane and sevoflurane is not fully understood [6] (chapter 6.3). The volatile agents have a $GABA_A$-mimetic effect and are calcium channel blockers. Their ability to cause muscle relaxation might be caused by inhibiting calcium entry into muscle cells [1] (chapter 8.6.1).

Contraindications and caution: Isoflurane and sevoflurane increase intracranial blood volume; this should be considered when patients have head trauma. Isoflurane and sevoflurane can also cause hypotension, decreasing cardiac output and blood flow in the kidneys and liver [3] (chapter 15, page 209-211).

6. Cardiovascular system

6.1 Effects of anesthesia on the cardiovascular system

Various volatile and injectable anesthetics negatively affect myocardial function in a dose-dependent manner by disturbing intracellular calcium balance. These agents reduce myocardial contractility and the diastolic function of the left ventricle. They also cause vasodilation, decreasing left ventricular afterload and depressing the baroreceptor reflex. Consequently, these effects lead to a lowered venous return, resulting in bradycardia, hypotension, and reduced cardiac output. Some anesthetics (for example isoflurane) can make the heart more sensitive to adrenaline, increasing the chance of arrhythmia during myocardial ischemia [3] (chapter 31, page 434).

6.1.1 Bradyarrhythmia

Bradyarrhythmia can significantly decrease cardiac output and tissue perfusion, leading to severe hypotension in anesthetized animals. During anesthesia, bradyarrhythmia like sinus bradycardia, first and second-degree atrioventricular block, sinus arrest, and atrial standstill can occur. A cause of bradyarrhythmia during general anesthesia is the administration of mu receptor agonist opioids and alpha-2 receptor agonists [3] (chapter 31, page 434).

6.1.2 Supraventricular tachyarrhythmia

Supraventricular tachyarrhythmias can reduce cardiac output due to compromised diastolic filling and shorter ejection and coronary perfusion time, potentially causing myocardial ischemia. During anesthesia, supraventricular tachyarrhythmias like sinus tachycardia, atrial tachycardia, and atrial fibrillation can occur. Supraventricular tachyarrhythmias can occur due to pain, anesthesia in a too-light plane, hyperthermia, hypotension, hypovolemia, hypoxemia, or hypercapnia. All these factors can cause an activation of the sympathetic nervous system, hence causing arrhythmia. It can also occur due to administration of anticholinergic drugs like atropine [3] (chapter 31, page 434).

6.1.3 Ventricular tachyarrhythmia

During anesthesia, ventricular arrhythmias like ventricular premature complexes, accelerated idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation can occur. Related to general anesthesia, ventricular tachyarrhythmias can occur due to hypoxemia, myocardial ischemia caused by hypotension, hypercapnia, or by the administration of thiopental or ketamine [3] (chapter 31, page 434-435).

6.1.4 Hypertension with tachycardia or bradycardia

The definition of hypertension is a MAP > 120 mmHg [1] (chapter 19). Hypertension increases myocardial work and oxygen demand, potentially leading to myocardial ischemia and arrhythmias. Hypertension can also cause long-term problems like retinopathy, blindness, and kidney failure. Sudden hypertension during general anesthesia indicates that the sympathetic nervous system has been activated, possibly caused by a too-light plane of the anesthesia, hypoxemia, or hypercapnia [3] (chapter 31, page 436).

Hypertension with tachycardia during anesthesia can be caused by a too-light plane of the anesthesia, making the nervous system able to process noxious stimuli, hypercapnia, hypoxemia, or hyperthermia. Hypertension with bradycardia might be caused by IV administration of alpha-2 agonists or increased intracranial pressure causing Cushing triad [1] (chapter 19). The Cushing triad causes increased sympathetic nervous system activity, peripheral vasoconstriction, and arterial blood pressure [7] (chapter 38, page 406). Intravascular volume overload might cause hypertension with tachycardia or bradycardia [1] (chapter 19).

6.1.5 Hypotension with tachycardia or bradycardia

The definition of hypotension is a MAP < 60-70 mmHg. Insufficient blood flow throughout the body causes inadequate oxygen supply and waste removal [3] (chapter 31, page 435).

Hypotension with tachycardia might be caused by hypovolemia. The hypovolemia can be absolute or relative. If it’s absolute, it might be caused by severe dehydration or loss of fluid. If it’s relative, it might be a consequence of either vasodilation caused by drugs (for example acepromazine) or redistribution caused by an adverse reaction to a drug or an anaphylactic reaction. Hypotension with tachycardia can also be caused by aorto-caval compression, pneumothorax, and cardiac tamponade or arrhythmias, causing a decreased cardiac output. Hypotension with bradycardia can be triggered by high doses of alpha-2 agonists and opioids, hyperkalemia, hypothermia, hypoglycemia, and hypoxemia [1] (chapter 19).

6.2 Potential long-term complications related to the cardiovascular system

As discussed in Chapter 6.3, hypoxia can potentially lead to myocardial damage [8].

6.3 Review of relevant studies

6.3.1 Myocardial damage

In a study named “Myocardial damage in cats that diet after anaesthesia” by J. S. Van Der Linde-Sipman et al. published in 1992, the potential connection between anesthesia and the development of cardiac lesions are investigated after the use of injectable anesthetics [8].

The death of 85 cats between 8 months and 15 years of age, which had died between 10 minutes and 6 weeks after anesthesia were investigated. The anesthetic agents used were ketamine-xylazine-atropine in 57 cats, ketamine-acepromazine-atropine in 11 cats, ketamine-xylazine in 5 cats, just ketamine in 5 cats, ketamine-atropine in 1 cat, and xylazine-atropine in 2 cats. The anesthetic agents used for the remaining 4 cats are unknown [8].

During the macroscopic investigation, it was found that all 85 cats had a varying degree of left atrial dilation. 5 of the cats had left ventricular hypertrophy. Endocardial and myocardial hemorrhages could be found in all 37 cats that died within 10 days after anesthesia. Additionally, all cats had lungs with congestion and edema, and congested liver. 25 cats had hydrothorax, 2 had hydropericardium, and 4 had aortic thrombosis. In 82 cats, the histological lesions occurred between anesthesia and death. During the microscopic investigation, it was found that the cats that had died within 6 hours after anesthesia, which was 36 cats, had separated muscle fibers indicating edema. Swelling of interstitial and endothelial cells in the myocardium could be found in animals that died 3-6 hours after anesthesia. Vacuolar, hyaline degeneration, and necrosis of muscle fibers could be seen in the cats who died 12 hours to 6 days after anesthesia. In the group of cats that died between 12 hours and 6 days after anesthesia, hemorrhages of the myocardium and endocardial lesions could also be found. The remaining 13 cats, who died between 8 days and 6 weeks after anesthesia, had almost the same lesions as those who died between 12 hours and 6 days, but the necrosis and degeneration of the muscle fibers were more extensive [8].

According to J. S. Van Der Linde-Sipman et al., because the lesions occurred at the same time, and most cats had the same type of lesions, it is suggested that anesthesia was an initiating factor in most of the cats. As mentioned above, in 82 of 85 cats, the microscopic lesions occur between anesthesia and death. Ketamine also seems to be a contributing factor [8]. The drug raises the heart rate, arterial blood pressure, and cardiac output, which consequently causes an increased workload for the myocardium and increased demand for oxygen [3] (chapter 14, page 197). Combining ketamine with atropine can lead to increased

heart rate and afterload, consequently leading to an increased demand for oxygen. When the heart rate reaches extremely high levels, the heart can no longer compensate for decreased stroke volume, leading to decreased cardiac output and coronary perfusion. Additionally, elevated afterload restricts the ejection fraction, consequently limiting cardiac output. J. S. Van Der Linde-Sipman et al. conclude that the anesthetic agents used led to myocardial hypoxia, and consequently myocardial damage and death. The cause of cardiomyopathy in cats frequently remains unclear, however findings from this study indicate that anesthesia might play a role in the occurrence of this condition [8]. The link between anesthesia and cardiomyopathy in cats is still just a hypothesis and more studies need to be conducted for confirmation.

7. Respiratory system

7.1 Effects of anesthesia on the respiratory system

General anesthesia affects the respiratory system by depressing the respiratory center in the brain stem and chemoreceptors centrally and peripherally. This reduces ventilatory drive, causing hypoventilation and increased CO_2 levels (hypercapnia). The volume of the lungs at the end of expiration is reduced, potentially causing atelectasis (partial or complete lung collapse) due to closed airways forcing the gas in the alveoli into the circulation via absorption. In cases of atelectasis, blood that flows to collapsed lung regions cannot participate in gas exchange, creating a situation called “right-to-left shunting” where deoxygenated blood bypasses lung ventilation and enters the systemic circulation directly. This process can lead to a drop in blood oxygen levels, potentially causing decreased O_2 levels in the blood (hypoxemia) [3] (chapter 31, page 428).

7.1.1 Hypercapnia

Hypercapnia, an increased amount of CO_2 in the blood, can be defined as $ETCO_2 > 60$ mmHg. Hypercapnia can occur due to hypoventilation triggered by airway or breathing system obstructions, compromised chest wall or diaphragm movement, and muscle relaxation during deep general anesthesia. Chest wall trauma, increased intrathoracic or intraabdominal pressure, and pulmonary parenchymal diseases can also lead to hypoventilation. Another cause is CO_2 rebreathing due to excessive dead space, damaged one-way valves in the anesthesia machine, or exhausted soda lime [1] (chapter 19).

7.1.2 Hypocapnia

Hypocapnia, when the amount of CO_2 in the blood is reduced, can be defined as an $ETCO_2 <$ 30-35 mmHg. If the $ETCO_2$ falls below 20 mmHg, the brain's blood flow will become impaired. It can be caused by hyperventilation with positive pressure ventilation. Hypocapnia can also occur if the anesthesia is too light, causing the animal to be able to process the noxious stimuli [1] (chapter 19).

7.1.3 Hypoxemia

Hypoxemia, a condition of low blood oxygen levels, can be defined as $PaO_2 < 100$ mmHg [1] (chapter 19). Cellular oxygen deficiency due to hypoxemia decreases oxidative phosphorylation, causing anaerobic metabolism with less efficient ATP production and accumulation of hydrogen and lactate ions. This causes metabolic acidosis and impacts vulnerable organs like the brain, heart, kidneys, and liver [3] (chapter 31, page 428-429).

The cardiovascular responses involve neural and humoral reflexes. Chemoreceptors and CNS stimulation trigger neural reflexes, while humoral reflexes involve catecholamines and the renin-angiotensin system. A combination of neural reflexes and humoral reflexes results in vasoconstriction. With mild hypoxemia, the sympathetic nervous system is activated and releases catecholamines. Consequently, the heart rate, stroke volume, vascular resistance, and cardiac output increase. Severe hypoxemia causes vasodilation, leading to a rapid decline in blood pressure. During anesthesia, the early signs of hypoxemia might be challenging to detect. Signs of hypoxemia might just be observed in the later stages as bradycardia, severe hypotension, or cardiovascular collapse. Hypoxemia increases the risk of cardiac arrhythmias due to the mismatch between myocardial oxygen supply and demand. The catecholamines released as a response to hypoxemia induce tachycardia, further increasing oxygen demand. This combination with reduced ventricular filling time and decreased coronary artery perfusion limits oxygen supply to the myocardium. Consequently, ventricular premature complexes, ventricular tachycardia, and ventricular fibrillation can occur [3] (chapter 31, page 428-429).

During anesthesia, hypoxemia can result from hypoventilation caused by an obstruction in the airway or the anesthetic breathing system. It can also occur due to an insufficient expansion of the lungs caused by either weak respiratory muscles or decreased neural control of ventilation, which can be a consequence of deep general anesthesia [1] (chapter 19).

7.2 Potential long-term complications related to the respiratory system

No research on long-term complications in the respiratory system caused by anesthesia in dogs and cats was found. However, the alterations anesthetic drugs cause during anesthesia can cause irreversible damage to other organ systems. Hypoxia can for instance lead to irreversible damage of myocardium [8] and CNS [9].

8. Nervous system

8.1 Effects of anesthesia on the nervous system

The aim of general anesthesia is to inhibit signals within the nervous system for a limited time. The exact mechanism of action of general anesthesia is not fully understood, but the inhibition of excitatory neurotransmitters and promotion of inhibitory neurotransmission could be a possibility [1] (chapter 1.3). The possible mechanism of action of the most used anesthetics is written about in chapter 5, named “Common anesthetic agents”.

8.2 Potential long-term complications related to the nervous system

There is more and more evidence that general anesthesia can lead to persistent damage to neural morphology and cognitive abilities in rodents and primates. This is believed to occur due to neural apoptosis and changes in synaptic connections. Interestingly, middle-aged adults seem to be unaffected, and there’s even a possibility that general anesthesia might offer neuroprotection during this particular phase of life, however this is not proven [1] (chapter 8.10.4). The same findings are not documented in dogs and cats, but it does open the possibility due to similar physiology.

8.2.1 Hypoxia

The cardiovascular system is also closely connected to the nervous system, and alterations of the cardiovascular system can have severe consequences and damage to the nervous system. Hypotension is a prevalent complication during general anesthesia [10] and can potentially alter oxygen delivery to the brain, which can cause brain damage [11, 12]. Loss of vision due to assumed hypoxia is reported in dogs and cats [11, 12].

8.3 Review of relevant studies

8.3.1 Cortical blindness

Cortical blindness is partial or complete vision loss due to a brain lesion. The eyes might be intact, but the brain cannot process visual information [13]. Possible causes of blindness after anesthesia include ischemic optic nerve neuropathy, central retinal artery occlusion, and undefined cerebral cortical ischemia. Hypotension, hypoxia, hypoventilation, apnea, improper oxygen flow meter setting, improper oxygen:nitrous oxide ratio, and faulty breathing system can contribute to blindness [9].

In an article published in the Veterinary Journal in 2012 called “Post-anesthetic cortical blindness in cats: Twenty cases” by J. Stiles et al., medical records of 20 cats that

experienced blindness or other neurological abnormalities after anesthesia were examined. None of these cats had previously experienced visual or neurological impairment. Of the 20 cats, 13 were anesthetized for dental procedures, 4 for endoscopic investigation, 2 for neutering, and 1 for urethral obstruction. Health problems diagnosed before the anesthesia were dental disease in 13 of the patients, chronic gastrointestinal tract disease in 3 of the patients, heart murmurs in 2 of the patients, diabetes mellitus in 1 of the patients, intestinal foreign body in 1 of the patients, and recurrent urinary tract disease in 1 of the patients. 3 of the cats had just blindness as a symptom, while the other 17 had additional neurological signs. 3 of the cats experienced cardiac arrest during the anesthesia, likely due to cerebral ischemia causing hypoxia. There were no complications recorded among the other 17 cats. One of the cats experienced cardiac arrest after induction with ketamine, another had a cardiac arrest after epidural administration of local anesthetic, and the third cat experienced a cardiac arrest after 25 minutes of anesthesia. 14 of the cats regained their vision, 4 cats remained blind, and 2 of the cats were still blind at the last examination about 2 weeks after the general anesthesia. A spring-held mouth gag was used in 16 out of the 20 cats, 12 out of the 13 undergoing dental procedures, and all 4 undergoing endoscopic procedures [11].

The article by J. Stiles et al. refers to two cases where cats exhibited blindness and other neurological signs after dental cleaning under general anesthesia [14, 15]. One of the cases reported that a 6-year-old male castrated cat experienced acute, bilateral blindness right after general anesthesia for dental cleaning. A blood test before the general anesthesia showed that the complete blood count, total protein, and glucose were normal. Ketamine and acepromazine were used for induction and 1% isoflurane and 100% oxygen for maintenance. With no history of illness or trauma, the cat experienced prolonged recovery and became acutely blind. Other symptoms detected after the anesthesia were anorexia, weight loss, right head tilt, and lethargy. The cat was euthanized about 2 weeks after the general anesthesia due to the poor prognosis presented by the veterinarian. Postmortem histopathologic examination of the brain showed bilateral microscopic lesions in several parts of the telencephalon (cerebrum). The lesions were characterized by gray matter neutrophil vacuolization, perivascular edema and gliosis. The diagnosis was severe, multifactorial, subacute neuronal necrosis with microcavitation and gliosis of the cerebral cortex and hippocampus. The cause of the blindness might be due to hypoperfusion. The authors suggest that the lesions were likely a direct result of the anesthetic procedure, specifically due to hypoperfusion [14]. The other case involved a 2-year-old cat that experienced blindness and decreased proprioceptive

response after anesthesia. The cat regained some vision and normal proprioception after 4 days [15].

In the article “Post-anesthetic cortical blindness in cats: Twenty cases” by J. Stiles et al., the cause of the blindness is presumed to be caused by cerebral ischemia. Despite the risks, the prognosis for cats that experienced cerebral ischemia under general anesthesia was generally good, with 70% regaining functional vision and 59% fully recovering from other neurological impairments. It is hypothesized that a spring-held mouth gag may potentially diminish cerebral blood flow via the maxillary artery by stretching the blood vessels and/or muscles in the same area [11].

J. Stiles et al. could not prove the hypothesis that the spring-held mouth gag could potentially lead to cortical blindness. However, M. Martin-Flores et al. published an article in 2014, building further on the theory from J. Stiles et al.. In the article from 2014, it was proven that a wide-open mouth in cats caused a reduction in blood flow of the maxillary artery. This was proven through electroretinography and magnetic resonance angiography [16].

A case report was published in 2009 by N. Alisauskaite et al.. The case report investigated the occurrence of cortical laminar necrosis after general anesthesia. Hypoxia, fluid overload, and hypoglycemia can lead to cortical laminar necrosis in dogs during general anesthesia [12, 17, 18].

In the case report by N. Alisauskaite et al., a 3-year-old dog experienced a sudden onset of blindness after waking up from general anesthesia for dental treatment. The dog was given medetomidine-buprenorphine-acepromazine IM as premedication, propofol as induction, and isoflurane as maintenance. Ringer’s acetate IV was also provided. The dog was monitored throughout the anesthesia and no complications or abnormal values were recorded, however blood pressure was not monitored. The dog was euthanized about a week after anesthesia due to lack of improvement [12].

N. Alisauskaite et al. assume that the cause of blindness was hypotension, which led to cerebral hypoperfusion and cortical laminar necrosis [12]. This case report shows the importance of blood pressure monitoring during general anesthesia.

8.3.2 Corneal damage

An article published in 2013 by Y. W. Park et al. investigates the risk of developing corneal ulcers after nonocular surgery with general anesthesia. Factors during anesthesia associated

with damage of the corneal epithelium are trauma by the personnel or equipment like laryngoscope and face mask, chemical injuries by antiseptics and inhalational anesthetics, reduced tear production caused by anticholinergic drugs or inhalational anesthetics, or incomplete closure of the eyelid [19–21].

The study involved 732 dogs, of which 14 developed corneal ulcer, resulting in a prevalence rate of 1.9%. In total 23 eyes were affected, both eyes in 9 dogs and only the left eye in the remaining 5 dogs. None of the dogs had any previous ophthalmic problems before the surgery. After treatment, the corneal ulcers resolved within 14 days without complications in 8 dogs (12 eyes). However, persistent corneal ulcers, which developed into sight-threatening complications, were observed in 2 dogs (4 eyes), lasting for 23 and 38 days, but they were successfully treated. Unfortunately, 2 dogs (3 eyes) died due to postsurgical complications 2 and 7 days after surgery, unrelated to the corneal ulcer. 1 dog (1 eye) had an uncertain prognosis due to not returning for a recheck examination. Eye lubricant was used after induction and at an interval of 30 minutes during anesthesia [19].

Y. W. Parker et al. discussed the risk factors for developing corneal ulcer after general anesthesia based on the study results. Decreased tear production caused by drugs and duration of the anesthesia, surgery on the nervous system and especially hemilaminectomy (7 out of 14 dogs), and a small skull (13 out of 14 dogs) in particularly brachycephalic breeds (11 out of 14 dogs) were identified as a risk factors [19].

The duration of anesthesia is a significant risk factor for developing corneal ulcer. Y. W. Parker et al. refer to an article stating that tear production is almost absent after 60 minutes of inhalational anesthesia [22]. A tear film usually protects the cornea, so when the tear production ceases, the chance of developing ulcers increases [19, 23] (reference 23: chapter 9, page 166)

Tranquilizers, sedatives and analgesics are all drugs that reduce tear production [19, 24, 25]. There are two mechanisms behind the reduction of tear production by these drugs. The first mechanism is caused by vasoconstriction of the vessels that supply the lacrimal gland [19, 25]. The second mechanism involves the neural regulation of the lacrimal gland, which these substances may impair by acting on both the peripheral and central lacrimogenic pathway [19, 26].

As mentioned, 11 of the 14 dogs developing corneal ulcers were brachycephalic. There is a difference in the innervation of the cornea in brachycephalic dogs and mesocephalic dogs.

Brachycephalic dogs have a lower nerve fiber density on the cornea than mesocephalic dogs, making the corneal sensitivity of brachycephalic dogs lower [19, 27]. Additionally, a lot of the brachycephalic dogs are lagophthalmos, making them unable to close their eyelids completely, a potential risk factor for corneal ulcer during surgery [19, 28].

9. Urinary system

9.1 Effects of anesthesia on the renal system

9.1.1 Oliguria, anuria

Oliguria (reduced urine output) or anuria (lack of urine output) during anesthesia is mainly caused by reduced renal perfusion and glomerular filtration rate. Volatile anesthetics and opioids, which are mu-receptor agonists, can increase ADH secretion, promoting fluid retention [3] (chapter 31, page 437).

9.2 Potential long-term complications related to the renal system

Impaired renal function

As discussed in Chapter 9.3.1, hypotension can cause impaired renal function [29].

9.3 Review of relevant studies

9.3.1 Acute kidney injury

Acute kidney injury caused by ischemia-reperfusion injury after hypoperfusion of the kidneys is a known risk of general anesthesia [3]. An article from 2022 by J. Davis et al. investigates the hypothesis that the urinary biomarkers neutrophil gelatinase-associated lipocalin, cystatin C, and gamma-glutamyl transpeptidase can be used to detect acute kidney injury earlier than serum creatinine, urine output, and urinalysis which is the standard markers used today to diagnose acute kidney injury [29]. The data from this study can also be used to look at the consequences of hypotension during general anesthesia.

In the study, 6 confirmed healthy male Greyhounds experienced induced severe hypotension during general anesthesia. The hypotension was caused by drawing blood from the dogs, and a MAP > 40 mmHg for 60 minutes was maintained. After 60 minutes with hypotension, an IV gelatin solution was administered to increase the MAP to > 60 mmHg for 3 hours. Urinary and blood serum concentrations of neutrophil gelatinase-associated lipocalin, cystatin C, gamma-glutamyl transpeptidase, serum creatinine, and urine output were measured at the beginning and every hour during anesthesia. All dogs were euthanized after the experiment, and renal tissue was examined with a light microscope and transmission electron microscope [29].

In 4 dogs, histological examination in the light microscope indicated structural damage to proximal renal tubular cells, mainly at the tubuloglomerular junction. 3 dogs had an IRIS grade 2 acute kidney injury, and 1 dog had an IRIS grade 1 acute kidney injury. The 2

remaining dogs out of the 6 had no histological renal abnormalities. Transmission electron microscope examinations were performed in the 4 dogs with IRIS grade 1 and 2 acute kidney injury. The transmission electron microscope examination showed acute tubular epithelial injury characterized by loss of the apical brush border, mitochondrial swelling, nuclear pyknosis, and cytoplasmic vacuolation. Detached cellular debris could be detected in some distal tubular lumen, and the glomeruli had some vacuolation of podocyte cytoplasm and segmental effacement of the foot processes. The study also detected an increase of neutrophil gelatinase-associated lipocalin, cystatin C, and Gamma-glutamyl transpeptidase in the urine before the rise in serum creatinine or decrease of urine output, which are standard diagnostic markers today for acute kidney injury [29].

The information on the long-term consequences of acute kidney injury in dogs is limited. A study from 2022 named “Long-term outcome of dogs recovering from acute kidney injury: 132 cases” followed 132 dogs with acute kidney injury who were hospitalized and alive 30 days after discharge. The study concludes that recovering dogs generally experience a good long-term outcome. The study also mentions that a good long-term prognosis is more about whether the kidney injury can be reversed than how bad it was initially [30]. Early diagnosis and treatment of acute kidney are therefore crucial for reducing the likelihood of long-term complications.

10. Gastrointestinal system

10.1 Effects of anesthesia on the gastrointestinal system

10.1.1 Liver

The hepatic metabolism of anesthetic agents should be considered, especially in the case of patients with impaired liver function. Alpha-2 adrenoreceptor agonists reduce blood flow and metabolism of drugs in the liver. However, this is not important in patients with normal functioning liver [3] (chapter 13, page 177).

10.2 Potential long-term complications related to the gastrointestinal system

10.2.1 Hepatic dysfunction

Hepatic dysfunction caused by inhalational anesthetics arises from direct and indirect effects on the liver. The direct effects involve impaired hepatocellular function and reduced drug metabolism capacity; however, these effects are minimal with isoflurane and sevoflurane. Indirect effects result from cardiovascular depression, leading to reduced hepatic perfusion, but this is easily managed with proper monitoring and correction of arterial blood pressure [3] (chapter 15, page 210-211).

10.3 Review of relevant studies

10.3.1 Hepatic dysfunction

Transient increase in the serum levels of the enzymes AST, ALT, GGT, LDH, ALP, and bilirubin can indicate damage to hepatocytes [31]. ALT is a liver-specific enzyme in carnivores, making ALT a good indicator of hepatocyte damage when increased. Serum AST is not exclusive to the liver as it originates from other body parts, such as cardiac and skeletal muscles, red blood cells, pancreas, and kidneys. An increase in AST only indicates possible liver damage; it is not a certain indicator alone as it is not liver-specific. GGT increases in case of cholestasis. ALP is produced throughout the body. However, only ALP originating from the liver and bone can be seen on a blood test. An increase of ALT, ALP, AST, and GGT together indicates hepatobiliary damage. Bilirubin is a by-product after the breakdown of hemoglobin, which takes place in the liver. Increasing conjugated and unconjugated serum total bilirubin concentration can indicate impaired liver function, cholestasis, or icterus [32, 33] (reference 32: chapter 2, page 45-46). LDH can be found in cells all over the body, and

serum levels of LDH are consequently increased in case of several disorders [34]. Relying solely on an elevation in LDH levels is insufficient for diagnosing hepatic dysfunction.

In a study published in 2003, named “Hepatic Effects of Halothane, Isoflurane or Sevoflurane Anaesthesia in Dogs” by A. Topal et al., the potential damage inhalational anesthetics can have on the liver are discussed and investigated. The study aimed to compare the levels of serum liver enzymes and total bilirubin concentrations in dogs undergoing anesthesia with halothane, isoflurane, or sevoflurane [35]. The negative impact halothane has on the liver is already widely known and documented, and A. Topal et al. refer to several articles about the negative hepatic impact of halothane in humans [36–39] and dogs [40].

In the study by A. Topal et al., 21 dogs were put under general anesthesia. Two days before the experiment, a physical examination, serum biochemical analysis, and WBC analysis were conducted, all indicating a normal, healthy result for all dogs. All 21 dogs were premedicated with xylazine IM and induced with propofol IV. All dogs were also intubated with an endotracheal tube and given Ringer’s solution IV. The study organized the dogs into three groups, each consisting of seven animals, to undergo anesthesia using 1.35% halothane, 2% isoflurane, and 3% sevoflurane, respectively. The anesthesia was maintained for 60 minutes. Venous blood samples were gathered before pre-medication and then 24 hours, 48 hours, 7 days, and 14 days after anesthesia. The enzyme activity of AST, ALT, ALP, GGT, LDH, and bilirubin concentration were measured. The study did not consider Xylazine and propofol used in all the dogs. Both drugs have some effect on the liver; however, all dogs got the same amount per body weight [35].

The study by A. Topal et al. found that all groups anesthetized with halothane, isoflurane, and sevoflurane had increased AST, ALT, and GGT activity. Within the group of dogs anesthetized with halothane, AST and ALT were increased during all 4 occasions of blood sampling after anesthesia. In the group of dogs anesthetized with isoflurane, elevated levels of AST and ALT were recorded between day 2 and 7 after the anesthesia. In the group of dogs anesthetized with sevoflurane, AST and ALT increased at day 7. GGT activity increased on day 2 and 7 after the use of halothane, and 7 days after the use of isoflurane and sevoflurane. None of the 21 dogs showed signs of hepatitis or liver failure after anesthesia [35].

A. Topal et al. state that while the changes in AST and ALT did not lead to liver failure, the enzymes likely originated from damaged liver cells. Hepatic dysfunction or subclinical

hepatic damage could arise, especially in the case of halothane and rarely with isoflurane. The study concludes that halothane negatively affects liver function to a greater extent than isoflurane and sevoflurane. However, isoflurane led to a more frequent increase in serum activities of liver enzymes than sevoflurane between day 2 and 7 after anesthesia [35].

An article published in 2012, named “Serum biochemical indicators of hepatobiliary function in dogs following anaesthesia with sevoflurane or isoflurane” by Z. Yuan et al., investigates the changes of total protein, AST, ALT, LDH, ALP, GGT and total bilirubin in the blood serum after anesthesia with sevoflurane or isoflurane [31].

In the study by Z. Yuan et al., 8 healthy dogs were put under general anesthesia with either MAC as 2.36% sevoflurane or 1.39% isoflurane delivered in oxygen. The dogs were induced by masks and later intubated with an endotracheal tube. The dogs were divided into 4 groups. The first group were given 1.0 MAC sevoflurane, the second group 1.5 MAC sevoflurane, the third group 1.0 MAC isoflurane, and the fourth group 1.5 MAC sevoflurane. The dogs were anesthetized on 4 occasions, with a minimum interval of 15 days between treatment, each lasting 5 hours. The same agent (sevoflurane or isoflurane) was administered to the same dog each time. IV fluids were given during anesthesia. Venous blood samples were taken before anesthesia, 24 hours, 2 days, 7 days, and 14 days after anesthesia [31].

The dogs anesthetized with 1.5 MAC isoflurane, 1.0 MAC sevoflurane, and 1.5 MAC sevoflurane had a significant increase of AST in the serum 24 hours after anesthesia, but it had returned to normal by 2 days. The dogs anesthetized with 1.5 MAC isoflurane and 1.5 MAC sevoflurane had significantly elevated ALT levels 24 hours after anesthesia, but this had returned to normal 2 days after the anesthesia. All four groups had a significant increase of serum ALP 24 hours after anesthesia, but it returned to normal by 2 days. The group anesthetized with 1.5 MAC isoflurane had a much higher level of AST 24 hours after anesthesia than the group anesthetized with 1.0 MAC isoflurane. Serum LDH concentration was significantly lower in the group anesthetized with 1.0 MAC sevoflurane than in the groups anesthetized with 1.0 MAC isoflurane and 1.5 MAC sevoflurane [31].

When studying the impact the inhalational anesthetics have on liver function, it is important to recognize that factors like hepatic perfusion influence hepatic enzyme activity, and this can be affected by factors like cardiac output and systemic vascular resistance, regulation of hepatic perfusion, body temperature, and hypercapnia. Several mechanisms have been proposed to explain the potential impact inhalational anesthetics can have on hepatocellular

integrity during or after anesthesia. The damage to the liver caused by inhalational anesthetics can result from the agent itself or its metabolites exerting hepatotoxic effects. This damage might also result from alterations in hepatic blood flow and increased calcium concentration within hepatocytes. Among these mechanisms, halothane has been linked to increased calcium concentration [31].

Z. Yuan et al. refer to an article from 1998 where the liver function after surgery with sevoflurane and isoflurane is investigated in humans. Isoflurane and halothane have a common metabolite named trifluoroacetyl acid. Trifluoroacetyl acid has been linked to possible hepatotoxicity due to its capacity to bind covalently with hepatocyte subcellular proteins after oxidative biotransformation by cytochrome P-450 [31, 41]. Z. Yuan et al. also refer to a case report from 2010 investigating the hepatotoxicity of sevoflurane. Sevoflurane-induced liver damage is thought to occur through several mechanisms, including elevated cytosolic free calcium levels, activation of enzymes responsible for metabolizing free radicals, and production of compound A (degradation product of sevoflurane) [31, 42].

11. Endocrine system

11.1 Effects of anesthesia on the endocrine system

11.1.1 Antidiuretic hormone

As mentioned in the chapter named “Urinary system”, increased ADH production can occur due to anesthesia with volatile anesthetics like isoflurane and sevoflurane, and opioids which are mu-receptor agonists [3] (chapter 31, page 437). Increased production of ADH can potentially reduce oxygen delivery throughout the body as ADH has the potential to cause vasoconstriction. Alpha-2 adrenoreceptor agonists can inhibit the release of ADH from the posterior hypophysis, which can lead to hypotension [3] (chapter 27, page 379-380).

11.1.2 Insulin

Hypoglycemia during general anesthesia can lead to significant damage due to the dependence on glucose by CNS. Hypoglycemia can lead to unexpected depth of the anesthesia, tachycardia, hypertension, delayed recovery, or failure to regain consciousness. It can also cause seizures or muscle tremors during the recovery period. Neonates, pediatric patients, and diabetic patients are at risk of developing hypoglycemia during general anesthesia [3] (chapter 31, page 436). It should also be noted that transient hyperglycemia can occur using alpha-2 adrenoreceptor agonists [3] (chapter 13, page 177).

11.1.3 Cortisol

Opioids and volatile inhalational anesthetics have the potential to decrease cortisol release, while etomidate inhibits the synthesis of cortisol [3] (chapter 27, page 383).

11.2 Potential long-term complications related to the endocrine system

11.2.1 Hyperglycemia

Inhalational anesthetics like sevoflurane and isoflurane can lead to hepatic insulin resistance during anesthesia, leading to hyperglycemia [43]. In humans, hyperglycemia in sick patients is linked to postoperative pneumonia, sepsis, urinary tract infection, acute renal failure, acute myocardial infarction, and death [44]. To my knowledge, the same research about the consequences hypoglycemia can have during surgery on dogs and cats has yet to be performed. However, these findings indicate that interoperative hypoglycemia can lead to long-term complications in dogs and cats.

11.3 Review of relevant studies

11.3.1 Insulin resistance

In an article published in 2016 named “Isoflurane and Sevoflurane Induce Severe Hepatic Insulin Resistance in a Canine Model” by S. P. Kim et al., the effect inhalational anesthetics have on the blood glucose level with the use of hyperinsulinemic-euglycemic clamp [43].

The hyperinsulinemic-euglycemic clamp is used in medical research to assess insulin sensitivity and glucose metabolism. Hyperinsulinemia is reached through a continuous infusion of insulin into the bloodstream. Simultaneously, glucose is given to reach euglycemia (stable glucose level). The aim of the hyperinsulinemic-euglycemic clamp is to measure how quickly insulin responds via glucose uptake from the bloodstream. The infusion rate of glucose needed to reach euglycemia indicates the body’s responsiveness to insulin [45].

56 dogs participated in the experiment. 32 dogs were awake during the experiment, and 24 were anesthetized. Those under general anesthesia were given acepromazine, atropine, and propofol, and maintained with either isoflurane or sevoflurane. The hyperinsulinemic-euglycemic clamp was performed by providing a tracer infusion of glucose and exogenous glucose IV. Somatostatin was also given to inhibit endogenous insulin secretion from the pancreas. After 120-180 minutes, insulin was given for the rest of the period, and blood samples were taken [43].

The blood samples showed that the glucose uptake from the bloodstream was about 20% lower in anesthetized animals than those awake. Anesthesia resulted in a 50% reduction in peripheral insulin sensitivity compared to awake animals, indicating peripheral insulin resistance. Additionally, anesthesia decreased liver insulin sensitivity, suggesting that those animals had significant hepatic insulin resistance. S. P. Kim et al. concluded that isoflurane and sevoflurane can cause severe hepatic insulin resistance and decreased glucose metabolism [43].

Another study from 2013 by Y. Yasuda et al. proved that propofol also had the potential to cause insulin resistance in rats [46]. Even though the subject of the study was rats, it opens the possibility that the drug can elicit a similar response in dogs and cats.

12. Immune system

12.1 Effects of anesthesia on the immune system

The body responds to anesthesia and surgery with stress, activating the nervous-, endocrine-, and immune systems simultaneously due to their close relationship [47].

12.2 Potential long-term complications related to the immune system

The stress that is triggered contributes to various postoperative complications, including immunosuppression, hyperthermia, sleep disturbances, impaired breathing, increased workload for the heart, ulcers, ileus, weight loss, delayed postsurgical healing, and potential growth of malignant tumors [47, 48].

The effect anesthesia has on the immune system has yet to be fully understood. However, recent studies have implied that anesthesia, especially inhalational, can be linked to cancer in dogs [49, 50]. Natural killer cells have a cytotoxic activity that allows them to destroy specific cells, such as cancerous cells. These cells die by releasing cytotoxic granules, causing apoptosis [51].

12.3 Review of relevant studies

12.3.1 Reduced natural killer cell cytotoxic activity

A 2013 study by T. Miyata et al. examined the impact of general anesthesia on the cytotoxic activity of natural killer cells against tumor cells in dogs. The cytotoxic activity of natural killer cells plays a vital role in the body's defense against cancer [7, 49].

13 healthy dogs between the ages of 1.5 and 2.1 years of age were included in the study. The dogs were anesthetized with propofol as induction and isoflurane during maintenance for 3 hours. Blood samples were taken before and 24 hours, 120 hours, and 192 hours after anesthesia. Peripheral lymphocytes were separated from adherent cells. The cytotoxic activity of natural killer cells was assessed through a colorimetric rose Bengal assay. No surgery was performed during anesthesia as this can interfere with the result [49].

The cytotoxic activity of natural killer cells showed a significant decrease 24 hours after anesthesia; however, the values returned to baseline levels at 120- and 192 hours post-anesthesia. Similar findings have been observed in humans, although surgery was also conducted in these cases [49, 52].

The reason for the reduction in cytotoxic activity is not clear, and neither is the potential consequences. T. Miyata et al. refer to other articles and propose that the decline in natural killer cytotoxic activity might arise from elevated cortisol due to stress, inference with interferon enhancement of natural killer activity, or a direct impact of isoflurane on lymphocytes [49, 53–55]. More research is needed on the consequence of immunosuppression following general anesthesia and the potential link between anesthesia and cancer development.

A study published in 2021 by E. Faroni et al. builds further on the theory from T. Miyata et al. The study investigates if anesthesia can cause diffuse large B-cell lymphoma relapse in dogs. 61 dogs with diffuse large B-cell lymphoma were included, and 18 were put under anesthesia for lymphadenectomy, computed tomography, plasma cell tumor excision, excision of leiomyosarcoma, or removal of foreign body. These 18 dogs were given methadone or butorphanol as analgesics, propofol for induction, and isoflurane or sevoflurane as maintenance [50].

15 out of the 18 dogs put under general anesthesia relapsed. Of the remaining 43 dogs that did not undergo anesthesia, 33 relapsed. The risk of relapse was 3 times higher after anesthesia [50]. Several other factors can cause relapse, which must be considered. However, the study raises awareness of anesthesia's possible risks to cancer patients.

13. Reproductive system

13.1 Effects of anesthesia on the reproductive system

As far as my knowledge extends, there is currently a lack of research regarding general anesthesia's impact on the reproductive system in veterinary medicine.

13.1.1 Use of anesthetics during pregnancy

In human medicine, concerns like teratogenicity, spontaneous abortion, and premature birth have been raised in connection to surgery during pregnancy [56].

Acepromazine, ketamine and thiopental are categorized as a drug which is safe to use during pregnancy with caution. Morphine can also be used with caution; however, methadone should be avoided at the end of pregnancy as it can cause respiratory depression and increased chance of stillbirth in humans and opens the possibility of the same outcome in animals. Benzodiazepines like diazepam and midazolam should be used cautiously during pregnancy and only as a last resort due to rapid passage across the placenta and substantial fetal uptake. Isoflurane is also considered safe to use with caution; however, the drug has been linked to fetotoxicity in animal studies. Also, alpha-2 adrenoreceptor agonists like xylazine should be avoided as they are linked with fetal mortality in dogs [3, 5, 57].

As a rule, should anesthetics used during pregnancy have a short duration of action and have the possibility of being antagonized. Additionally, should the lowest possible dose be used, and local anesthetics should be considered as an option when possible [3] (chapter 26, page 369).

13.2 Potential long-term complications related to the reproductive system

13.2.1 Teratogenicity

All anesthetic drugs can potentially be teratogenic as they interfere with mitosis and DNA synthesis; however, there are no clear answers about the exact damage these drugs can cause to the fetus. In human medicine, barbiturates and propofol have frequently been used during pregnancy without any known consequences for the fetus [56].

14. Musculoskeletal system

14.1 Effects of anesthesia on the musculoskeletal system

Muscle relaxation is a part of general anesthesia and can be reached via the inhibition of acetylcholine. Acetylcholine can be inhibited via blockage of synthesis, blockage of release, or inhibition of the effect of acetylcholine on the postsynaptic muscle membrane. Additionally, inhalational anesthetics block calcium channels [1] (chapter 17.1.2).

14.2 Potential long-term complications related to the musculoskeletal system

14.2.1 Malignant hyperthermia

Malignant hyperthermia affects skeletal muscles in dogs. It is characterized by a hypermetabolic response and unregulated release of intracellular calcium stored in the sarcoplasmic reticulum of skeletal muscles into myoplasm. It is linked with the use of volatile inhalational anesthetics (isoflurane, sevoflurane) and depolarizing muscle relaxants (succinylcholine) [58–60]. Common findings during malignant hyperthermia in dogs are increased CO_2 in the blood, hyperthermia, arrhythmia, metabolic acidosis, and myoglobinuria [61]. Malignant hyperthermia can potentially cause kidney failure, liver failure, myocardial damage, and muscle necrosis. Worst case can the condition lead to death [59, 62]. Dogs with RYR-1 gene mutation are more at risk of developing malignant hyperthermia [63].

14.3 Review of relevant studies

14.3.1 Malignant hyperthermia

A 2012 case study by C. Adami et al., “Unusual perianesthetic malignant hyperthermia in a dog” presented an incident where a Siberian Husky experienced malignant hyperthermia on 2 occasions with a 5-day interval. Malignant hyperthermia occurred after butorphanol, propofol, and isoflurane administration during the first incidence. During the second incidence, ketamine and propofol were given. The dog did not have a RYR-1 gene mutation [61].

In the case study, the dog had increased lung sounds, 39.3°C rectal temperature, and a significant increase of creatine kinase, AST, and ALT 5 days after the first incidence [61]. An elevation in ALT levels can indicate haptic dysfunction, while elevated AST levels may suggest hepatic dysfunction as well as muscle necrosis [32, 33] (reference 32: chapter 2, page 45-46). Creatinine kinase is mainly found in muscle tissue. Therefore, increased creatinine

kinase can be used to diagnose muscular damage [64] (page 203). The owner reported a good general condition of the dog 3 months after the incidents [61].

This case was unusual as the dog did not have a RYR-1 gene mutation and developed malignant hyperthermia without inhalational anesthetics. C. Adami et al. raised several theories on why this dog experienced malignant hyperthermia. One possibility could be that the anesthesia machine contained traces of volatile inhalational anesthetist during the second incidence. Another possibility could be that the dog had a preexisting undiagnosed condition [61].

In another case study from 2018 named "Unusual hyperthermia related to general anesthesia in an Anatolian shepherd dog" by O. Guzel et al., a similar incidence to the case study by C. Adami et al. is described where a dog experienced malignant hyperthermia on two occasions with an interval of 4 days. During the first incidence, the dog was given xylazine, ketamine, and isoflurane as anesthetics. Hyperthermia occurred 40 minutes after administration of isoflurane. During the second incidence, propofol was the only anesthetic agent given before hyperthermia occurred 15 minutes later [65].

Blood collected on day 5 showed a significant increase in WBCs, glucose, urea nitrogen, creatinine, AST, ALT, and creatinine kinase. WBC had returned to normal 2 days later. However, urea nitrogen, AST, and ALT were still significantly high about 2 weeks later [65]. Impaired clearance of blood urea nitrogen by the kidneys can cause a buildup of blood urea nitrogen in the bloodstream [33] (chapter 2, page 47). The dog was euthanized shortly after due to lack of improvement [65].

After anesthesia, monitoring is critical to reduce potential damage and optimize recovery. Blood-gas should be measured repeatedly to correct metabolic acidosis. Additionally, serum electrolytes, creatinine kinase, myoglobin, and lactate should be measured [60, 66]. Arrhythmias should also be prevented with ECG monitoring and possible administration of procainamide [59, 60, 62]. Osmotic diuretics and loop diuretics should be given to avoid buildup of myoglobin and proteins, as kidney failure caused by rhabdomyolysis can occur [60, 67].

15. Conclusion

In this thesis, I have explored the potential long-term complications associated with general anesthesia in small animals. Scientific literature and case studies have shown that while general anesthesia is a crucial tool in veterinary medicine, facilitating numerous surgical and diagnostic procedures, it does not come without risk and consequences. There are certainly more long-term consequences of general anesthesia than those existing in literature today, but they have yet to be recognized or proven.

This thesis also highlights the importance of vigilant monitoring during general anesthesia. Instruments used during general anesthesia should also be considered as these can contribute to complications, particularly the spring-held mouth gag in cats linked with blindness.

Determining whether complications following general anesthesia are irreversible can sometimes be challenging, given that euthanasia is frequently chosen if no improvement is seen, or the cost of treatment is out of the question for the owner. However, as veterinary medicine continues to advance, safer and more educated use of anesthetic agents will hopefully be used in the future.

16. Summary

Within the cardiovascular system, combining ketamine and atropine is linked to myocardial hypoxia and consequently myocardial damage in cats. Anesthesia in cats can also play a crucial role in the development of cardiomyopathy; however, more research is needed to support this hypothesis.

Hypoxia and hypotension alter the delivery of oxygen to the brain. Loss of vision after general anesthesia has been documented in dogs and cats, and hypoxia is assumed to be the cause. Reduction of tear production by tranquilizers, sedatives, and analgesics can be a predisposition for corneal damage, and brachycephalic breeds seem to be especially at risk.

Hypotension is also recognized as a potential contributor to kidney damage. A limited small-scale study involving the induction of hypotension during general anesthesia further supports this, revealing that 4 out of 6 dogs developed acute kidney injury due to reduced kidney perfusion during general anesthesia.

Cardiovascular depression resulting in reduced hepatic perfusion can potentially damage liver cells. Furthermore, it was found that isoflurane more frequently increases liver enzymes in serum than sevoflurane. Not surprisingly, the same study found that halothane negatively affects liver function to the greatest extent out of these three inhalational anesthetics. Other studies also supported the negative effect inhalational anesthetics have on the liver.

Anesthetic agents can also cause alterations within the endocrine system. Hepatic insulin resistance and, consequently, hyperglycemia can occur due to inhalational anesthetics. The long-term complications in dogs and cats are not documented; however, hyperglycemia is linked to infections, acute renal failure, and acute myocardial infarction in humans.

In the immune system, anesthetics are found to reduce the cytotoxic activity of natural killer cells. This cytotoxic activity seems particularly important in cancer patients to prevent metastasis or relapse. One study indicated that the chance of relapse in cancer patients was 3 times higher if they were put under anesthesia than those not anesthetized.

Research about the adverse effects of general anesthesia in small animals on the reproductive beyond pregnancy is non-existent. During pregnancy, caution with anesthetic agents should be kept as incautious use can lead to teratogenicity, abortion, or premature birth.

Inhalational anesthetics are linked to malignant hyperthermia, and dogs with RYR-1 gene mutation are especially at risk. Malignant hyperthermia is challenging to predict, but when it occurs, early detection is critical to optimize recovery.

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Thesis progress report for veterinary students

Name of student:	**Jorunn Nordrum**
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Name and title of the supervisor:	Dr. habil. Miklós Pál Dunay, DVM, PhD, Assoc. Prof.
Department:	Department and Clinic of Surgery and Ophthalmology
Thesis title:	**Potential long-term complications of general anesthesia in small animals – Literature review**

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	03	05	Confirmation of thesis title and deadline for submission of thesis.	
2.	2023	03	20	Presentation of relevant literature found so far. Suggestion of chapters for the thesis.	
3.					
4.					
5.					

Thesis progress grade achieved at the end of the first semester: **5**

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	09	07	Submitting first draft. Review of first draft.	
2.	2023	11	01	Review of the last version of the thesis.	
3.	2023	11	02	Final approval	
4.	2023	11	03	Submitting thesis	
5.					

Thesis defence grade achieved at the end of the second semester: 5

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

ÁLLATORVOSTUDOMÁNYI EGYETEM Szülészeti és Szemészeti Tanszék és Klinika BUDAPEST 1787

.....
signature of the supervisor

Signature of the student: Jorunn Nordrum

Signature of the secretary of the department: .....

Date of handing the thesis: 03.11.2023