Sevoflurane Anaesthesia in Dogs : Clinical Implications and Applications

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DEDICATION

To my parents, for their lifelong love and encouragement.
To Geert, my support in bad days.
To Bram, the twinkle in my eyes.

Ingeborgh

CONTENTS

LIST OF ABBREVIATIONS

AA %	end tidal anaesthetic agent percentage
AR	artificial respiration
ASA	american society of anaesthesiologists
BSA	body surface area
BWT	body weight
CBF	cerebral blood flow
CI	cardiac index
CO	cardiac output
CO_2ET	end tidal carbon dioxide percentage
CPAP	continuous positive airway pressure
CV	controlled ventilation
DAP	diastolic arterial blood pressure
DPAP	diastolic pulmonary artery pressure
F_A	alveolar anaesthetic concentration
F_i	inspired concentration
FiAA %	inspiratory anaesthetic agent concentration
FiO_2	inspiratory oxygen fraction
Halo	halothane
HCO_3^-	plasma bicarbonate concentration
HPV	hypoxic pulmonary vasoconstriction
HR	heart rate
ID	internal diameter
IM	intramuscular
IPPV	intermittent positive pressure ventilation
Iso	isoflurane
ITP	intrathoracic pressure
IV	intravenous
LA	long acting
LVSWI	left ventricular stroke work index
MAC	minimum alveolar concentration
MAP	mean arterial blood pressure
Min-max	minimum and maximum
MPAP	mean pulmonary artery pressure
MVV	minute ventilation volume
OLV	one lung ventilation
P_A	alveolar partial pressure
PAP	pulmonary artery pressure
$PaCO_2$	arterial carbon dioxide tension
PCV	packed cell volume
PCWP	pulmonary capillary wedge pressure

PEEP	positive end expiratory pressure
Pinsp	inspiratory pressure
PO	per os
PO_2	arterial oxygen tension
PVR	pulmonary vascular resistance
RAP	right atrial pressure
RR	respiratory rate
RVSWI	right ventricular stroke work index
SAP	systolic arterial blood pressure
SBC	standard bicarbonate concentration
SBE	standard base excess
SC	subcutaneous
Sevo	sevoflurane
SI	stroke index
SPAP	systolic pulmonary artery pressure
SpO_2 %	peripheral haemoglobin saturation
SpV	spontaneous ventilation
SV	stroke volume
SVR	systemic vascular resistance
TLV	two lung ventilation
TV	tidal volume
VAP	vascular access port

GENERAL INTRODUCTION

The last decades a very impressive progress has been made in diagnostic as well as surgical techniques. As a consequence the need for a safe and stable long-standing anaesthesia during these procedures increases. Inhalation anaesthetics are very useful for this purpose. Halothane has being used for several decades in veterinary medicine and is still a valuable compound in many clinical settings.

However, halothane is not an ideal anaesthetic drug. This is not surprising as an ideal volatile anaesthetic compound has to fulfil many criteria: minimal or no depressing effects on vital functions such as respiration and circulation, rapid onset of action, beneficial interaction with premedication and anaesthesia-inducing drugs, not to mention low health hazard for the anaesthetists, low flammability and the lack of need for expensive vaporizers.

The last decades several new volatile anaesthetics have been developed such as isoflurane, desflurane and sevoflurane in order to obtain drugs with more beneficial and less side effects than the previous ones. Some of these drugs like isoflurane have been studied extensively in dogs, in experimental as well as clinical settings. The results of such studies indicate that new drugs may be superior for some but not all aspects leading to nuanced conclusions.

Sevoflurane has been studied widely in humans. The findings are interesting in order to have an idea of the profile of this almost unknown drug in veterinary medicine. In humans its lack of airway pungency and mainly its low blood-gas solubility induce a fast induction and recovery from anaesthesia. Sevoflurane has little influence on cerebral perfusion and intracranial pressure. Depression of cardiac output is only reported at higher concentrations. Both characteristics make it the agent of choice in neurological and cardiac

patients. However one should be careful by extrapolating these results to canine medicine. Therefore several studies were undertaken in dogs in order to investigate some clinical implications and applications of sevoflurane.

In the first part of this thesis (chapter 1 and 2) physicochemical and pharmacological properties of sevoflurane are extensively reviewed and compared with other inhalation anaesthetics.

In the second part own studies on sevoflurane in dogs are described. These studies deal with several pharmacological and clinical aspects of sevoflurane anaesthesia: recovery times and haemodynamics in comparison to other anaesthetics (chapter 3); influence of ventilation mode (chapter 4) and thoracoscopy (chapter 5) on cardiopulmonary parameters; vascular access port implantation (chapter 6) in order to study the influence of sufentanil long-acting premedication on haemodynamics (chapter 7) and analgesic effects (chapter 8) of sevoflurane.

SCIENTIFIC AIMS

1/ To compare the recovery times and clinical haemodynamic parameters of sevoflurane, isoflurane and halothane anaesthesia in mongrel dogs.

2/ To investigate the influence of ventilation mode (spontaneous ventilation, IPPV and PEEP) on cardiopulmonary parameters in sevoflurane anaesthetized dogs.

3/ To determine the effects of intrathoracic pressure elevation on cardio-respiratory parameters during sevoflurane anaesthesia with continuous two-lung ventilation for thoracoscopy in dogs.

4/ To describe the vascular access port implantation for blood sampling and continuous blood pressure measurement in dogs.

5/ To examine the haemodynamic influences of a long-acting formulation of sufentanil administered at different time intervals in sevoflurane anaesthetized dogs.

6/ To evaluate antinociceptive and sedative effects of premedication with a long-acting formulation of sufentanil during and after sevoflurane anaesthesia in dogs.

CHAPTER 1

SEVOFLURANE: PHYSICO-CHEMICAL PROPERTIES AND MAC

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INTRODUCTION

Recently two new inhalant anaesthetic agents were commercialised in Europe, sevoflurane and desflurane. Both agents fit the mould of several other new anaesthetic agents and adjuvants. They permit greater control over the course of anaesthesia and more rapid recovery from anaesthesia than do their predecessors. In this review a survey was put together on the properties of sevoflurane in comparison with other recently developed inhalant anaesthetic agents (desflurane, isoflurane, halothane, enflurane). Furthermore, the possible usefulness of sevoflurane in anaesthesia of companion animals, in particular in dogs and cats was highlighted. The influences of sevoflurane on several body systems will be described in the second chapter.

HISTORY OF INHALANT ANAESTHETIC AGENTS (Table 1)

The earliest recorded attempts to induce anaesthesia appear to have been performed in humans. The ancients used opiates, alcohol, asphyxia, and even rather primitive techniques as compression of the carotid arteries to alleviate pain during surgical intervention.

In 1800, Sir Humphrey Davy suggested that nitrous oxide might have anaesthetic properties. Shortly thereafter in 1824, H. H. Hickman demonstrated that pain associated with surgery in dogs could be alleviated by inhalation of a mixture of nitrous oxide and carbon dioxide (Thurmon et al., 1996).

It was not until 1842 that ether was used for human anaesthesia. Jackson was the first clinician to employ ether

extensively in animals in 1853 (Jackson, 1853). Although chloroform was discovered by Liebig in 1831, it only was used in 1847 for general anaesthesia in animals by Flourens (Dadd, 1854). Diethyl ether and chloroform had marked side effects including arrhythmogenic effects, cardiovascular and respiratory depression and liver toxicity. In addition, some practical objections were the flammability and explosiveness of ether (Hall and Clarke, 1991).

Waters was the first to clinically use cyclopropane in human anaesthesia in 1933. Gregory developed the use of cyclopropane for experimental animal anaesthesia. From the fifties on, it was routinely used in several animal species in Great Britain. Practical problems rose again with its high flammability and explosiveness (Hall and Clarke, 1991). Since 1941 trilene (trichloro-ethyleen) has been widely used. Trilene had good analgesic effects; it was non-flammable, nor irritating. Nevertheless, its anaesthetic properties and muscle relaxation were insufficient (Vickers et al., 1978).

Fluroxene (2,2,2,trifluoroethyl-ether) was developed by Shukyse in 1951. This anaesthetic agent gave a rapid induction of anaesthesia with a dose related cardiopulmonary depression. However, it was extremely flammable and toxic after repeated use especially in animals (Hall and Clarke, 1991).

Already in 1940 methoxyflurane (2,2-dichloro-1,1-difluoroethylmethylether) was synthesized, although it was only commercialised in 1958. Methoxyflurane was a potent, non-flammable anaesthetic agent with good analgesic properties (Artusio et al., 1960). Its high blood-gas solubility was accompanied by a prolonged induction and recovery time. The recorded post-anaesthetic renal

failure was due to fluoride ion release during metabolisation of methoxyflurane (Mazze et al., 1971).

Table 1. Historical overview of volatile anaesthetic agents.

AGENTS	***YEAR****	ADVANTAGES	**DISADVANTAGES**
Nitrous oxide	1800	analgetic properties low blood-gas solubility	low analgetic potency in animals
Ether	1842	potent anaesthetic agent	inflammable, irritating high blood-gas solubility
Chloroform	1847	potent anaesthetic agent	hepatic and renal toxicity arhytmogenicity
Cyclopropaan	1933	low blood-gas solubility	Inflammable Explosive
Trichloroethyleen (trilene)	1941	good analgesia non-irritating	weak anaesthetic agent toxic breakdown in soda-lime
Halothane	1956	potent anaesthetic agent low toxicity	unstable in light
Methoxyflurane	1958	potent anaesthetic agent analgetic properties	high blood-gas solubility metabolised to fluorine
Enflurane	1958	potent anaesthetic agent low blood-gas solubility	epileptic properties
Isoflurane	1971	potent anaesthetic agent low metabolisation degree low blood-gas solubility	airway pungency
Desflurane	1987	low metabolisation degree extremely low blood-gas solubility	specialised vaporiser technology airway pungency
Sevoflurane	1990	potent anaesthetic agent low metabolisation degree low blood-gas solubility	renal toxicity?

* Year routinely used in human practice.

Halothane was introduced in veterinary anaesthesia in 1956, after its development for human anaesthesia by Sweking in 1951 (Suckling, 1957). Halothane is non-explosive and relatively stable. It gives a relatively fast induction of and recovery from anaesthesia and is less toxic than previously used inhalant anaesthetic agents. As with all volatile anaesthetic agents a dose related cardiopulmonary depression occurs (Short, 1987). In 1958 enflurane was introduced in human anaesthesia as a potent and slightly irritating volatile anaesthetic agent. Induction and recovery from anaesthesia are uneventful due to the low blood-gas solubility. Yet, higher enflurane concentrations have epileptic properties in dogs, cats and horses (Stevens et al., 1983, Oshima et al., 1985). In the early seventies isoflurane was developed by Terrell (Wade and Stevens, 1981). Isoflurane has a low blood-gas solubility resulting in short induction and recovery times.

In the continued search for less reactive, more potent and non-inflammable volatile anaesthetic agents focus on halogenation of these compounds has predominated. Chlorine and bromine especially convert many compounds of low anaesthetic potency into more potent drugs. Fluorination although improving stability, produces less potent compounds than addition of chlorine or bromine (Targ et al., 1989b). The lighter the halogens, the lower the anaesthetic potency of the compounds.

Up to now the search for developing new volatile anaesthetic agents with a higher safety margin, minimal cardiovascular depression and permitting a rapid and precise control of alveolar anaesthetic concentration, is continued. This resulted in the recent development of sevoflurane and desflurane, two anaesthetics permitting a flexible control of anaesthesia maintenance and inducing a rapid recovery.

Research on sevoflurane and desflurane develops parallel to one other.

Desflurane was recently commercialised in Europe. It has the lowest blood-gas solubility of all contemporary volatile anaesthetic agents. Besides its relatively low anaesthetic potency (high concentrations needed) and its airway irritating property; its high vapour pressure (specialized vaporizer technology required) is also a disadvantage for its practical use (Eger, 1993; Young and Apfelbaum, 1995).

Sevoflurane was developed in the seventies (Wallin et al., 1975) and since 1980 it is extensively examined in human and veterinary anaesthesia, especially on an experimental basis in the beginning. Since 1990 it can be used in clinical human anaesthesia. And finally in 1996 sevoflurane was registered for human anaesthesia in Belgium.

MOLECULAR STRUCTURE AND PHYSICAL PROPERTIES OF SEVOFLURANE (Table 2a +b)

The chemical structure of inhalation anaesthetics and their physical properties are important determinants of their actions and safety of administration. All contemporary volatile anaesthetic agents are organic compounds except nitrous oxide (N_2O). Sevoflurane is a methyl-propyl-ether with 7 fluorine atoms and a molecular weight of 200.1 (Aida et al., 1994). The chemical structure of sevoflurane (CFH_2-O-$CH(CF_3)_2$) is responsible for its kinetic properties.

Fluorination of the carbon group resulted in a low blood-gas partition coefficient (0.68), which is considerably lower compared to

halothane, enflurane and isoflurane (Eger, 1994). The low blood-gas solubility produces the following properties: 1/ more rapid increase in alveolar anaesthetic concentration during induction of anaesthesia, 2/ more precise control of alveolar anaesthetic concentration during maintenance of anaesthesia and 3/ more rapid decrease in alveolar anaesthetic concentration during elimination. The human tissue-blood partition coefficients of sevoflurane in the brain (1.70), fat (48.0), kidneys (1.20), liver (1.80) and muscles (3.10) are intermediate between isoflurane en halothane (Steffey, 1996). A low brain-blood partition coefficient is advantageous for a rapid control and adjustment of anaesthetic depth; whereas a low fat-blood partition coefficient is of primordial importance for a rapid recovery from anaesthesia (Jones, 1990).

The solubility characteristics of sevoflurane in rubber and plastic are lower compared to isoflurane and halothane (Targ et al., 1989a). Consequently, the anaesthetic circuit extracts less agent during anaesthetic administration and redistributes less agent to rebreathed gases during elimination. This can be important since losses of volatile anaesthetic by circuit absorption may compromise measurements of anaesthetic uptake (Eger et al., 1998).

The boiling point and vapour pressure of sevoflurane are comparable with those from halothane, isoflurane and enflurane. Hence, conventional precision vaporisers without specific technical requirements can be used. On the contrary, the boiling point and vapour pressure of desflurane are completely different from the other volatile anaesthetic agents requiring specialised vaporizer technology for desflurane. Furthermore, sevoflurane doesn't contain thymol or any other preservative, in contrast with the less stable halothane.

Thymol is much less volatile than the inhalant anaesthetic agents and over time collects within the vaporisers leading to malfunctioning.

Table 2 a : Physico-chemical properties of recent volatile anaesthetic agents. Modified from Steffey E.P. in Lumb & Jones' Veterinary Anesthesia Chapt.11 (1996).

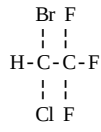
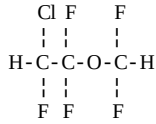
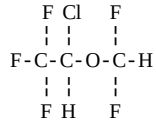
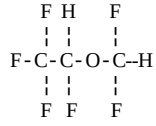
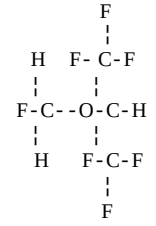
AGENT	**TRADENAME**	**COLOUR CODE**	**CHEMICAL STRUCTURE**	**BLOOD-GAS PARTITION COEFFICIENT** At 37°C	***RUBBER-GAS PARTITION* COEFFICIENT** at roomtemp.
halothane	Fluothane®	red		2.54	120
Enflurane	Ethrane®	orange		2.00	74
Isoflurane	Forene®	purple		1.46	62
desflurane	Suprane®	blue		0.42	/
sevoflurane	Sevorane®	yellow		0.68	14.0
Nitrous Oxide	/	blue		0.47	1.2

Table 2 b : Physico-chemical properties of recent volatile anaesthetic agents. Modified from Steffey E.P. in Lumb & Jones' Veterinary Anesthesia Chapt.11 (1996).

AGENT	TRADENAME	BOILING POINT	VAPOUR PRESSURE at 20°C at 24°C	% METABOLISATION
halothane	Fluothane®	50.2 °C	243 mmHg 288 mmHg	20-25
Enflurane	Ethrane®	57 °C	172 mmHg 207 mmHg	2.4
Isoflurane	Forene®	49 °C	240 mmHg 286 mmHg	0.17
desflurane	Suprane®	23.5 °C	664 mmHg /	0.02
sevoflurane	Sevorane®	59 °C	160 mmHg 197 mmHg	3.0
Nitrous Oxide	/	-89 °C	/ /	0.004

ANAESTHETIC PROPERTIES OF SEVOFLURANE

* Inhalation Induction (Figure 1)

The aim in administering an inhalation anaesthetic agent to a patient is to achieve an adequate partial pressure of anaesthetic in the brain to cause a desired level of central nervous system depression. The rate of change of anaesthetic depth is of obvious clinical importance and is directly dependent upon the rate of change in anaesthetic tensions in the various media in which it is taken up before reaching the brain. Inhalation anaesthetics move down a series of partial pressure gradients from regions of higher tension to those of lower tension until equilibrium is established over the several compartments. The anaesthetic agent travels from vaporizer to breathing circuit, from circuit to lungs, from lungs to arterial blood, and

finally, from arterial blood to body tissues (see figure1). Of these the alveolar partial pressure (P_A) of the anaesthetic agent is most crucial. The brain has a high blood supply and the anaesthetic in arterial blood rapidly equilibrates with brain tissue.

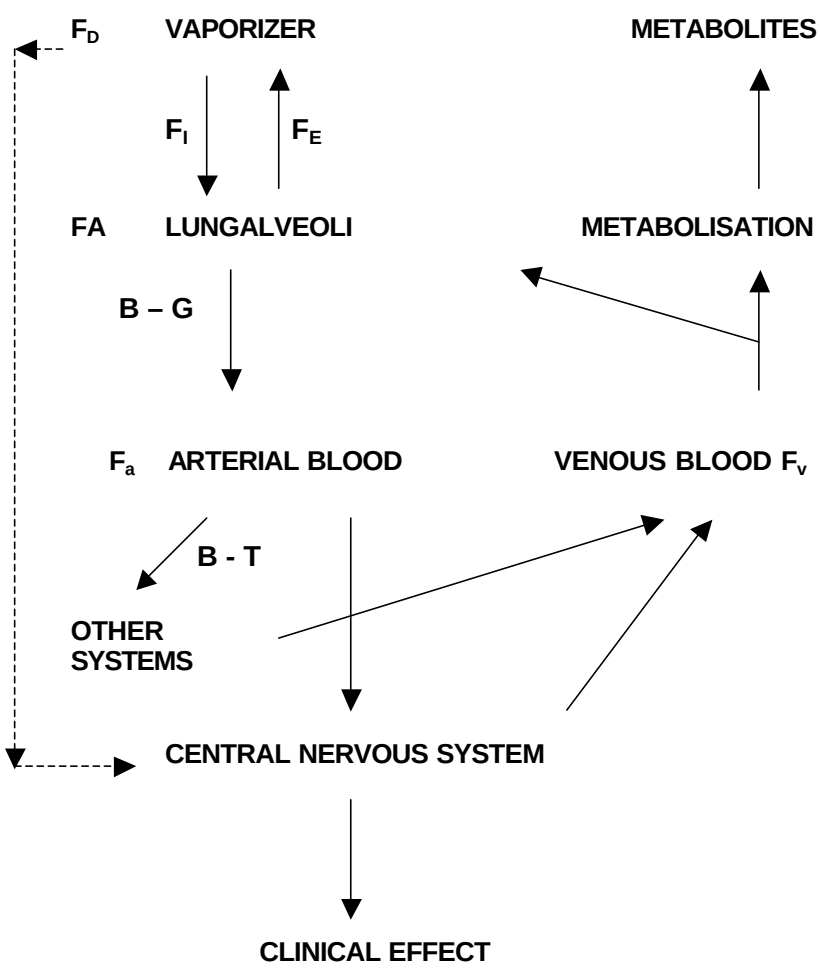
The rate of increase in alveolar anaesthetic concentration (F_A) toward the concentration inspired (F_I) during induction relates inversely to solubility of the potent agent in blood (Yasuda et al., 1991a; Yasuda et al., 1991b). Sevoflurane induces a rapid increase in F_A/F_I ratio due to its low blood-gas solubility (Eger, 1994). A more rapid increase in F_A/F_I suggests the potential for a more rapid induction of anaesthesia. Administering N_2O in conjunction with the volatile anaesthetic agent can influence the alveolar anaesthetic concentration. Very early in the administration of N_2O the rate of rise of the alveolar concentration of the concurrently administered inhalation anaesthetic is increased. This is commonly referred to as the “second gas” effect, and this phenomenon can be applied clinically to speed anaesthetic induction (Eger, 1963). Yet, the benefits provided by N_2O appear minimal in dogs when low solubility inhalation agents such as isoflurane and sevoflurane are used for mask induction (Mutoh et al., 2001c). In dogs the F_A/F_I ratio of sevoflurane (0.75 ± 0.06) is greater compared to isoflurane and halothane (resp. 0.60 ± 0.05 and 0.25 ± 0.02); resulting in a smooth and rapid induction of inhalation anaesthesia (Kazama and Ikeda, 1988).

Mask- or inhalation induction technique is routinely used in human paediatric anaesthesia and is also applicable in veterinary anaesthesia. An important problem with inhalation induction is the resistance of the animals against proper placement of the facemask leading to inhalation of an inadequate concentration of volatile anaesthetic agent. A second problem is the possible occurring airway irritation induced by the anaesthetic agent. This pungency results in hypersalivation, apnoea, coughing, breath-holding, laryngo- and

bronchial spasms and increased airway secretions. These undesirable responses result from irritation of the mucosa of the nasal passages, pharynx and larynx, which may impair smooth induction of anaesthesia and lead to airway obstruction and associated hypoxia and hypercapnia in dogs, cats and humans. Mutoh et al. (1995) described that inhalation induction with 2.5 MAC isoflurane in dogs was accompanied with relatively more struggling compared to induction with 2.5 MAC sevoflurane. Upper-airway administration of sevoflurane, halothane and isoflurane with concentrations used for mask induction induced milder reflex inhibition of breathing with sevoflurane. Lack of respiratory reflexes attributable to stimulation of the nasal passages may contribute to speed of onset and promote a smoother induction with sevoflurane (Mutoh et al., 2001a; Mutoh et al., 2001b).

The pungency of sevoflurane parallels that of halothane; this makes them the less pungent volatile anaesthetic agents. Both inhalant anaesthetics can be applied for mask induction in human and small animal anaesthesia (Sarner et al., 1995; Lerman et al., 1996; Blair et al., 2000). The differences in induction speed and airway irritability have not been confirmed in cats. Hikasa et al. (1996) did not see any difference in induction speed between halothane, isoflurane and sevoflurane. Possible explanations for these different findings could be the administered premedication and the slow and gradual induction technique applied. Sevoflurane mask induction is suitable in feline practice because of its good quality of induction in most cats and dogs (Johnson et al., 1998; Tzannes et al., 2000; Mutoh et al., 2001c; Lerche et al., 2002). Desflurane on the other hand is not recommended for inhalation induction in paediatric anaesthesia due to its high pungency with laryngeal spasms, coughing and increased airway secretions (Eger, 1994).

Fig.1: The flow pattern of inhaled anaesthetic agents during anaesthetic induction and recovery.



FD: delivered anaesthetic concentration by the vaporizer
FA: alveolar anaesthetic concentration
FI: inspiratory anaesthetic concentration
FE: expiratory anaesthetic concentration
Fa: arterial anaesthetic concentration
Fv: venous anaesthetic concentration
B – G: blood – gas solubility
B – T: blood – tissue solubility

*** Maintenance of anaesthesia**

Maintenance of a constant level of anaesthesia with an inhalant anaesthetic agent may be equated to the maintenance of a constant alveolar anaesthetic concentration. A precise control of anaesthetic depth on basis of vaporizer settings is desirable in clinical practice. The difference between the concentration of anaesthetic agent delivered (F_D) from a vaporizer and the F_A may be used to define the degree of control of the anaesthetic level obtained with an inhalant agent during maintenance of anaesthesia (Eger, 1994). A ratio of F_D/F_A that approaches 1.0 indicates precise control, and deviations from 1.0 less control. The F_D/F_A ratio depends on the anaesthetic agent, the anaesthetic system (rebreathing degree) and the fresh gas flow. Anaesthetic uptake and rebreathing determine the proximity of F_D/F_A to 1.0: a smaller uptake (lower solubility and greater tissue equilibration) and diminished rebreathing (i.e., a higher inflow rate, a higher fresh gas flow rate) provide a value closer to 1.0. Furthermore, cardiac output and alveolar ventilation have an important influence on the F_D/F_A ratio of a volatile anaesthetic agent.

The low blood-gas solubility of sevoflurane even in combination with an economical flow rate of 1-2 L/min permits to estimate the alveolar anaesthetic concentration from the delivered concentration by the vaporizer.

The use of an agent-specific analyser facilitates a precision over the control of maintenance of anaesthesia, regardless of solubility by measuring inspiratory and end tidal anaesthetic gases.

*** Recovery from anaesthesia**

Recovery from inhalation anaesthesia depends on solubility and concentration of the volatile agent, duration of anaesthesia and

metabolisation percentage (Lerman et al., 1996). The lower solubility of sevoflurane permits a more rapid decrease in F_A at the end of anaesthesia. Its low fat solubility assures a rapid elimination regardless of anaesthesia duration.

In humans a positive correlation (r = 0.517) was found for isoflurane between total anaesthetic exposure or dose (MAC-hours, see further) and recovery time. After sevoflurane anaesthesia MAC-awake (the average of the bracketing alveolar anaesthetic concentration that allows and prevents the response to verbal command during recovery from anaesthesia; Stoelting et al., 1970) was independent of anaesthetic duration in adults (Campbell et al., 1995). Hikasa et al. (1996) showed that recovery times in cats were significantly shorter after 90 minutes of sevoflurane anaesthesia compared to halothane anaesthesia, but only slightly shorter compared to isoflurane anaesthesia.

Inhalation anaesthetic agents are not chemically inert. They undergo varying degrees of metabolism primarily in the liver, but also to a lesser degree in the lung, kidney and intestinal tract (Rehder et al., 1967; Holaday et al., 1970). Especially methoxyflurane and to a lesser extent halothane have longer recovery times caused by their extended metabolisation (Carpenter et al., 1986).

More recent volatile anaesthetic agents have shorter emergence times greatly due to their low extent of biotransformation (see table 2). Important elimination routes from the body are the lungs, and of minor clinical importance through faeces, urine, transpiration, percutaneous loss and eventually through the surgical site (Stoelting and Eger, 1969; Fassoulaki et al., 1991; Lockhart et al., 1991).

Nevertheless, in comparison with isoflurane and desflurane, sevoflurane still has a relatively high metabolisation percentage, yet it has a rapid recovery. This is probably related to the low fat solubility of sevoflurane resulting in low deposition of the anaesthetic agent in body fat tissue. Body fat tissue functions as depot for the volatile anaesthetic agent during elimination.

The pharmacokinetic profile of sevoflurane resulting in rapid emergence times is especially useful after ambulatory anaesthesia in human anaesthesia. Time intervals from stopping the delivery of the anaesthetic to specific emergence and recovery parameters (e.g., time to extubation, opening of the eyes, emergence, orientation, response to commands, etc.) are shorter when compared to anaesthesia using volatile agents with higher blood-gas solubilities (e.g. isoflurane, enflurane) (Frink et al., 1992; Smith et al., 1992; Campbell et al., 1995; Eriksson et al., 1995; Philip et al., 1996; Aono et al., 1997; Ebert et al., 1998; Song et al., 1998 ; Robinson et al., 1999). In comparison with halothane time interval between end of anaesthesia and response to commands is reduced with 33% after sevoflurane anaesthesia (Lerman et al., 1996).

Fast recovery from sevoflurane, however, is likely to be accompanied by postoperative delirium, which is considered due to the early appearance of pain (Naito et al., 1991; Lerman et al., 1996; Aono et al., 1997). Especially in children who did not receive any analgesic or regional anaesthesia, the incidence of agitation and excitement during emergence from sevoflurane was greater than the incidence after halothane or propofol anaesthesia (Lerman et al., 1996; Beskow and Westrin, 1999; Picard et al., 2000). The excitement was probably due to inadequate postoperative analgesia and a fast recovery of cognitive functions (Lerman, 1995). In animals early pain

perception will probably occur if inadequate postoperative analgesia is provided.

MINIMUM ALVEOLAR CONCENTRATION (MAC) (Table 3)

MAC is defined as the minimum alveolar concentration of a volatile anaesthetic agent that prevents a reaction on a standardised pain stimulus (a haemostatic forceps clamped on the tail or a standardised electric pulse) in 50% of a population (Merkel and Eger, 1963; Laster et al., 1993). Thus MAC corresponds to the effective $dose_{50}$ or ED_{50}; half of the subjects are anaesthetized and half have not yet reached that level (De Jong and Eger, 1975, Quasha et al., 1980).

MAC-values are used to compare the anaesthetic potency of different volatile anaesthetic agents. The term potency refers to the quantity of an inhalant anaesthetic that must be administered to cause a desired effect (e.g. general anaesthesia). Equipotent doses are useful for comparing effects of inhalation anaesthetics on vital organs.

MAC-values from volatile anaesthetic agents are inversely related to their oil-gas solubility (Lerman, 1993). The anaesthetic potency of a volatile anaesthetic agent is also inversely related with the MAC-value. Sevoflurane has an intermediate anaesthetic potency and a low oil-gas solubility leading to a relatively high MAC-value. Halothane and isoflurane are relatively more potent volatile anaesthetic agents with a high oil-gas partition coefficient and a low MAC-value.

Table 3 : Minimal alveolar concentration (MAC) of volatile anaesthetic agents in dogs, cats and humans.

AGENT	MAC-VALUE*	SPECIES	REFERENCES
Halothane	0.77 0.89 1.19	man dog cat	Saidman et al., 1967 Kazama et al., 1988 Drummond et al., 1983
Enflurane	1.68 2.06 2.37	man dog cat	Gion et al., 1971 Steffey and Howland, 1978 Drummond et al., 1983
Isoflurane	1.15 1.39 1.63	man dog cat	Stevens et al., 1975 Steffey and Howland, 1977 Steffey and Howland, 1977
Desflurane	6.00/ 7.25 7.20 9.79	man dog cat	Rampil et al., 1991 Doorley et al., 1988 McMurphy et al., 1995
Sevoflurane	1.71 2.36 2.58	man dog cat	Katoh and Ikeda, 1987 Kazama et al., 1988 Scheller et al., 1990

In a single species the variability in MAC is generally small and is only minimally influenced by age, gender, body temperature, pregnancy, administered premedication, duration of anaesthesia and N_2O administration (Saidman and Eger, 1964; Palahniuk et al., 1974; Steffey et al., 1977; Heard et al., 1986; Katoh et al., 1987; Glosten et al., 1990; Ewing et al., 1993; Katoh et al., 1994). In humans a marked decrease in sevoflurane MAC is observed with increasing age, except for a small rise in MAC between birth and the age of 6 months (Katoh et al., 1993a; Nakajima et al., 1993; Inomata et al., 1994). Nitrous oxide (60% end tidal) reduces the MAC-value of sevoflurane with 60% in adults and with 24% in young children (Lerman et al., 1994). Hence,

N_2O is frequently used in combination with volatile anaesthetic agents since less volatile agent is needed and fewer side effects occur. To get important benefits of N_2O, it is usually administered in high-inspired concentrations. Nitrous oxide has less value in the anaesthetic management of animals because the anaesthetic potency of N_2O is only half that found for humans (Eger et al., 1965; Steffey et al., 1974; DeYoung et al., 1980; Hornbein et al., 1982). MAC-values of several inhalant anaesthetic agents were determined in dogs and cats (see Table 3). The addition of 66% inspired nitrous oxide reduces the mean end tidal halothane concentration with 39%, with 26% for isoflurane and with 23% for sevoflurane in cats (McMurphy and Hodgson, 1995; Hikasa et al., 1996).

Fentanyl, a potent and short acting narcotic analgetic agent, has a low hypnotic effect and reduces in a dose-dependent manner the MAC-awake of sevoflurane. In contrast, morfine is a less potent and longer acting opioid with less influence on the MAC-awake of sevoflurane (Katoh et al., 1993b).

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CHAPTER 2

SEVOFLURANE: INFLUENCES ON BODY SYSTEMS.

ECONOMIC CONSIDERATIONS.

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SUMMARY

In this chapter the influences of sevoflurane on the different vital systems are discussed. It shows that sevoflurane has little influence on brain perfusion and intracranial pressure. Cardiac output only decreases at high sevoflurane concentrations and coronary circulation is maintained. Sevoflurane induces a dose dependent respiratory depression and lacks airway pungency. Its low metabolisation percentage and minimal influence on total liver perfusion make it extremely useful for patients with liver dysfunction. Nevertheless, for animals with renal insufficiency some caution is adviced, since the compound A and fluoride issues merit further investigation. At this moment a possible renal toxicity has only been proved in rats.

Furthermore, the economic considerations on the use of sevoflurane in clinical practice are discussed. In the near future the use of sevoflurane will be affordable in veterinary practice.

INTRODUCTION

The chemical and physical properties of sevoflurane concerning induction, maintenance and recovery from anaesthesia were discussed in the first chapter.

Furthermore, the knowledge of the influences on the different vital systems is of primary importance for using a new inhalant anaesthetic agent since this can lead to the prevention and treatment of potential side effects during anaesthesia. Therefore, the effects of sevoflurane on central nervous system, cardiovascular system,

respiratory system, in addition to hepatic and renal effects together with economic considerations are discussed.

EFFECTS ON CENTRAL NERVOUS SYSTEM

Cerebral perfusion (cerebral blood flow: CBF) is influenced by the so-called cerebral autoregulation mechanism (Brian, 1998). The cerebral autoregulation is a sensitive physiologic mechanism keeping CBF constant within a cerebral perfusion pressure between 50 and 150 mm Hg protecting the brain against acute changes in arterial blood pressure.

All traditional inhalant anaesthetic agents (halothane, isoflurane and enflurane) decrease cerebral vascular resistance leading to an increased intracranial pressure (Hörmann et al., 1997). The abolishment of cerebral autoregulation in a dose-dependent matter by inhalation anaesthetic agents can be a problem during intracranial surgery or in patients with head trauma. Between agents a great difference exists in influencing degree of cerebral perfusion and pressure (Ogawa et al., 1997). Halothane and enflurane influence cerebral autoregulation in humans by dilation of cerebral vessels and increase in CBF (Miletich et al., 1976). In healthy sevoflurane anaesthetized patients cerebral autoregulation remains well preserved unto 1.5 MAC (Summors et al., 1999). Moreover, even in patients with ischaemic cerebrovascular diseases autoregulation is not disturbed at 0.88 MAC sevoflurane (Kitaguchi et al., 1993; Cho et al., 1996; Gupta et al., 1997). It can be concluded that in common with other volatile anaesthetic agents, sevoflurane has a "weak" intrinsic, dose-dependent cerebral vasodilatory effect (Bundgaard et al., 1998). However, this effect is less than that reported for halothane, isoflurane and desflurane at equipotent anaesthetic concentrations. Because of

this weak intrinsic vasodilatory action, sevoflurane is unlikely to cause a significant increase in intracranial pressure. Sevoflurane has therefore a haemodynamic profile favouring its use in neuro-anaesthesia (Matta et al., 1999).

In dogs the different inhalant anaesthetic agents have specific influences on cerebral perfusion. Halothane decreases cerebral vascular resistance leading to increased cerebral perfusion (Theye and Michenfelder, 1968). Isoflurane and enflurane induce a dose-related decrease in cerebral vascular resistance (Cucchiara et al., 1974; Michenfelder and Cucchiara, 1974; Artru, 1983; Scheller et al., 1990). The same goes for the two recently developed inhalation anaesthetics, sevoflurane and desflurane: in dogs a dose-mediated decrease in cerebral vascular resistance occurred associated with an increased cerebral perfusion (Scheller et al., 1990; Lutz et al., 1990). Desflurane reduces cerebral vascular resistance with 67% between 0.5 and 2 MAC; however, at higher concentrations between 1.5 and 2 MAC a further increase of CBF is limited by occurring hypotension (Lutz et al., 1990). The same phenomenon is seen during isoflurane anaesthesia. In general, the degree of occurring cerebral vasodilatation during inhalation anaesthesia is as follows: desflurane > halothane > enflurane > isoflurane ≈ sevoflurane (Todd and Drummond, 1984; Lutz et al., 1990; Takahashi et al., 1993).

Besides the direct influence of the volatile anaesthetic agent on CBF, the indirect role of carbon dioxide (CO_2) on brain perfusion has to be taken into account. Carbon dioxide is a potent cerebral vasodilator. Hypercapnia exhausts the cerebral vasodilator response to changes in perfusion pressure reducing the autoregulatory capacity (Raichle and Stone, 1972). In contrast, hypocapnia increases cerebral vascular tone resulting in improved cerebral autoregulation (Paulson

et al., 1972). During inhalation anaesthesia hypercapnia (increase in $PaCO_2$) often occurs due to hypoventilation leading to cerebral vasodilatation accompanied by increased CBF and intracranial pressure. During brain surgery a decreased brain perfusion is advisable and can be achieved by hyperventilation of the patients (Cold et al., 1998). The low arterial CO_2 concentration induces cerebral vasoconstriction and a decreased CBF. In humans for every change in $PaCO_2$ with 1 mm Hg CBF alters with 1-2 ml/100 g/min (Pickard et al., 1977). If $PaCO_2$ decreases from 35-40 mm Hg to 20-25 mm Hg CBF decreases with 40-50%. On the other hand, a further decrease in $PaCO_2$ has no influence on CBF (Alexander et al., 1968). Cats have a mean cortical blood flow of 86 ml/100 g/min; a difference of 1.7 ml in CBF was observed after a change in $PaCO_2$ with 1 mm Hg (Sato et al., 1984).

In humans cerebrovascular reaction on changes in $PaCO_2$ remain unaffected during sevoflurane and desflurane anaesthesia leading to a beneficial decreased CBF and intracranial pressure with hypocapnia (Kitaguchi et al., 1993; Ornstein et al., 1993; Cho et al., 1996; Nishiyama et al., 1997; Bundgaard et al., 1998; Mielck et al., 1999). Another study showed that hypocapnia induced reduction of intracranial pressure was slightly more effective during the administration of isoflurane than sevoflurane (Nishiyama et al., 1999a). Hypocapnia can also be used in dogs to achieve an effective decrease in CBF and intracranial pressure at 1 and 2 MAC isoflurane and sevoflurane (McPherson et al., 1989; Takahashi et al., 1993). However, when using halothane or enflurane even at low concentrations in dogs cerebral vasoconstriction induced by hypocapnia can be abolished (Artru 1983; Ogawa et al., 1997). On the other hand, in cats CBF can be reduced by hyperventilation with

hypocapnia during halothane and isoflurane anaesthesia (Drummond and Todd, 1985). In conclusion, cerebral pressure autoregulation and CO_2 –responsiveness during brain surgery are best preserved in sevoflurane or isoflurane anaesthetized hyperventilated patients.

In humans sevoflurane, isoflurane and desflurane induce a depression in electroencephalogram (EEG) activity without the occurrence of epileptiform activity (Eger et al., 1971; Rampil et al., 1991; Kuroda et al., 1996;). Recently, periodic epileptiform discharges were observed on EEG during single-breath sevoflurane induction. The epileptiform EEG activity was of short duration and led to no untoward effects after anaesthesia in healthy patients (Vakkuri et al., 2000). A study in cats showed that sevoflurane suppresses central nervous system background activities but has little effect on the reactive properties of the brain in light stages (2% sevoflurane), and facilitates them in relatively deep (5% sevoflurane) stages of anaesthesia. These data support the hypothesis that sevoflurane may have convulsive properties in cats similar to enflurane (Osawa et al., 1994). With enflurane at high concentrations seizure activity was seen on EEG, especially during hypocapnia (Neigh et al., 1971). As in human anaesthesia enflurane induced seizure activity on EEG during auditory stimulation in dogs when used at concentrations above 1 MAC (Scheller et al., 1990). Desflurane differs from the other anaesthetics in that the effect of higher concentrations of desflurane on EEG activity may be limited with time (Lutz et al., 1990). In healthy dogs no epileptiform activity was registered on EEG during sevoflurane and isoflurane anaesthesia and this during normocapnia, hypocapnia as well as during intense auditory stimulation (Scheller et al., 1990).

Sevoflurane has a haemodynamic profile favouring its use in neuro-anaesthesia due to its minimal influence on brain perfusion and CO_2 – responsiveness, both in human and veterinary medicine (Baker, 1997). Furthermore, the fast and smooth recovery from anaesthesia after sevoflurane is useful for a rapid postoperative neurological evaluation of the patient. Special attention should therefore be given to postoperative analgesia as one of the main causes for postoperative excitation.

EFFECTS ON CARDIOVASCULAR SYSTEM

Like all other volatile anaesthetic agents sevoflurane induces a dose-dependent cardiovascular depression. The influence of sevoflurane on several cardiovascular parameters will be discussed: heart rate (HR), cardiac output (CO), myocardial contractility, coronary circulation and systemic blood pressure. Comparable to other volatile anaesthetics a relatively stable heart rate has been reported during sevoflurane anaesthesia in humans, even in children with congenital heart disease (Ebert et al., 1995; Malan et al., 1995; Rivenes et al., 2001). A stable heart rate is favourable for myocardial oxygen consumption and for myocardial perfusion time. However, an increase in heart rate was reported during sevoflurane anaesthesia in dogs from 1.2 MAC on (Bernard et al., 1990; Mutoh et al., 1997). The increased heart rate was mainly due to baroreceptor-reflex induced by systemic hypotension. In dogs and humans sevoflurane has less negative influence on baroreceptor-reflex function than isoflurane (Tanaka and Nishikawa, 1999). No difference in compromising baroreceptor-reflex was observed between sevoflurane and isoflurane when increasing the MAC above 2 (Bernard et al., 1990). Arterial baroreflex function is an important neural control system for

maintaining cardiovascular stability. Halothane has less influence on heart rate in small animals, a slight increase was observed in dogs, while a small decrease occurred in cats. On the other hand, desflurane and isoflurane induced a non dose-dependent increase in heart rate in dogs (Grandy et al., 1989; Merin et al., 1991; Pagel et al., 1991a; Clarke et al., 1996;).

Sympathetic nerve stimulation (e.g. tachycardia, hypertension) as reported to occur in humans after desflurane induction, is not observed during sevoflurane mask induction (Ebert and Muzi, 1993; Moore et al., 1994; Weiskopf et al., 1994; Ebert et al., 1995; Muzi et al., 1996). The neurocirculatory excitation seen with rapid increases in desflurane did not occur with sevoflurane. The airway irritation associated with desflurane in humans may be involved in the marked activation of the neuro-endocrine axis (Ebert and Muzi, 1993; Weiskopf et al., 1994).

Volatile anaesthetic agents can sensitise the myocardium to adrenaline-induced premature ventricular depolarisations presumably due to the depression of sinus node automaticity, the slowing of atrio-ventricular nodal and His-Purkinje's conduction, and the hyperpolarisation and shortening of the refractoriness of Purkinje's fibre (Atlee, 1985). In humans and dogs sevoflurane does not change the sensitivity of the myocardium to the arrhythmogenic effect of exogenously administered adrenaline (Imamura and Ikeda, 1987; Hayashi et al., 1988; Navarro et al., 1994). The dose of adrenaline required with sevoflurane is higher than that required with halothane and enflurane, and similar to that with isoflurane in dogs (Imamura and Ikeda, 1987; Hayashi et al., 1988). This was also reported in cats, the effect of sevoflurane on the sensitisation of the feline myocardium to the arrhythmogenic effect of adrenaline was significantly less than

that of halothane and not different from isoflurane (Hikasa et al., 1996).

In sevoflurane anaesthetized men myocardial depression mainly occurs due to the negative inotropic property of sevoflurane, although this is less pronounced compared to halothane (Malan et al., 1995; Holzman et al., 1996; Rivenes et al., 2001). A dose-related decreased myocardial contractility was also observed in dogs during sevoflurane anaesthesia and was comparable with the depression seen with isoflurane and desflurane (Bernard et al., 1990; Pagel et al., 1991b; Harkin et al., 1994; Pagel et al., 1994; Hettrick et al., 1996). Depression of myocardial contractility by sevoflurane may be due to a block of the transmembrane calcium influx and is accompanied by a decrease in stroke volume (Bernard et al., 1990; Hatakeyama et al., 1993; Park et al., 1996). Cardiac output will only decrease from 2 MAC on, because the initial decrease in stroke volume at lower sevoflurane concentrations is abolished by tachycardia (Bernard et al., 1990; Lowe et al., 1996).

Global coronary circulation remains intact in sevoflurane anaesthetized dogs even during myocardial ischaemia. Nevertheless, a small decrease in coronary vascular resistance was observed in dogs (Bernard et al., 1990). This might lead to the so-called “coronary steal” effect. Coronary steal is defined as a marked redistribution of myocardial blood flow from ischaemic to normal zones; this can lead to exacerbation of myocardial ischaemia in patients with coronary artery disease (Warltier et al., 1980; Gross and Warltier, 1981). Isoflurane and to a lesser degree halothane, induce a coronary steal effect in dogs because of their coronary vasodilating properties (Buffington et al., 1987; Priebe, 1988). In contrast, sevoflurane lacks potent coronary vasodilating properties in dogs, which are necessary

to cause this effect (Kersten et al., 1994; Kitahata et al., 1999). Since sevoflurane is a less potent coronary vasodilator than isoflurane, it preserves coronary blood flow reserve and diminishes the potential for coronary steal (Larach and Schuler, 1991; Hirano et al., 1992; Ebert et al., 1997; Tomiyasu et al., 1999; Crystal et al., 2000).

In humans, as in companion animals sevoflurane induces a dose-related hypotension partly due to decreased peripheral resistance and partly to a reduced stroke volume (Ebert et al., 1995; Malan et al., 1995; Lowe et al., 1996; Mutoh et al., 1997). Halothane, isoflurane, desflurane and enflurane also induce a dose-dependent decrease in arterial blood pressure in dogs and cats (Steffey and Howland, 1977; Steffey and Howland, 1978; Frink et al., 1992c, McMurphy and Hodgson, 1996).

In conclusion, cardiovascular influences of sevoflurane are similar to those of isoflurane, but favourable to those of halothane. Sevoflurane only decreases cardiac output during high concentrations and offers protection against catecholamine induced arrhythmias. Moreover, adequate coronary circulation is maintained offering potential benefits for anaesthetizing cardiac patients.

EFFECTS ON RESPIRATORY SYSTEM

Sevoflurane induces a dose-related respiratory depression in both humans and companion animals (Doi et al., 1986; Doi and Ikeda, 1987; Tamura et al., 1991; Mutoh et al., 1997). The depression in ventilatory function is characterized by a decrease in tidal volume with increasing depth of anaesthesia and a moderate increase in $PaCO_2$. The decrease in tidal volume is not adequately compensated for by an increase in respiration rate, which leads to hypoventilation.

Respiratory depression is mediated by central depression of the medullar respiratory neurons and by a decrease in diaphragmatic contractility (Doi et al., 1988; Ide et al., 1991; Ide et al., 1992).

Isoflurane induces a similar respiratory depression in dogs. Tidal volume remains higher during enflurane anaesthesia compared to sevoflurane, but respiratory rate is more decreased (Mutoh et al., 1997). During halothane anaesthesia in dogs respiratory rate is higher and tidal volume lower compared to sevoflurane (Mutoh et al., 1997). From 1.4 MAC on sevoflurane anaesthesia is accompanied by a more pronounced respiratory depression in humans compared to equipotent concentrations of halothane (Doi and Ikeda, 1987). Dose-related respiratory depression is also reported during desflurane anaesthesia both in humans, dogs and cats (Lockhart et al., 1991; Clarke et al., 1996; McMurphy and Hodgson, 1996).

Sevoflurane induces bronchodilation in dogs by inhibition of histamine- or acetylcholine-induced bronchial muscle contractions (Katoh and Ikeda, 1991). Isoflurane but mainly halothane abolished histamine-induced bronchoconstriction in a dose-dependent manner (Brown et al., 1993). In human anaesthesia sevoflurane may be a worthwhile alternative to the traditional choice of halothane as an adjunct to prevent and manage intraoperative bronchospasm (Rooke et al., 1997). Sevoflurane is as effective as isoflurane in attenuating bronchoconstriction associated with anaphylaxis in dogs and may be a useful alternative for the other volatile agents in the treatment of bronchospasm in asthma or anaphylaxis (Mitsuhata et al., 1994).

Lack of pungency is an important characteristic for volatile anaesthetic agents used for mask induction. Airway reflexes such as apnoea, breath-holding, laryngospasm and hypersecretion as well as

excitement can occur during induction (Harvey, 1992). These undesirable responses are believed to be the result of irritation of the mucosa of the nasal passages, pharynx and larynx, which may impair smooth induction of anaesthesia and lead to airway obstruction and associated hypoxia and hypercapnia in dogs, cats and humans (Yurino and Kimura, 1993; Steffey, 1994; Mutoh et al., 1995). The degree of airway irritation varies with the type of inhalant (Doi and Ikeda, 1993). In contrast with isoflurane, sevoflurane and halothane cause less airway irritation, less stimulation of the cough reflex and less reflex inhibition of breathing in both dogs and humans (Inomata et al., 1994; Green, 1995; Kandasamy and Sivalingam, 2000; Klock et al., 2001; Mutoh et al., 2001a; Mutoh et al., 2001b; Mutoh et al., 2001c). Rapid induction of anaesthesia (sevoflurane > isoflurane >> halothane) is of great importance in preventing excitation during mask induction. The risk for cardiopulmonary problems and overdosage increases during long inhalation inductions. Mask induction in healthy dogs is fast and accompanied by less excitation when using sevoflurane. However, isoflurane, enflurane and halothane are associated with longer induction times and more resistance from the animals on mask placement (Mutoh et al., 1995). Until now sevoflurane is a very suitable volatile anaesthetic for inhalation induction in humans and small animals (Doi and Ikeda, 1992; Doi and Ikeda, 1993).

HEPATIC EFFECTS

All volatile anaesthetic agents are primarily metabolised in the liver to a different extent. Normal liver functioning is necessary for metabolisation and elimination of most volatile anaesthetic. In contrast, metabolism of sevoflurane does not contribute to termination of clinical drug effect, unlike more extensively metabolised drugs as

halothane (Kharasch, 1995). Only a limited amount (3.3% in humans and 2.5% in dogs) of absorbed sevoflurane is metabolised in the liver by cytochrome P_{450} $2E_1$ enzymes, in dogs metabolic pathways are not yet described (Table 1) (Martis et al., 1981; Shiraishi and Ikeda, 1990). Sevoflurane is metabolised to hexa-fluoro-isopropanol and inorganic fluoride. Hexa-fluoro-isopropanol is conjugated with glucuronic acid and excreted in the urine as a non-toxic glucuronide conjugate (Figure 1) (Holaday and Smith, 1981; Martis et al., 1981; Kharasch et al., 1995b). Sevoflurane metabolites do not bind to liver proteins decreasing the risk for direct liver toxicity by formation of antibodies (Young and Apfelbaum, 1995). Furthermore, the production of free radicals or other reactive metabolites as during halothane metabolism was not observed (Kharasch, 1995). Free radicals are partially responsible for post-anaesthetic liver damage (Ray and Drummond, 1991; Frink and Brown, 1994). In addition, only four cases of liver dysfunction could be related to previous sevoflurane exposure in men (Shichinohe et al., 1992; Watanabe et al., 1993; Bruun et al., 2001).

Table 1 : Biotransformation of volatile anaesthetic agents in humans

AGENT	% METABOLISATION	REFERENCE
Halothane	20-25	Rehder et al., 1967. Cascorbi et al., 1970.
Enflurane	2,4	Chase et al., 1971.
Isoflurane	0,17	Holaday et al., 1975.
Desflurane	0,02	Eger, 1994.
Sevoflurane	3,3	Shiraishi and Ikeda, 1990.

Post-anaesthetic liver damage can also be caused by local hypoxaemia due to inadequate hepatic circulation. Total liver perfusion is assured by the hepatic arterial blood flow and the portal venous blood flow. During sevoflurane anaesthesia in dogs a decrease in hepatic arterial circulation was reported at 2 MAC. Arterial circulation remained constant at lower anaesthetic concentrations. On the other hand, portal venous circulation decreased at 1.5 and 2 MAC. In conclusion, total liver perfusion only decreased at high sevoflurane concentrations (2 MAC) (Frink et al., 1992c). During isoflurane anaesthesia in dogs hepatic arterial blood flow remained constant at 2 MAC, while portal venous perfusion only decreased slightly. This resulted in a constant total liver perfusion even at higher anaesthetic levels of isoflurane (Bernard et al., 1992). Halothane and to a lesser extent enflurane induced a marked decrease in hepatic arterial and portal venous circulation in dogs (Frink et al., 1992c).

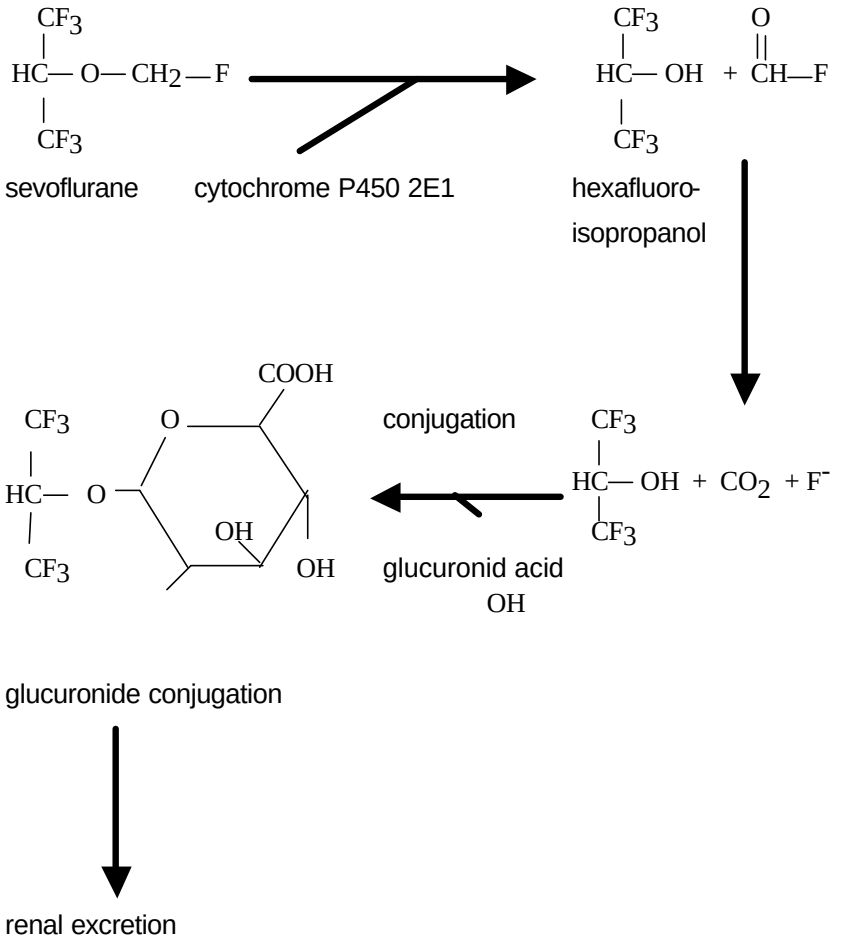
A recent study reported that isoflurane induced an increase in serum levels of liver enzymes more frequently than did sevoflurane 3 to 14 days after anaesthesia (Nishiyama et al., 1999b). Standard hepatocellular enzymes were within normal range, while a clinically non-significant increase of indirect bilirubine was reported after sevoflurane anaesthesia in men (Frink et al., 1992a; Newman et al., 1994; Ebert et al., 1998; Ebert and Arain, 2000; Suttner et al., 2000). Even in patients with minimal or no hepatic metabolic capacity, such as those with diminished enzyme activity or with intrinsic liver disease, recovery from sevoflurane anaesthesia should not be affected significantly (Kharasch et al., 1995b). Moreover, sevoflurane and isoflurane only give a decrease in total liver perfusion at higher concentrations, which are seldom necessary in clinical practice using balanced anaesthesia protocols. In conclusion, in patients with liver malfunctioning sevoflurane or isoflurane are preferably used, since

both volatile anaesthetic agents have a low metabolisation degree (sevoflurane: 3.3% and isoflurane: 0.17%) and are thought to be less hepatotoxic compared to halothane and enflurane.

RENAL EFFECTS

The introduction of sevoflurane into clinical human anaesthesia has been clouded by concerns about the potential risk of nephrotoxicity after its use. Two theoretical sources for the nephrotoxicity after sevoflurane are the plasma concentration of inorganic fluoride, an *in vivo* metabolite of sevoflurane and the so called "compound A", an *in vitro* degradation product of sevoflurane in the presence of soda lime and baralyme. The metabolism of sevoflurane involves enzymatic breakdown leading to the generation of fluoride ions. Fluoride ions are potentially toxic and can cause renal failure (Mazze, 1984). Because evidence of methoxyflurane renal dysfunction was not observed when peak fluoride concentrations were less than 50 µmol/l, this concentration was considered to be the threshold of fluoride nephrotoxicity (Cousins and Mazze, 1973). In clinical anaesthesia with sevoflurane some transient fluoride plasma concentrations of more than 50 µmol/l were measured in humans (Frink et al., 1992a; Kobayashi et al., 1992; Stickler et al., 1994; Munday et al., 1995). And yet, no clinically relevant kidney failure was reported in humans. Even in patients with pre-existing renal impairment no further deterioration occurred after sevoflurane anaesthesia (Melotte et al., 1994; Nuschler et al., 1994). For children and obese persons the use of sevoflurane did not increase the risk for potential renal toxicity, although, obesity was reported to increase the fluoride production (Frink et al., 1993; Levine et al., 1996).

Fig. 1 : Metabolisation of sevoflurane (adapted from Frink et al., 1992a)



Because of previous clinical results the initial “fluoride-rule” of methoxyflurane should not be applied to sevoflurane anaesthesia (Frink et al., 1992a; Kobayashi et al., 1992; Frink et al., 1994). Human kidney microsomes metabolise methoxyflurane and to a much lesser extent sevoflurane to inorganic fluoride. Sevoflurane is predominantly metabolised by cytochrome P450 2E1 in the liver. In contrast, no significant amounts of P450 2E1 have been found in human kidneys

(de Waziers et al., 1990; Kharasch et al., 1995c). Therefore, human renal fluoride concentrations after sevoflurane anaesthesia are considerably lower than serum fluoride concentrations. Hence, serum fluoride concentration after sevoflurane is probably of little importance for renal damage, even when the 50 µmol/l threshold is exceeded (Kharasch et al., 1995a).

In a study on biotransformation of sevoflurane in dogs (2.5 %) maximum serum fluoride concentrations were considerably lower than those associated with nephrotoxicity in rats; respectively 18.5 µmol/l and 20.0 µmol/l after 3 and 4% sevoflurane exposures (Martis et al., 1981). These fluoride concentrations were not expected to induce renal damage.

Of more concern than fluoride production during sevoflurane metabolisation, is its interaction with CO_2 absorbents, which generates several degradation products. In modern anaesthesia, low fresh gas flows (< 2 L/min) are common practice in order to reduce costs of volatile anaesthetics and to avoid environmental pollution as well as to preserve heat and humidify the inspired gas. Yet, all volatile anaesthetics can be degraded by the lime in the circle absorber system. Desflurane, enflurane and isoflurane react with dry absorbents forming CO (Fang et al., 1995). Sevoflurane on the other hand reacts with absorbents by formation of degradation products called compounds A-E (Cunningham et al., 1996). The amounts of compounds B, C, D and E were negligible whereby compounds C, D and E were only found in *in vitro* studies using closed containers filled with sevoflurane and sodalime (Wallin et al., 1975; Hanaki et al., 1987). The most significant substance is compound A, a vinyl ether, which has dose-dependent nephrotoxic properties inducing tubular necrosis in rats. Clinically significant effects of this degradation in

humans are still controversial (Bito et al., 1997; Kharasch et al., 1997; Mazze and Jamison, 1997). Exposure of rats to high sevoflurane concentrations is also detrimental for liver, lungs and central nervous system (Gonsowski et al., 1994a). Compound A production and accumulation in a circle absorber system is dependent on sevoflurane concentration, the type of absorber material (baralyme or soda lime), the water content of the absorbent, absorbent temperature, freshness of the CO_2-absorbent, CO_2-production, fresh gas flow rates and type of anaesthetic machine (Bito and Ikeda, 1991; Liu et al., 1991; Frink et al., 1992b; Wong and Lerman, 1992; Ruzicka et al., 1994; Osawa and Shinomura, 1998; Bito et al., 1998; Goeters et al., 2001; Yamakage et al., 2001;). In the former absorbents, NaOH and KOH appear to enhance the production of compound A and CO by degrading volatile anaesthetics (Stabernack et al., 2000). New absorbents containing $Ca(OH)_2$ or $Li(OH)_2$ could eliminate any potential hazards from the toxic compounds by decreasing the production of compound A and CO (Higuchi et al., 2000; Yamakage et al., 2000). The new material is an effective carbon dioxide absorbent and is chemically unreactive with sevoflurane, enflurane, isoflurane and desflurane (Murray et al., 1999; Mchaourab et al., 2001).

The lethal concentration in 50% (LC_{50}) of compound A in rats equaled 331 ppm, 203 ppm and 127 ppm for a 3-h, 6-h and 12-h exposure period (Gonsowski et al., 1994a en b). In a recent study on low-flow sevoflurane anaesthesia in dogs concentrations of compound A in the anaesthetic circuit were less than values reported to produce renal toxicosis and death in rats (Muir and Gadawski, 1998). In all reported sevoflurane studies compound A concentration remained far below the toxic margin in humans (Frink et al., 1992b; Bito and Ikeda, 1994; Frink et al., 1994; Bito and Ikeda, 1995; Kharasch et al., 1997; Kharasch and Jubert, 1999; Igarashi et al., 1999). Moreover, Rolly

and Versichelen (1998) found amounts of compound A of 6 to 9 ppm using soda-lime as CO_2-absorbent. In a recent study using a high-flow (7.0 l/min) closed-circuit PhysioFlex apparatus (Dräger, Lübeck, Germany) with soda-lime and computer-controlled liquid injection of sevoflurane compound A concentrations were significantly lower (6 ppm) than in conventional (14.3 ppm), valve-based machines during closed-circuit conditions. Lower absorbent temperatures, resulting from the high flow appear to account for the lower compound A formation (Versichelen et al., 2000). Furthermore, recent studies revealed that humans may be less susceptible to compound A renal toxicity than rats, since the beta-lyase pathway responsible for nephrotoxic metabolites of compound A is 10- to 30-fold less active in humans than in rats (Altuntas and Kharasch, 2001; Altuntas and Kharasch, 2002)

Renal functioning is mainly assessed by changes in serum creatinine or blood urea nitrogen (BUN). These conventional markers do not evaluate tubular function and are insensitive measures of glomerular filtration (Shemesh et al., 1985). They are usually within the normal range after “high-flow” (Frink et al., 1994; Higuchi et al., 1994; Obata et al., 2000) and “low-flow” sevoflurane anaesthesia (Kharasch et al., 1997; Bito et al., 1997; Eger et al., 1997; Higuchi et al., 1998; Groudine et al., 1999; Obata et al., 2000). Even in patients with moderately impaired renal function low-flow sevoflurane anaesthesia had similar effects on renal function compared to isoflurane (Higuchi et al., 2001). In specific experimental studies several specific and sensitive biomarkers were used for evaluation of renal function. These biomarkers bind on enzymes released with kidney damage. Despite the sensitive tests no difference in renal enzyme excretion between sevoflurane and isoflurane was found (Bito et al., 1997; Kharasch et al., 1997; Kharasch et al., 2001). Eger et al.

(1997; 1999) on the other hand, associated low flow (2 l/min during 8 hours) sevoflurane in humans with a transient renal injury in the glomerulus, the proximale and distale tubuli, in contrast to desflurane anaesthesia where no renal damage was observed. However, the reliability of urinary biomarkers as indicator for clinical significant kidney injuries in humans is still controversial (Baines, 1994).

The Food and Drug Administration (FDA) approved the clinical use of sevoflurane regarding some precautions. A minimal flow of 2 l/min for exposures greater than 1 hour should be respected in semi-closed systems. Until more information on degradation (compound A) and metabolisation (fluoride) of sevoflurane is available, sevoflurane is not recommended for using in patients with impaired kidney function (Mazze and Jamison, 1995; 1997).

ECONOMIC CONSIDERATIONS

Do the benefits of sevoflurane compensate for the associated higher costs in comparison to halothane and isoflurane in clinical anaesthesia practice? Cost considerations are of increasing importance when choosing anaesthetic techniques and drugs. Different factors have an influence on the price of volatile anaesthetics. The immediate cost of an inhaled anaesthetic results from an interplay between 4 main factors: 1/ the cost per ml of liquid anaesthetic, 2/ the volume of vapour that results from each ml of liquid, 3/ the effective potency of the anaesthetic, 4/ the fresh gas flow.

First of all, there is the price imposed by the manufacturer (Weiskopf and Eger, 1993). At this moment the price of 1 ml of sevoflurane is a decisive factor for its use in veterinary practice. This price is still considerably high in comparison with halothane and to a

lesser extent with isoflurane. The purchasing cost will probably be reduced in the near future, since sevoflurane is rapidly gaining ground in human anaesthesia at the expense of halothane and isoflurane.

Secondly, the amount of vapour produced from 1 ml liquid anaesthetic influences anaesthetic costs. The amount of vapour produced is a function of the specific gravity and molecular weight of the volatile anaesthetic, respectively 168 g and 1.467 g/ml for desflurane, 184.5 g and 1.50 g/ml for isoflurane and 200 g and 1.505 g/ml for sevoflurane. The amount of produced vapour from 1 ml decreases with 7% as follows: desflurane > isoflurane > sevoflurane (Eger, 1994).

Furthermore, there are the factors inherent to the used anaesthetic agent, as anaesthetic potency and blood-gas solubility of the volatile anaesthetic agent (Bach et al., 1997; Philip, 1997). A lower blood-gas solubility of an anaesthetic accords the same level of control at a lower fresh gas flow rate than is achieved at a higher fresh gas flow with a more soluble anaesthetic (Weiskopf and Eger, 1993). The anaesthetic potency of sevoflurane is smaller compared to halothane and isoflurane, but sevoflurane has a substantially lower blood-gas partition coefficient. Low blood-gas solubility permits a rapid and precise control of anaesthetic depth during anaesthesia induction and maintenance, even with a relatively low flow. Halothane and isoflurane need higher, less economic fresh gas flows to adjust anaesthetic depth. Finally, the delivered concentration of the anaesthetic by the vaporiser is responsible for the anaesthetic consumption and not the alveolar concentration. The difference between both is wasted. The low blood-gas solubility of sevoflurane decreases the difference between inspired and end tidal concentration leading to less waste and better control of anaesthesia.

As already mentioned, the applied fresh gas flow is also of great importance for anaesthetic cost savings. The main waste with an inhalant anaesthetic is the one induced by unnecessarily high carrier gas flows (Rosenberg et al., 1994). The lower the fresh gas flow, the less volatile anaesthetic is wasted (Camu and Van De Velde, 1997; Suttner and Boldt, 2000). In closed circuit only a fresh gas flow that supplies vapours required by the patient is used. This produces the least cost, but also the least control of anaesthetic depth. Nevertheless, the FDA suggested recently a minimal flow of 1 l/min for exposures up to 1 hour in semi-closed systems to reduce the potential risk for renal damage by accumulation of degradation products of sevoflurane (Mazze and Jamison, 1997; Gentz and Malan, 2001).

Another benefit of sevoflurane, especially in human anaesthesia is its fast recovery which could result in decreased hospitalisation costs. For veterinary anaesthesia, however, the capital costs include the expense of agent-specific vaporisers and of converting or purchasing gas analysers. To reduce expenses an enflurane vaporiser could be used for sevoflurane, since both anaesthetics have a similar vapour pressure, 172 mm Hg for enflurane and 160 mm Hg for sevoflurane (chapter 1 table 2). In addition, the anaesthetic potency of both anaesthetics is similar: MAC of enflurane in dogs is 2.06 and 2.36 for sevoflurane (chapter 1 table 3). When using an enflurane vaporiser type Enfluratec 4 for sevoflurane administration the MAC-output is reduced with 21 % to 31 % in comparison with a specific sevoflurane vaporiser (Abel and Eisenkraft, 1996). Nevertheless, the use of an enflurane vaporiser for sevoflurane is not recommendable, since the limited vaporiser output could lead to insufficient surgical anaesthetic depth. In short term second-hand sevoflurane vaporisers will be available for veterinary anaesthesia.

CONCLUSION

Considering the multiple benefits of sevoflurane in veterinary anaesthesia, there will certainly be a future for sevoflurane in anaesthesia of dogs and cats. In patients with renal impairment some precautions are advised, since more experience and studies on the compound A and fluoride issues are necessary. Due to a rapid advance of sevoflurane in human anaesthesia price reductions are expected in the near future justifying the use of sevoflurane in modern veterinary practice.

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INTRODUCTION TO CHAPTERS 3/ 4

In these chapters the clinical aspect of the anaesthetic protocol is emphasised. The majority of articles describe recovery times and cardiorespiratory influences of sevoflurane anaesthesia in studies with an experimental anaesthetic set-up. In contrast, the amount of information gathered under clinical circumstances with a standard anaesthetic protocol is rather limited. In most experimental studies on sevoflurane in dogs the anaesthetic protocol is reduced to the strict minimum to eliminate potential influences of other anaesthetic drugs. Therefore, premedication and induction with intravenous anaesthetic agents are excluded. Instead, anaesthesia is induced and maintained solely by the volatile anaesthetic agent (sevoflurane). In the present work the anaesthetic protocol included a standard premedication, since preanaesthetics drugs are of major importance under clinical circumstances.

Premedication decreases stress before induction of anaesthesia, facilitates manipulations and contributes to a smooth induction and recovery from anaesthesia. Moreover, opioids are often included in premedication reducing the severity and duration of post-operative pain. The so-called “pre-emptive analgesia” is of major importance for the patient. For these reasons premedication with a neurolept-analgesic mixture including droperidol and fentanyl can be justified. Influences of droperidol on recovery times and cardiorespiratory parameters are probably not neglectable because of its long-lasting action, and hence can not be ruled out. Fentanyl, on the other hand, has a rapid onset of effect (1-2 minutes and is short-acting (20-30 minutes). Accordingly, no effects on recovery times and only initial influences on cardiorespiratory parameters could be expected.

Induction of anaesthesia is mainly achieved by intravenous anaesthetics because of their rapid onset of action and ease of administration. Propofol was preferred in the present study due to its unique pharmacokinetic properties and clinical advantages. It has a specific extrahepatic metabolism and is rapidly cleared from the body. After bolus injection, plasma concentrations decrease rapidly due to redistribution of the drug to the brain and other highly perfused tissues. It provides a rapid and smooth induction of anaesthesia and a fast excitement-free recovery with no hangover-effect. Although the elimination half-life of propofol is long (330 minutes in dogs), this is not clinically relevant and should not influence recovery times after 1 hour of inhalation anaesthesia. Influences on cardiopulmonary parameters under sevoflurane anaesthesia during spontaneous and controlled ventilation might be observed the first 30 minutes of the standardised anaesthetic period. This was not considered a problem since surgical preparation of the dogs was performed during the first hour of anaesthesia.

Chapter 3 discusses the recovery times after clinical sevoflurane anaesthesia compared with more frequently used inhalant anaesthetic agents (isoflurane and halothane). The aim was to investigate the advantage of the low blood-gas solubility of sevoflurane compared to the other volatile anaesthetic agents for the recovery times in premedicated dogs. In chapter 4 cardio-pulmonary parameters of sevoflurane anaesthesia during spontaneous and controlled ventilation at different MAC values are described using a

CHAPTER 3

RECOVERY TIMES AND EVALUATION OF CLINICAL HEMODYNAMIC PARAMETERS OF SEVOFLURANE, ISOFLURANE AND HALOTHANE ANAESTHESIA IN MONGREL DOGS.

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SUMMARY

In the present study the influence of 3 volatile agents {halothane, isoflurane and sevoflurane} in oxygen at 2 concentrations (1.5 and 2 MAC) in 6 dogs on non-invasive cardio-respiratory parameters (heart and respiratory rates, non-invasive blood pressures at 15, 30, 60 minutes and after extubation) and on the recovery times (appearance of the first eyelid reflex, emergence time) after clinical anaesthesia was studied (cross-over design). After premedication with fentanyl-droperidol (5 μg/kg and 0.25 mg/kg IM) and induction with propofol (5 mg/kg IV) six dogs were randomly anaesthetised for one hour for a standard neurologic stimulation test.

A wide individual variation in respiration rate (induced by an initial hyperpnea) was observed in the 1.5 MAC protocols, without significant differences between the 3 different volatile agents. Heart rate was significantly lower during 1.5 and 2 MAC halothane when compared to isoflurane and sevoflurane. An increase from 1.5 to 2 MAC induced significant decreases in diastolic (DAP) and mean arterial blood pressure in all groups without significant changes in the systolic arterial pressures. Only DAP in sevoflurane protocol was significantly lower at 1.5 and 2 MAC compared to halothane. Time had no significant influences on the non-invasive blood pressures in all protocols. Extubation induced a significant increase of all parameters in all protocols. Time for a first eyelid reflex was significantly longer after 2 MAC compared to the 1.5 MAC protocol. There was no significant difference between the 3 anaesthetic agents. Although emergence time was longest for halothane at both anaesthetic concentrations, no significant difference in emergence time was observed for the 3 volatile agents.

INTRODUCTION

Sevoflurane (CFH2-O-CH(CF3)2) is a volatile anaesthetic agent developed in the early seventies (Wallin et al., 1975). This drug has specific characteristics including a low blood/gas partition coefficient (0.69) (Strum and Eger, 1987). The low solubility partly contributes to a rapid induction of and emergence from anaesthesia compared to other volatile anaesthetics such as halothane, enflurane and isoflurane (Smith et al., 1992; Lerman et al., 1996; Steffey, 1996; Aono et al., 1997; Ebert et al., 1998). Sevoflurane has a low pungency and produces little to no airway irritability compared to isoflurane but especially to desflurane. This positive effect results in little to no airway responses (coughing or laryngeal spasm), allowing a smooth mask induction in children and small animals (Doi and Ikeda, 1992; Doi and Ikeda, 1993; Inomata et al., 1994; Lerman et al., 1996; Muzi et al., 1996).

A lot of research has been performed in man, in particular about the emergence time of sevoflurane compared to other fast acting anaesthetic agents such as isoflurane, desflurane and propofol (Smith et al., 1992; Ebert et al., 1998; Song et al., 1998). Only a limited number of reports on this subject are available in small animals. Johnson et al. (1998) reported the induction and recovery characteristics of sevoflurane, in comparison with isoflurane in adult unpremedicated experimental dogs using mask induction. However, mask induction without premedication is seldom used under clinical circumstances. In clinical trials sevoflurane was compared to halothane after propofol or thiopentone induction (Oliva et al., 2000). The present study was performed to determine the differences in emergence times and related parameters during and after a clinical

standard anaesthesia in spontaneously breathing adult dogs. Commonly used non-invasive cardio-respiratory parameters were also compared. The anaesthetic protocol included a standard neurolept-analgesic premedication and propofol induction.

MATERIALS AND METHODS

The study was approved by the Ethical committee of the Faculty of Veterinary Medicine, Ghent University (filenumber: 97/12). Six adult male mongrel dogs weighing 18 to 35 kg from 3 to 7 years were used for the study. The dogs were dewormed and vaccinated at a regular basis. Clinical examination and a blood analysis (standard kidney and liver function tests) confirmed the health status of the animals before the study. No specific medication altering anaesthetic or analgesic requirements were administered at least 1 month before the experiments.

Study Protocol

The dogs were randomly assigned to 6 anaesthetic protocols of 1 hour (including halothane (Halo), isoflurane (Iso), and sevoflurane (Sevo), each at 1.5 and 2 MAC) using a cross over design. The minimum interval between 2 successive studies was 2 weeks. Food but not water was withheld for 12 hours before each experiment. Body weight, heart (HR) and respiratory (RR) rates were obtained in the unpremedicated dogs.

Premedication and Induction of Anaesthesia

The dogs were premedicated 30 minutes before induction of anaesthesia with fentanyl-droperidol IM (respectively 5 µg/kg and 0.25 mg/kg of body weight BWT) (Thalamonal®, Janssen-Cilag, Berchem, Belgium). Induction of anaesthesia was performed using propofol (5

mg/kg of BWT) (Rapinovet®, Mallinckrodt Veterinary, Stockholm, Sweden) intravenously over 15-20 seconds. After loss of the swallowing reflex the dogs were orally intubated (endo-tracheal tube 9 or 12 mm ID, Rüsch, Germany).

Maintenance of Anaesthesia

A circle system (Titus®, Dräger, Lübeck, Germany) with an agent specific calibrated precision out of circuit vaporiser (Vapor 19,3®, Dräger, Lübeck, Germany) was used throughout the study. The soda lime (Dräger Sorb 800®, Dräger, Lübeck, Germany) was renewed before each experiment and the whole system was air dried between the experiments. The anaesthetic circuit was flushed with 100% oxygen for 5 minutes before the experiment and afterwards filled with the desired inspiratory anaesthetic concentration of the specific volatile agent using a fresh gas flow of 2 l/min oxygen. The intubated dogs were connected to an anaesthetic circuit and anaesthesia was continued for 1 hour. No intravenous infusions were administered during the trial.

Measurements and Monitoring

A multi anaesthetic gas analyser (Capnomac Ultima®, Datex Engstrom Instrumentarium Corp., Helsinki, Finland) was calibrated (Quick Cal TM calibration gas®, Datex Engstrom Instrumentation Corp., Helsinki, Finland) before each experiment. Inspiratory oxygen fraction (FiO_2), end-tidal anaesthetic agent percentage (AA %), end-tidal carbon dioxide percentage (CO_2ET %) and RR were recorded continuously (sampling of 200 ml/min at Y-piece, sample scavenged). The vaporizer settings were adjusted throughout the experiment to maintain an end-tidal anaesthetic concentration of 1.5 and 2 MAC of each specific volatile agent. The used MAC values throughout the

study were 2.36 vol% for Sevo, 1.39 for Iso and 0.89 for Halo (Steffey and Howland, 1977; Steffey and Howland, 1978; Kazama et al., 1988). HR and peripheral haemoglobin saturation (SpO_2 %) were monitored continuously using a pulse oxymeter (N-20PA Nellcor Puritan Bennett®, Pleasanton, California, USA) with the probe placed on the tongue.

Non-invasive systolic and diastolic arterial blood pressures (SAP, DAP) were obtained after 15, 30 and 60 minutes of anaesthesia using a Doppler flow detector. The indirect blood pressures were obtained by placing a paediatric cuff above a Doppler device (Ultrasonic Doppler Flow Detector, Model 811-B®, Parks Medical Electronics, Inc., Aloha, Oregon U.S.A.) around the radial area of the foreleg of the dogs.

A standardised neurologic stimulation test was performed during the anaesthesia in each anaesthetized dog. Briefly, motor evoked potentials were recorded from the extensor carpi radialis muscle of the forelimb after magnetic stimulation of the radial nerve, and from the cranial tibial muscle of the hindlimb after magnetic stimulation of the sciatic nerve. Reference values were established for onset latencies and peak-to-peak amplitudes of these potentials. After 1 hour of anaesthesia the dogs were allowed to recover while breathing ambient air in a quiet room without stimulation. The time period between the disconnection of the circuit and the reappearance of the first eyelid reflex was recorded. Emergence time was defined as the time from end of anaesthesia to extubation without external stimulus. HR, RR, SAP and DAP were recorded immediately after extubation.

Statistical analysis

Mean arterial blood pressure (MAP) was calculated using the following equation: MAP = 0.33 (SAP-DAP) + DAP (Trim, 1994).

Continuous dependent variables, i.e. HR, RR, MAP, SAP and DAP were checked for normality and, if necessary, transformed in order to obtain a normal distribution. A $\log_e$-transformation was necessary for RR. Statistical evaluation was done with repeated measures ANOVA (PROC MIXED, SAS 6.12, SAS Institute Inc.). Time was considered a repeated measure, treatment and dose fixed effects, and dog a random effect nested within treatment and dose.

Dependent variables expressing a fraction, i.e. FiO_2, end-tidal anaesthetic agent percentage, and SpO_2 %, were evaluated with repeated measures ANOVA (GLIMMIX Macro, SAS 6.12, SAS Institute Inc.), using the same model as described for continuous dependent variables.

The effect of treatment and dose on the time to a positive eyelid reflex and a positive swallowing reflex following discontinuation of anaesthesia was analysed with ANOVA (PROC MIXED, SAS 6.12; SAS Institute Inc.). A p-value < 0.05 was considered significant. The results of the different recorded and calculated parameters are expressed as mean values ± standard deviation.

RESULTS

The magnetic motor evoked potentials protocol had no effect on the different parameters investigated during the different anaesthetic protocols. HR did not change significantly over time for

each individual volatile agent. There were no significant differences in HR between the 2 anaesthetic concentrations of each agent and between the Sevo and Iso protocols. HR during 1.5 and 2 MAC Halo was significantly lower compared to similar Sevo and Iso protocols (table 1A and 1B).

A significant decrease in RR over time was present in the 1.5 MAC protocols, whereby large individual variations were observed. Although much lower and stable RR's were present in the 2 MAC protocols, no significant differences were observed between the different agents at 1.5 and 2 MAC concentrations. Extubation induced a significant increase in RR in all protocols (table 1A and 1B).

No specific differences were observed for DAP over time for each agent. DAP in 1.5 MAC protocols was significantly different from 2 MAC protocols for all agents ($p = 0.04$). DAP of the 1.5 and 2 MAC Sevo was significantly lower than Halo ($p = 0.01$), but not significantly different from the Iso protocol. Extubation induced a significant increase in DAP in all protocols (table 1A and 1B). Although no specific differences were observed for SAP over time between the different agents and between the different anaesthetic concentrations, the lowest SAP was recorded at 2 MAC Sevo. Extubation induced a significant increase in SAP in all protocols (table 1A and 1B). No specific differences were present for calculated MAP over time of the different agents; the lowest MAP was recorded during Sevo anaesthesia. The MAP at 1.5 MAC was significantly higher than MAP in 2 MAC protocols for all agents. Extubation induced a significant increase in MAP in all protocols (table 1A and 1B).

Table 1 a : Cardiorespiratory parameters measured in 6 mongrel dogs during and after 1.5 MAC isoflurane (Iso), sevoflurane (Sevo) and halothane (Halo) anaesthesia

VARIABLE	ANAEST. AGENT	1.5 MAC ANAESTHETIC CONCENTRATION			
		15'	30'	60'	after extubation
HR Beats/min	Iso	83.8 ± 27.4*	88.0 ± 19.1*	90.8 ± 14.4*	102.0 ± 23.8*
	Sevo	88.0 ± 17.7*	88.8 ± 14.4*	101.0 ± 10.7*	95.5 ± 20.4*
	Halo	74.5 ± 30.3	68.8 ± 17.8	74.3 ± 18.4	102.3 ± 29.8
RR Breaths/min	Iso	30.7 ± 33.6|	22.5 ± 25.3|	12.3 ± 8.9|	27.5 ± 13.2
	Sevo	26.7 ± 31.8|	13.8 ± 15.0|	16.5 ± 21.6|	35.0 ± 42.3
	Halo	26.7 ± 26.4|	19.8 ± 20.2|	15.7 ± 11.0|	26.7 ± 26.7
DAP Mm Hg	Iso	61.3 ± 16.7|	62.7 ± 16.5|	62.5 ± 17.8|	92.7 ± 22.3
	Sevo	55.8 ± 10.4|,*	52.5 ± 11.6|,*	57.5 ± 11.5|,*	85.5 ± 15.3*
	Halo	62.0 ± 11.2|	64.0 ± 13.6|	66.2 ± 13.7|	79.7 ± 11.3
SAP Mm Hg	Iso	119.7 ± 23.1|	116.7 ± 20.1|	114.7 ± 25.2|	170.3 ± 25.6
	Sevo	110.0 ± 17.1|	106.7 ± 19.8|	109.0 ± 17.7|	157.0 ± 28.6
	Halo	121.2 ± 23.6|	120.2 ± 22.9|	126.0 ± 20.7|	155.3 ± 28.4
MAP Mm Hg	Iso	80.5 ± 18.6|	80.3 ± 17.2|	79.7 ± 19.4|	118.2 ± 22.3
	Sevo	73.8 ± 11.9|	70.5 ± 13.6|	74.5 ± 12.8|	109.0 ± 19.2
	Halo	81.5 ± 15.1|	82.3 ± 16.3|	85.7 ± 15.8|	104.5 ± 16.2
FiO_2	Iso	0.90 ± 0.019|	0.91 ± 0.015|	0.91 ± 0.021|	No Data
	Sevo	0.87 ± 0.055|,*	0.88 ± 0.012|,*	0.89 ± 0.012|,*	As not applicable
	Halo	0.90 ± 0.015|	0.90 ± 0.012|	0.90 ± 0.014|	
SpO_2 %	Iso	96.3 ± 1.2	97.2 ± 2.2	97.0 ± 2.4	
	Sevo	96.7 ± 1.6	97.2 ± 1.9	96.7 ± 1.2	
	Halo	96.7 ± 1.9	96.5 ± 2.5	97.3 ± 1.6	
CO_2 ET %	Iso	4.7 ± 1.6*	5.6 ± 0.6*,°	5.9 ± 0.8*,°	
	Sevo	4.8 ± 1.7*	6.1 ± 0.5*,°	6.2 ± 1.0*,°	
	Halo	4.1 ± 1.3	4.5 ± 0.8	4.6 ± 0.5	

| significantly different from time after extubation P = 0.05
° significantly different from time 15' P = 0.05
* significantly different from halothane P = 0.05
Data are expressed as mean ± SD
Abbreviations variables: see text

Table 1 b : cardiorespiratory parameters measured in 6 mongrel dogs during and after 2 MAC isoflurane (Iso), sevoflurane (Sevo) and halothane (Halo) anaesthesia

VARIABLE	ANAEST. AGENT	2 MAC ANAESTHETIC CONCENTRATION 15'	30'	60'	after extubation
HR beats/min.	Iso	87.3 ± 23.7 *	92.5 ± 15.8*	98.8 ± 11.4*	98.0 ± 28.6 *
	Sevo	91.3 ± 13.5 *	94.3 ± 6.7*	99.3 ± 12.2*	96.0 ± 21.5 *
	Halo	70.0 ± 23.7	70.3 ± 15.2	79.0 ± 9.6	93.0 ± 18.8
RR breaths/min.	Iso	11.7 ± 8.2 |	11.7 ± 7.3|	8.2 ± 4.6|	49.3 ± 28.7
	Sevo	7.5 ± 3.5 |	7.2 ± 4.0|	6.2 ± 4.6|	25.7 ± 5.4
	Halo	12.8 ± 2.7 |	12.0 ± 3.6|	12.8 ± 4.9|	27.3 ± 8.5
DAP mm Hg	Iso	55.3 ± 12.6 #,|	49.2 ± 10.7#,|	52.7 ± 17.8#,|	78.5 ± 13.6 #
	Sevo	46.0 ± 11.1 #,|,*	41.7 ± 12.4#,|,*	37.7 ± 12.8#,|,*	75.7 ± 7.6 #
	Halo	60.3 ± 12.0 #,|	60.5 ± 14.8#,|	62.3 ± 14.4#,|	77.0 ± 22.5 #
SAP mm Hg	Iso	107.2 ± 21.6 |	98.3 ± 23.8|	103.3 ± 28.2|	155.8 ± 25.9
	Sevo	92.5 ± 18.3 |	88.7 ± 26.7|	83.0 ± 24.1|	145.3 ± 17.4
	Halo	114.5 ± 21.8 |	113.0 ± 26.4|	119.0 ± 26.3|	154.5 ± 44.9
MAP mm Hg	Iso	72.5 ± 15.2 #,|	65.8 ± 14.4#,|	69.3 ± 21.1#,|	103.8 ± 17.3 #
	Sevo	61.3 ± 13.2 #,|	57.2 ± 16.9#,|	52.5 ± 16.4#,|	98.8 ± 8.4 #
	Halo	78.3 ± 15.1 #,|	77.8 ± 18.1#,|	80.5 ± 18.3#,|	102.5 ± 28.6 #
FiO_2	Iso	0.88 ± 0.012 |	0.88 ± 0.012|	0.89 ± 0.012|	No Data
	Sevo	0.90 ± 0.036 *,|	0.89 ± 0.028 *,|	0.89 ± 0.020 *,|	As not applicable
	Halo	0.91 ± 0.016 |	0.91 ± 0.019|	0.91 ± 0.024|	
SpO_2 %	Iso	96.5 ± 2.0	95.2 ± 1.9	96.5 ± 1.9	
	Sevo	90.8 ± 13.7	96.0 ± 2.7	97.2 ± 1.9	
	Halo	96.8 ± 1.2	96.8 ± 0.7	97.0 ± 1.5	
CO_2 ET %	Iso	5.7 ± 0.8 *	6.0 ± 0.8*,°	6.6 ± 0.8*,°	
	Sevo	6.2 ± 0.5 *	6.8 ± 0.4*,°	5.8 ± 2.9*,°	
	Halo	5.1 ± 0.8	5.2 ± 0.8	5.3 ± 0.8	

significantly different from 1.5 MAC P = 0.05
| significantly different from time after extubation P = 0.05
° significantly different from time 15' p = 0.05
* significantly different from halothane P = 0.05
Data are expressed as mean ± SD
Abbreviations variables: see text

There were no significant changes in SpO_2 % during the anaesthesia period between the different anaesthetic agents and the different MAC protocols. FiO_2 during Sevo was significantly lower than during the halothane protocol (table 1A and 1B). CO_2ET % was significantly lower during the Halo protocol compared to Sevo and Iso at both MAC values. At 15 minutes after induction CO_2ET % was significantly lower compared to 30 and 60 minutes in the Iso and Sevo protocols (table 1A and 1B).

The time recorded for the reappearance of the first eyelid reflex was not significantly different between all agents (table 2). Halo anaesthesia was characterized with longer recovery times at both anaesthetic concentrations, except for time to positive eyelid reflex at 2 MAC; whereas Iso 1.5 MAC induced the shortest reappearance period of the eyelid reflex, but it was not statistically significant. A significant longer reappearance time ($p = 0.04$) was present in all 2 MAC protocols (Sevo > Halo > Iso).

Table 2 : recovery times in seconds (s) after 60 minutes anaesthesia using 1.5 and 2 MAC Isoflurane (Iso), sevoflurane (Sevo) and halothane (Halo) in 6 mongrel dogs

VARIABLE	ANAESTHETIC AGENT	ANAESTHETIC CONCENTRATION	
		1.5 MAC	2 MAC
Time to first positive Eyelid reflex (s)	Iso	188.3 ± 63.9	237.0* ± 107.4
	Sevo	201.8 ± 72.9	389.8* ± 281.0
	Halo	241.5 ± 137.3	290.2* ± 196.1
Time to extubation (s)	Iso	682.2 ± 540.7	797.0 ± 482.9
	Sevo	631.7 ± 479.7	946.0 ± 515.5
	Halo	820.5 ± 462.0	1168.7 ± 319.9

* significantly different from 1.5 MAC (P = 0.05)

Sevo 1.5 MAC induced a faster extubation time but not in the 2 MAC protocol (table 2). At both MAC protocols the longest extubation time was after Halo anaesthesia; but this difference was not significant. Overall, no significant differences were calculated between the different agents and the different MAC protocols.

DISCUSSION

In experimental studies there are quite a lot of differences in cardio-respiratory parameters and emergence times between isoflurane, sevoflurane and halothane (Bernard et al., 1990; Merin et al., 1991; Pagel et al., 1991; Ebert et al., 1998). However clinically those differences are not always clear (Oliva et al., 2000; Tacke et al., 2000). To simulate clinical anaesthesia, the dogs in this study were premedicated and induction was done with an intravenous anaesthetic agent. But premedication and induction certainly influence the cardio-respiratory and recovery parameters. The dogs received a neuroleptanalgesic mixture, fentanyl and droperidol, as premedicant agent. Droperidol is a butyrophenone tranquilizer causing sedation with decreased motor activity and tranquilization similar to acepromazine (Thurmon et al., 1996). Furthermore it gives a high incidence of post-operative sedation, which can influence the recovery profile (Bissonnette et al., 1999). Fentanyl is an opioid agonist with a short duration of action; the peak effect lasts less than 30 minutes. Droperidol has a long duration of action that extends beyond the analgesic effects of fentanyl (Moore and Dundee, 1961). The drug combination of droperidol and fentanyl induces an intense analgesic effect of relatively short duration. In dogs, this mixture produces sedation, analgesia, immobilization, respiratory depression and/or

panting, α_1-adrenergic blockade, a decrease in blood pressure and bradycardia (Thurmon et al., 1996).

In the present study anaesthesia was induced with propofol, a short acting induction agent, with rapid metabolisation (Shafer et al., 1988). Since propofol has a fast redistribution from highly perfused tissues (e.g. brain) into less-well perfused tissues, plasma levels of propofol decline rapidly (Shafer, 1993). And because of its high metabolic clearance rate, which is approximately ten times faster than that of thiopentone, we can assume that the emergence time is minimally influenced by propofol (Shafer, 1993; Smith et al., 1994). For those reasons we chose propofol as induction agent. Oliva et al. (2000) compared sevoflurane with halothane recovery after propofol and thiopentone induction. Shorter extubation times after propofol induction with both inhalant anaesthetics were reported. But induction technique will have progressively less influence on post-anaesthetic recovery as the duration of anaesthesia increases, mainly because the washout period of an anaesthetic agent is determined by the duration of anaesthesia and its oil/gas partition coefficient (Stoelting and Eger, 1969).

Equipotent doses using minimum alveolar concentration multiples were used in this study to allow a comparison not only of the recovery time, but also of clinically useful non-invasively measured cardio-respiratory parameters in dogs. Monitoring is essential during clinical anaesthesia in dogs. We preferred non-invasive techniques including anaesthetic gas analysis, capnography, pulse oxymetry and non-invasive blood pressure measurements. Although the Doppler blood pressure technique is less accurate than invasive techniques, it is certainly acceptable under clinical circumstances (Stepien, 2000).

In the present study heart rate during halothane anaesthesia was significantly lower than during isoflurane and sevoflurane anaesthesia at both anaesthetic concentrations. There was no significant difference in heart rate between isoflurane and sevoflurane anaesthesia. In non-premedicated dogs sevoflurane induces a rise in heart rate from 1.2 MAC on (Bernard et al., 1990; Mutoh et al., 1997). Activation of the baroreceptor-reflex, induced by a decreased arterial blood pressure, was reported to be mainly responsible for this rise in heart rate. Isoflurane also gives an increased heart rate in non-premedicated dogs (Merin et al., 1991). In contrast, halothane has little influence on heart rate in dogs (Pagel et al., 1991). These findings might be an indication for a less depressant effect to baroreceptor-reflex function with Sevo and Iso compared to Halo (Bernard et al., 1990; Pagel et al., 1991).

All volatile anaesthetic agents cause a dose-related respiratory depression in dogs (Doi et al., 1986; Mutoh et al., 1997). This decrease in respiratory rate results in hypoventilation with increasing CO_2ET %. The respiratory depression is also characterized by a decrease in tidal volume for all anaesthetic agents (Doi et al., 1986; Mutoh et al., 1997). In our study respiration rate decreased in all anaesthetic protocols whereby 2 MAC induced a lower respiration rate compared to 1.5 MAC. However, there was a clear difference between the protocols; halothane anaesthesia was accompanied by higher respiration rates compared to isoflurane and sevoflurane. This finding was also reflected in a lower CO_2ET % during halothane anaesthesia. It is also consistent with literature since halothane was reported to induce a smaller decrease in respiration rate (Mutoh et al., 1997). During the initial 15 minutes of anaesthesia at 1.5 MAC with all

agents, there was a large individual variation in respiration rate. This variation was probably due to the premedication with fentanyl-droperidol, which can cause panting in dogs. This initial tachypnoea can be a problem for achieving a stable anaesthesia at a low anaesthetic concentration. Panting did not occur at 2 MAC, probably because a deeper anaesthetic stage was reached faster.

Volatile anaesthetic agents induce a dose-related decrease in arterial blood pressure (Steffey and Howland, 1977; Frink et al., 1992). This decrease in blood pressure is partly caused by a decreased peripheral vascular resistance and partly by a decrease in stroke volume (Malan et al., 1995; Lowe et al., 1996; Mutoh et al., 1997). MAP and DAP at 1.5 MAC were significantly higher than MAP and DAP in 2 MAC protocols for all agents. SAP was also higher at 1.5 MAC, but the difference was not significant. At both anaesthetic concentrations the MAP, SAP and DAP were lowest for sevoflurane. Only DAP from sevoflurane at both anaesthetic concentrations was significantly lower compared to DAP from isoflurane and halothane. This can be attributed to a decrease in peripheral vascular resistance as mentioned in literature (Mutoh et al., 1997). In contrast, the hypotension induced by halothane anaesthesia occurs mainly because of direct myocardial depression (Paddleford, 1999; Stowe et al., 1991). Oliva et al. (2000) found also a decrease in arterial blood pressure during sevoflurane anaesthesia compared to base line values. In our study blood pressure is lower during sevoflurane anaesthesia compared to halothane and isoflurane. Because of this greater decrease in arterial blood pressure with sevoflurane, heart rate in compensation was probably higher than during halothane anaesthesia, due to the baroreceptor-reflex (Pagel et al., 1991).

The FiO_2 during sevoflurane anaesthesia was significantly lower compared to halothane and isoflurane anaesthesia. This can easily be explained by the lower anaesthetic potency of sevoflurane. The MAC from sevoflurane 2.36 vol% is considerably higher than the MAC from halothane and isoflurane (resp. 0.89 and 1.39) (Steffey et al., 1977; Kazama et al., 1988). To reach the same anaesthetic depth a higher concentration of sevoflurane is necessary and the FiO_2 will be lower. SpO_2 % was constant during the anaesthesia period with all agents and with both MAC values. This could be expected considering the high, inspired oxygen fractions.

Recovery from inhalation anaesthesia is underlies several influences. Anaesthetic recovery is mostly influenced by the blood/gas partition coefficient of the anaesthetic agent. A low blood/gas partition coefficient allows more rapid drug elimination and results in a shorter emergence time. The blood/gas partition coefficient of halothane and isoflurane in man is respectively 2.54 and 1.46. The blood/gas solubility of sevoflurane (0.68) is much lower and similar to that for nitrous oxide (0.47) (Strum and Eger, 1987; Steffey, 1996). This indicates that the anaesthetic recovery of sevoflurane would be more rapid than that with the other two inhalant anaesthetics. Based on blood/gas solubility the length of the emergence time would increase in this order: sevoflurane < isoflurane < halothane.

Of minor importance is the oil/gas partition coefficient. It has an influence on potency and washout speed of volatile agents. The oil/gas partition coefficient is 47 for sevoflurane, 91 for isoflurane and 224 for halothane (Steward et al., 1973; Wallin et al., 1975; Strum and Eger, 1987). The higher the oil/gas partition coefficient, the greater the potency of the anaesthetic agent. With a smaller oil/gas partition

coefficient, there is less transfer and storage of anaesthetic into the lipid tissue. The washout speed of the inhalation anaesthetic will be much higher in contrast with anaesthetics with a higher oil/gas partition coefficient (Steffey, 1996).

Low metabolism can facilitate anaesthetic recovery but only in a limited way. The metabolisation percentages in man for halothane, isoflurane and sevoflurane are respectively 20-25%, 0.17% and 3% (Cascorbi et al., 1970; Holaday et al., 1975; Eger, 1994). The smaller the metabolisation percentage of an inhalation anaesthetic agent, the faster the anaesthetic recovery will be (Carpenter et al., 1987).

Other factors such as alveolar ventilation, cardiac output and duration of anaesthesia have also an influence on recovery from inhalation anaesthesia (Stoelting and Eger, 1969; Carpenter et al., 1987). Even the rebreathing circuit itself can reduce the rate of recovery, because at the end of anaesthesia it is still containing some anaesthetic agent in the rubber parts of the system. To prevent this negative influence on recovery times, we disconnected the patient from the anaesthetic system at the end of the anaesthesia period.

Factors also influencing inhalation anaesthetic elimination from the body are percutaneous loss and intertissue diffusion of agents. However, these influences are of little clinical importance (Lockhart et al., 1991; Carpenter et al., 1987).

Possible parameters for evaluation of anaesthesia recovery in dogs are eyelid and swallowing reflexes and, time to sternal recumbency. As was expected in our study the time for a first positive eyelid reflex was significantly shorter at the lower anaesthetic dosage

of the three anaesthetic agents. Surprisingly at both anaesthetic concentrations the time for a first positive eyelid reflex was the shortest with isoflurane. On the other hand at 1.5 MAC the time to a first positive eyelid reflex was longest for halothane and at 2 MAC it was longest for sevoflurane. But the differences between the three anaesthetic agents were not significant, since wide individual variations were present between individuals per anaesthetic agent. As mentioned above this is easily explained by the greater blood/gas and oil/gas solubility of halothane. The washout of anaesthetic from alveoli of more soluble anaesthetics is more gradually in time, than the washout from less soluble anaesthetics (Eger, 1992). For sevoflurane at 2 MAC the time for a first positive eyelid reflex was longer than for the other anaesthetic agents. This could be attributed to a decrease in cardiac output and a decrease in ventilation (Steffey, 1996). The respiration rate for sevoflurane at 2 MAC was the lowest and heart rate higher than with halothane. This higher heart rate might be attributed to the low arterial blood pressure and a low cardiac output at this stage of anaesthesia, and together with the low respiration rate this could explain why the time for a first positive eyelid reflex is longest for sevoflurane at 2 MAC. During halothane anaesthesia at 2 MAC the respiration rate was higher and heart rate much lower, together with a higher arterial blood pressure than during sevoflurane anaesthesia. This can be an explanation for a shorter time to a positive eyelid reflex with halothane at 2 MAC, although the blood/ gas solubility of halothane is much higher than for sevoflurane. Furthermore, it is more difficult to show the kinetic advantages of less soluble anaesthetics, as sevoflurane, after anaesthetic exposures of less than 1 hour compared to anaesthetic exposures of more than 1 hour (Eger and Johnson, 1987). After short-duration anaesthetic exposures a minimal difference in recovery will exist between any of

the volatile anaesthetics because there will be little time to saturate tissue groups. It also has been reported in rodents that the differences in times to recovery endpoints between anaesthetics are smaller when low concentrations of the anaesthetics are used (Eger and Johnson, 1987). In addition there are the residual effects of droperidol and fentanyl, exerting an effect on cognitive functioning. This might nullify any kinetic advantage of the less-soluble anaesthetic sevoflurane over isoflurane and halothane.

There were no statistically significant differences in emergence times between the 3 anaesthetic agents, although the emergence time was the longest for halothane at both anaesthetic concentrations. Like for the eyelid reflex this can be explained by the high blood/ gas and oil/gas solubility of halothane in combination with its higher metabolisation percentage (20-25%) (Cascorbi et al., 1970). At 1.5 MAC the emergence time was the shortest for sevoflurane, but at 2 MAC isoflurane had a shorter emergence time, although the difference was not significant and very small. In conclusion, clinically there is little difference in emergence times between halothane, isoflurane, and sevoflurane in premedicated dogs after 1 hour of inhalation anaesthesia.

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CHAPTER 4

THE INFLUENCE OF VENTILATION MODE (SPONTANEOUS VENTILATION, IPPV AND PEEP) ON CARDIOPULMONARY PARAMETERS IN SEVOFLURANE ANAESTHETIZED DOGS.

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SUMMARY

The purpose of this study was to investigate the cardiopulmonary influences of sevoflurane (Sevo) in oxygen at 2 anaesthetic concentrations (1.5 and 2 MAC) during spontaneous and controlled ventilation in dogs. After premedication with fentanyl-droperidol (5 µg/kg and 0.25 mg/kg IM) and induction with propofol (6 mg/kg IV) 6 dogs were anaesthetized for 3 hours. Three types of ventilation were compared: spontaneous ventilation (SpV), intermittent positive pressure ventilation (IPPV), and positive end expiratory pressure ventilation (PEEP, 5 cm H_2O).

Heart rate, haemoglobin oxygen saturation, arterial blood pressures, right atrial and pulmonary arterial pressure, pulmonary capillary wedge pressure and cardiac output were measured. End tidal CO_2 percentage, inspiratory oxygen fraction, respiration rate and tidal volume were recorded using a multi gas analyzer and a respirometer. Acid-base and blood gas analyses were performed. Cardiac index, stroke volume, stroke index, systemic and pulmonary vascular resistance, left and right ventricular stroke work index were calculated.

Increasing the anaesthetic concentration during sevoflurane anaesthesia with spontaneous ventilation induced a marked cardiopulmonary depression; on the other hand, HR increased significantly, but the increases were clinically not relevant.

The influences of artificial respiration on cardiopulmonary parameters during 1.5 MAC sevoflurane anaesthesia were minimal. In contrast, PEEP ventilation during 2 MAC concentration had more

pronounced negative influences, especially on right cardiac parameters. In conclusion, at 1.5 MAC, a surgical anaesthesia level, sevoflurane can be used safely in healthy dogs during spontaneous and controlled ventilation (IPPV and PEEP of 5 cm H_2O).

INTRODUCTION

Sevoflurane (CFH_2-O-$CH(CF_3)_2$) is a recently developed volatile anaesthetic agent currently used in human anaesthesia. Sevoflurane has a low blood-gas partition coefficient of 0.69 (Strum and Eger, 1987). This low blood-gas solubility contributes to a more rapid induction of, and emergence from anaesthesia compared to halothane, enflurane, and isoflurane (Smith et al., 1992; Lerman et al., 1996; Aono et al., 1997; Ebert et al., 1998). The low blood-gas solubility also permits an easier control in anaesthetic depth. The minimum alveolar concentration (MAC) value of sevoflurane in dogs is 2.36 % (Kazama and Ikeda, 1988).

A lot of research has been performed in man, but only a limited number of reports on cardiopulmonary parameters during sevoflurane anaesthesia are available in small animals (Bernard et al., 1990; Oliva et al., 2000; Tacke et al., 2000). Mutoh et al. (1997) reported the cardiopulmonary effects of sevoflurane, in comparison to halothane, enflurane, and isoflurane in adult unpremedicated dogs using mask induction. However, mask induction without premedication is seldom used under clinical circumstances. The principal goal of the present study was to evaluate the effects of spontaneous and controlled ventilation (IPPV and PEEP) on cardiopulmonary parameters in sevoflurane anaesthetized premedicated dogs.

MATERIALS AND METHODS

Instrumentation and measurements

The study was approved by the Ethical Committee of the Faculty of Veterinary Medicine, Ghent University (filenumber: 97/12). Six, ASA I male mongrel dogs weighing 29 ± 7.30 kg (mean ± standard deviation) from 3 to 7 years were used for the study. The dogs were vaccinated and dewormed at a regular base. Clinical examination and a blood analysis confirmed the health status of the animals before the study. No specific medication altering anaesthetic or analgesic requirements were administered at least 1 month before the experiments.

Food, but not water was withheld for 12 hours before each experiment. The dogs were premedicated 30 minutes before induction with fentanyl-droperidol IM (respectively 5 µg/kg and 0,25 mg/kg of body weight BWT) (Thalamonal®, Janssen-Cilag, Berchem, Belgium). Induction of anaesthesia was performed using propofol (6 mg/kg of BWT) (Rapinovet®, Mallinckrodt Veterinary, Stockholm, Sweden) intravenously over 15-20 seconds. After loss of swallow reflex the dogs were orally intubated (endotracheal tube 9 to 12 mm ID, Rüsch, Germany).

A circle system (Titus®, Dräger, Lübeck, Germany) with a precision out of circuit vaporiser (quick lock system) (Vapor 19,3®, Dräger, Lübeck, Germany) was used throughout the study. The soda lime (Dräger Sorb 800®, Dräger, Lübeck, Germany) was renewed before each experiment. The whole system was air dried between the experiments. The anaesthetic circuit was flushed with 100% oxygen for 5 minutes before the experiment and afterwards filled with sevoflurane 1.5 MAC (1.5 $\times$ 2.36 % (Kazama and Ikeda, 1988)) using

a fresh gas flow of 2 L/min oxygen. No intravenous infusions were administered during the trial.

Monitoring included a calibrated (Quick Cal™ Calibration Gas, Datex-Ohmeda Corp., Helsinki, Finland) multi anaesthetic gas analyser (Capnomac Ultima®, Datex Engstrom Instrumentation Corp., Helsinki, Finland) for determination of the following parameters: inspiratory anaesthetic agent concentration (FiAA %), inspiratory oxygen fraction (FiO_2), end tidal CO_2 concentration (ET CO_2 %) and respiratory rate (RR). Samples were taken at the Y-part (Straight Adapter®, Datex-Engstrom Instrumentarium Corp., Helsinki, Finland) with a rate of 200 mL/min and were scavenged. Tidal volume (TV) was monitored with a respirometer (Volumeter®, Dräger, Lübeck, Germany). TV and RR were adjusted if necessary during the experiment to keep a normal $PaCO_2$ level between 35 and 45 mm Hg (Hartsfield, 1996). The vaporizer settings were adjusted throughout the experiment to maintain an end-tidal anaesthetic concentration of 1.5 and 2 MAC sevoflurane by monitoring the inspiratory sevoflurane concentration. Heart rate (HR) and peripheral haemoglobin saturation (SpO_2%) were monitored continuously using a pulse oximeter (N-20PA Portable Pulse Oximeter®, Nellcor Puritan Bennett Inc., Pleasanton, CA, U.S.A.) with the probe placed on the tongue.

During the first hour of anaesthesia the dogs were instrumented for the experiment. A thermodilution catheter (Swan-Ganz® catheter, 7.5 french, American Edwards Laboratories, Santa Ana, U.S.A.) was placed in the left jugular vein of the dog through an introducer (Percutaneous Sheath Introducer Set®, Arrow, Reading, U.S.A.). The thermodilution catheter was advanced into the pulmonary artery using the characteristic pressure waveforms on the display of the pressure monitor (Hellige Servomed SMV 104®, Germany). The proximal port of the thermodilution catheter was positioned in the right atrium. The

distal port and thermistor were positioned in the pulmonary artery in a way that by inflating the balloon of the catheter wedge position was achieved. Mean (MPAP), systolic (SPAP), diastolic (DPAP) pulmonary artery pressure, right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP) were measured by connecting the thermodilution catheter to the pressure transducer (Monitoring-set®, Vascumed N.V., Ghent, Belgium) using an extension tube (Lectrocath®, 150 cm, cap. 1.60 mL, Vygon, Ecouen, France) filled with heparinised saline (5 I.U. heparin per ml). The pressure transducer was placed at the level of the heart of the dog.

The thermodilution catheter was connected to the cardiac ouput computer (COM-1®, American Edwards Laboratories, Santa Ana, U.S.A.) and a closed injectate delivery system (CO-set®+, Model 93-610, Baxter Healthcare Corporation, Edwards Critical –Care Division, Irvine, U.S.A.). Several cardiac output (CO) determinations were performed using 5 ml of a saline 0.9% solution at room temperature injected into the right atrium. The mean value from three results close to each other was used as actual value. Blood temperature of the dog and injection temperature of the saline solution were measured using the cardiac output computer.

A catheter (Vasocan®Braunüle, 22 gauge, B.Braun, Melsungen, Germany) was surgically placed into the right femoral artery. The catheter was connected to the pressure transducer (Monitoring-set®, Vascumed N.V., Ghent, Belgium) by means of extension tubing filled with heparinised saline. The pressure transducer was placed at the level of the heart of the dog. The mean (MAP), systolic (SAP) and diastolic arterial blood pressure (DAP) were measured using a calibrated blood pressure monitor (Hellige

Servomed SMV 104®, Germany). Arterial blood was collected in heparinized 2 ml syringes and stored on ice for measurement of blood gas tensions and acid-base balance (PCV, pH, pCO_2, pO_2, plasma bicarbonate concentration (HCO^{3-}), and standard base excess (SBE)) with a blood gas analyzer calibrated at 37°C (ABL5®, Radiometer Copenhagen, Denmark).

Experimental Design

The dogs were anaesthetised during the instrumentation period at a concentration of 1.5 MAC sevoflurane breathing spontaneously (SpV) before the first measurements were done. These measurements were used as baseline values. Afterwards the concentration of sevoflurane was increased to 2 MAC and a stabilisation period of 20 minutes was respected before the next measurements. Then the dogs were ventilated using IPPV (Ventilog 3, Dräger, Lübeck, Germany), the anaesthetic concentration was reduced back to 1.5 MAC and afterwards increased to 2 MAC. Between each alteration in anaesthetic concentration or ventilation pattern, 20 minutes of stabilisation time was respected before new measurements were done. At the end the dogs were ventilated with a PEEP of 5 cm H_2O and a concentration of 1.5 MAC and 2 MAC. Again 20 minutes of stabilisation time was respected before each measurement. The entire experimental protocol was finished after 180 minutes (Table1).

After the experiment, catheters were removed and postoperative analgesia (buprenorphine 10 µg/kg IM q 6h (Temgesic®, Schering-Plough, Hull, England) was administered before transferring the dogs to the recovery room. The dogs received amoxycillin clavulanate (8.75 mg/kg/day SC, Synulox® Ready-To-Use,

Pfizer Animal Health) during 5 days to prevent wound infection. Anaesthesia and recovery were uneventful.

Table 1: Time Schedule.

TIME (minutes)	SEVO CONCENTRATION VENTILATION PATTERN	ACTION
T0	1.5 MAC SpV	induction
		instrumentation
T60		measurement 1
	2 MAC SpV	
T80		measurement 2
	1.5 MAC IPPV	
T100		measurement 3
	2 MAC IPPV	
T120		measurement 4
	1.5 MAC PEEP	
T140		measurement 5
	2 MAC PEEP	
T160		measurement 6

Calculations

Calculated values were determined as follows: (Gross et al., 1990)

Body surface area (BSA; m^2)

$$BSA = \frac{\text{Body Weight (g)}^{2/3} \times 10.1}{10^4}$$

Cardiac index (CI; L/min/m²)

$$CI = \frac{CO}{BSA}$$

Stroke volume (SV; mL/beat)

$$SV = \frac{CO}{HR} \times 1000$$

Stroke index (SI; mL/beat/m²)

$$SI = \frac{SV}{BSA}$$

Systemic vascular resistance (SVR; dynes.sec/cm^5)

$$SVR = \frac{MAP - RAP}{CO} \times 80$$

Pulmonary vascular resistance (PVR; dynes.sec/ cm^5)

$$PVR = \frac{MPAP - PCWP}{CO} \times 80$$

Left ventricular stroke work index (LVSWI; g.m/m²)

$$LVSWI = \frac{1.36\ (MAP - PCWP)}{100} \times SI$$

Right ventricular stroke work index (RVSWI; g.m/m²)

$$RVSWI = \frac{1.36\ (MPAP - RAP)}{100} \times SI$$

Statistical analysis

The results of the different recorded parameters are expressed as mean ± standard deviation. Statistical analysis for each parameter was done with repeated measures analysis of variance. Continuous dependent variables were analysed with Proc Mixed (SAS v8, SAS Institute Inc., SAS Campus Drive, Cary, NC, USA).

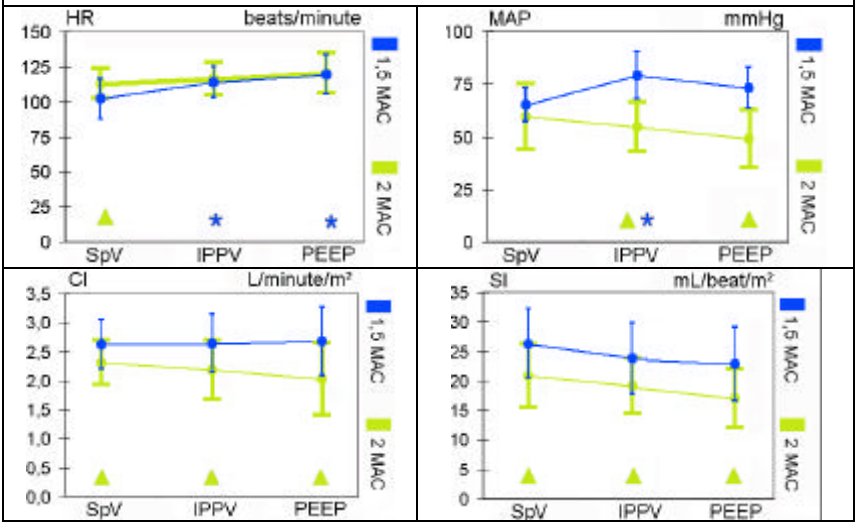
Dependent variables expressing a proportion were analysed with Glimmix Macro (SAS v8) using a logit link function and a binomial error term. Time (i.e. treatment) was considered a repeated measure, and dogs a random effect. An autoregressive covariance structure of order 1 was included in the analyses to take correlations between measurements at different time point intervals into account.

RESULTS

Cardiovascular effects induced by SpV and CV (IPPV and PEEP) in 1.5 and 2 MAC sevoflurane anaesthesia:

At 1.5 MAC HR increased significantly during IPPV and PEEP compared to SpV ($p = 0.01$ and $p = 0.004$). The increase during CV was non-significant at 2 MAC. The HR during SpV at 2 MAC was significantly higher compared to 1.5 MAC ($p = 0.01$). (Fig.1).

Fig. 1. The influences of SpV and CV on HR, MAP, CI and SI in Sevoflurane and 2 MAC) anaesthetized dogs. ▲ significantly different from 1.5 MAC * significantly different from SpV. Values are expressed as mean ± standard deviation



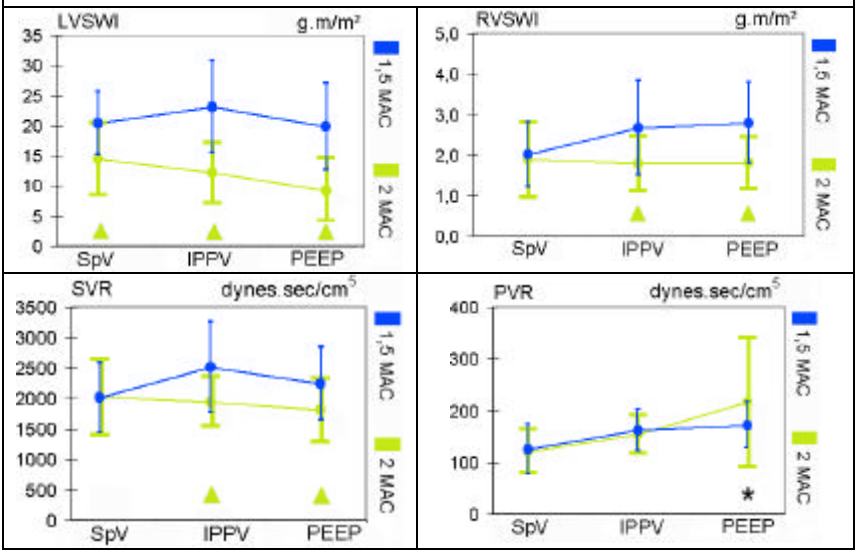
MAP, SAP, and DAP increased significantly during the IPPV 1.5 MAC Sevo protocol compared to SpV ($p = 0.01$). On the other hand, 2 MAC IPPV and PEEP induced a non-significant decrease of these parameters. Blood pressures were significantly lower at 2 MAC Sevo CV compared to 1.5 MAC Sevo ($p = 0.0001$) (Fig.1).

In the 1.5 MAC protocol only RAP during IPPV was significantly lower compared to PEEP ($p = 0.02$). RAP during 2 MAC PEEP was significantly higher than SpV and IPPV ($p = 0.05$ and $p = 0.03$). RAP of 2 MAC CV was significantly higher compared to 1.5 MAC.

MPAP in the 1.5 MAC protocol increased significantly during IPPV and PEEP compared to SpV (IPPV was also significantly different from PEEP) ($p = 0.001$). The MPAP of 2 MAC Sevo also increased during CV; but the differences were only significant for PEEP compared to SpV and IPPV ($p = 0.001$). The MPAP of the 1.5 MAC SpV was significantly lower than 2 MAC ($p = 0.02$). SPAP and DPAP during 1.5 MAC increased when CV was applied; PEEP was significantly different from SpV for both parameters ($p = 0.01$) and from IPPV for DPAP ($p = 0.01$). The increase of SPAP and DPAP was non-significant in the 2 MAC protocol. 2 MAC during SpV induced a significant increase in SPAP and DPAP compared to 1.5 MAC ($p = 0.04$).

At 1.5 MAC PCWP increased significantly during CV, this increase was significant during PEEP compared to SpV ($p = 0.007$) and for PEEP compared to IPPV ($p = 0.007$). At 2 MAC only the increase in PCWP during PEEP compared to IPPV was significant ($p = 0.02$). 2 MAC during SpV and IPPV induced a significant increase in PCWP compared to 1.5 MAC ($p = 0.0009$ and $p = 0.03$).

Fig. 2 : The influences of SpV and CV on LVSWI, RVSWI, SVR and PVR in sevoflurane (1.5 and 2 MAC) anaesthetized dogs. ▲ significantly different from 1.5 MAC ; ✱ significantly different from SpV. Values are expressed as mean ± standard deviation



CV induced no significant changes in CO and CI, SV, SI and LVSWI in both MAC protocols. 2 MAC anaesthesia induced signicant lower values compared to 1.5 MAC for these parameters. (Fig. 1 and 2). CV induced a non-significant rise in RVSWI and SVR during the 1.5 MAC protocol. On the contrary at 2 MAC there was a slight decrease in RVSWI and SVR during CV compared to SpV. During 2 MAC CV there was a significant decrease in RVSWI and SVR compared to 1.5 MAC ($p = 0.006$). (Fig. 2). CV induced a non-significant increase in PVR in both MAC protocols; only PEEP was significantly different from SpV ($p = 0.04$). (Fig. 2).

Table 2 : Influences of SpV and CV on cardiovascular parameters in sevoflurane (1.5 and 2 MAC) anaesthetized dogs.

VAR	VENT	SEVO CONCENTRATION		VAR	VENT	SEVO CONCENTRATION	
		1,5 MAC	2 MAC			1,5 MAC	2 MAC
HR	SpV	102 ± 14	113 ± 10.8 *	CO	SpV	2.5 ± 0.6	2.2 ± 0.5 *
beats	IPPV	114 ± 10.8 °	116 ± 11.6	L/min	IPPV	2.5 ± 0.7	2 ± 0.5 *
per min.	PEEP	119 ± 14.1 °	121 ± 14.5		PEEP	2.5 ± 0.7	1.9 ± 0.7 *
MAP	SpV	65 ± 8.1	59 ± 15.6	CI	SpV	2.62 ± 0.43	2.31 ± 0.38 *
mm Hg	IPPV	79 ± 11.2 °	55 ± 11.7 *	L/min/m²	IPPV	2.64 ± 0.5	2.18 ± 0.51 *
	PEEP	73 ± 9.5	49 ± 13.7*		PEEP	2.67 ± 0.59	2.02 ± 0.62 *
SAP	SpV	92 ± 11	84 ± 19.5	SV	SpV	24.91 ± 7.83	19.69 ± 6.22 *
mm Hg	IPPV	112 ± 18 °	78 ± 21.6 *	mL/beat	IPPV	22.24 ± 7.01	17.72 ± 5.23 *
	PEEP	99 ± 23	70 ± 25.5 *		PEEP	21.46 ± 7.12	16.07 ± 6.06 *
DAP	SpV	54 ± 7.5	50 ± 12.8	SI	SpV	26.28 ± 5.93	20.86 ± 5.4 *
mm Hg	IPPV	66 ± 10.9 °	44 ± 10 *	mL/beat/m²	IPPV	23.59 ± 6.04	18.97 ± 4.71 *
	PEEP	59 ± 10	42 ± 10.3 *		PEEP	22.79 ± 6.28	16.94 ± 4.95 *
RAP	SpV	5.8 ± 3.4	6 ± 3.3 |	LVSWI	SpV	20.46 ± 5.23	14.39 ± 6.05 *
mm Hg	IPPV	5.2 ± 3.5 |	6.3 ± 3.7 *|	g*m/m²	IPPV	23.09 ± 7.68	12.31 ± 5.07 *
	PEEP	6.5 ± 3.2	7.5 ± 3.6 *		PEEP	19.89 ± 7.22	9.24 ± 5.29 *
MPAP	SpV	11.3 ± 3.4	13 ± 4 *	RVSWI	SpV	2.03 ± 0.79	1.89 ± 0.93
mm Hg	IPPV	13.2 ± 4 °|	13 ± 4.1 |	g*m/m²	IPPV	2.67 ± 1.15	1.8 ± 0.68 *
	PEEP	15.3 ± 3.3 °	15 ± 3.1°		PEEP	2.79 ± 0.99	1.81 ± 0.65 *
SPAP	SpV	18 ± 4.1	20 ± 5.2 *	SVR	SpV	2015.7 ± 571.2	2022.8 ± 625.23
mm Hg	IPPV	20.5 ± 3.9	20 ± 4.5 |	dynes*sec/cm^5	IPPV	2511.3 ± 746	1948.6 ± 411.63*
	PEEP	22.7 ± 2.8 °	23 ± 5.1		PEEP	2243.4 ± 599.7	1807.7 ± 524.49*
DPAP	SpV	5.8 ± 3.5	7.5 ± 3.8 *	PVR	SpV	125.42 ± 47.58	121.2 ± 43.03
mm Hg	IPPV	6.7 ± 3.3 |	7.5 ± 4	dynes*sec/cm^5	IPPV	162.23 ± 40.2	154.1 ± 36.48
	PEEP	9.5 ± 4.9 °	9.5 ± 5		PEEP	171.49 ± 45.08°	216.67 ± 124.45°
PCWP	SpV	7.7 ± 3.7	9.3 ± 4.3 *				
mm Hg	IPPV	8.3 ± 4.2 |	9.3 ± 3.5 *|				
	PEEP	10.2 ± 3.1 °	11 ± 4				

Data are expressed as mean ± standard deviation
* significantly different from 1,5 MAC p = 0,05
| significantly different from PEEP p = 0,05
° significantly different from SpV p = 0,05
Abbreviations of variables: see text

Effects of SpV and CV (IPPV and PEEP) on blood gas variables and respiratory parameters in 1.5 and 2 MAC sevoflurane anaesthesia:

The 1.5 MAC CV protocol induced a decrease in $PaCO_2$ compared to SpV, this decrease was only significant for IPPV compared to SpV ($p = 0.05$). At 2 MAC there was also a decline in $PaCO_2$ during CV, this decrease was significant for IPPV and PEEP compared to SpV (resp. $p = 0.0004$ and $p = 0.01$). $PaCO_2$ during SpV was significantly higher at 2 MAC sevoflurane compared to 1.5 MAC ($p = 0.01$). There was no significant difference in PaO_2 at any anaesthesia stage.

There was a significant rise in pH during CV compared to SpV ($p = 0.003$), only the rise during PEEP compared to SpV at 1.5 MAC was not significant. pH was significantly lower at 2 MAC compared to 1.5 MAC anaesthetic concentration during SpV ($p = 0.009$). SBC increased significantly during IPPV and PEEP compared to SpV at 2 MAC (resp. $p = 0.04$ and $p = 0.03$). There was no significant difference in PCV at any anaesthesia stage. There were significant but small changes in blood temperature during 2 MAC compared to 1.5 MAC ($p = 0.0002$).

The inspiratory pressure increased significantly during CV compared to SpV at both anaesthetic concentrations ($p = 0.0001$) and there was also a significant increase in inspiratory pressure during PEEP compared to IPPV ($p = 0.0001$). TV remained constant in all anaesthesia stages, but with large individual variations. There was no significant difference in RR between the 3 different types of ventilation, but RR was significantly lower at 2 MAC compared to 1,5 MAC during SpV ($p = 0.02$). $ETCO_2$% decreased significantly during CV compared to SpV at both MAC protocols. The 2 MAC SpV

protocol induced a significant increase in $ETCO_2$% compared to 1.5 MAC (p = 0.004).

Table 3: Influences of SpV and CV on pH, blood gas analysis and respiratory parameters in sevoflurane anaesthetized dogs.

VARIABLE	VENT	SEVOFLURANE CONCENTRATION			
		1.5 MAC		2 MAC	
BLOODTEMP. (°C)	SpV	38.7 ±	0.5	38.8 ±	0.4 *
	IPPV	38.8 ±	0.4 |	38.9 ±	0.4 * |
	PEEP	39 ±	0.5 °	39.1 ±	0.5 * °
PCV	SpV	35 ±	8.9	36 ±	8.4
	IPPV	35 ±	7.5	34 ±	9.5
	PEEP	36 ±	10.6	36 ±	9.8
pH	SpV	7.255 ±	0.06	7.212 ±	0.08 *
	IPPV	7.312 ±	0.03 °	7.303 ±	0.02 °
	PEEP	7.295 ±	0.02	7.287 ±	0.03 °
$PaCO_2$ (mm Hg)	SpV	47 ±	9.9	56 ±	15.6 *
	IPPV	40 ±	4.6 °	40 ±	2.4 °
	PEEP	43 ±	1.5	44 ±	3.5 °
PaO_2 (mm Hg)	SpV	530 ±	28.5	513 ±	62.1
	IPPV	551 ±	28.1	539 ±	22.5
	PEEP	480 ±	109.3	547 ±	15.1
RR (breaths/min.)	SpV	14 ±	14.3	9 ±	6.6 *
	IPPV	16 ±	3.6	14 ±	2.9
	PEEP	14 ±	1.9	15 ±	1.9
TV (ml)	SpV	451 ±	230.7	453 ±	181.5
	IPPV	402 ±	116.9	402 ±	91.1
	PEEP	420 ±	116.9	390 ±	105.2
Pinsp. (mm Hg)	SpV	-0.3 ±	0.8	0 ±	1.3
	IPPV	9 ±	1°|	10 ±	1.4 °|
	PEEP	14 ±	2.3 °	13 ±	2 °
CO_2% ET	SpV	6.3 ±	1.2	7.5 ±	1.8 *
	IPPV	5.3 ±	0.3 °	5.4 ±	0.6 °
	PEEP	5.6 ±	0.6°	5.6 ±	0.8 °
SBC (mEq/ l)	SpV	18.83 ±	1.47	18.5 ±	1.76
	IPPV	19.8 ±	1.17	19.8 ±	1.17 °
	PEEP	20 ±	0.63	20 ±	0.89 °

Data are expressed as mean ± standard deviation

* significantly different from 1, 5 MAC (p = 0,05)

° significantly different from SpV (p = 0,05)

| significantly different from PEEP (p = 0,05)

Abbreviations of variables: see text

DISCUSSION

Sevoflurane is a recently developed inhalational anaesthetic agent, which is presently very popular in human anaesthesia (Eger, 1994; Young and Apfelbaum, 1995). Until now, few studies with sevoflurane in dogs under clinical anaesthesia circumstances are available (Oliva et al., 2000; Tacke et al., 2000). The cardiopulmonary influences of sevoflurane in experimental dogs were already reported but the design of these studies included no premedication but a mask induction (Bernard et al., 1990; Mutoh et al., 1997). The present study was performed to investigate the cardiopulmonary effects in 1.5 and 2 MAC sevoflurane anaesthetized dogs using a clinical protocol including standard premedication and induction. Moreover, the influences of different modes of controlled ventilation (IPPV and PEEP) were compared with the spontaneous breathing pattern.

Spontaneous ventilation (SpV) is mostly used during clinical anaesthesia in dogs. However, this mode of breathing is often accompanied with hypoventilation. A moderate increase in $PaCO_2$ has certainly beneficial effects on the occurring cardiovascular depression, whereby the increased $PaCO_2$ is a potential stimulator of the sympathetic nerve system (Cullen and Eger, 1974). Artificial respiration (AR) overcomes the occurring hypoventilation. AR is also required when intrathoracic surgery is necessary or the patient is curarized.

Inhalation anaesthetics including sevoflurane induce a dose-dependent cardiopulmonary depression in all animals (Aida et al., 1996; Bernard et al., 1992; Grosenbaugh and Muir, 1998). The MAC of sevoflurane in dogs has been established to be 2.36 volume % (Kazama and Ikeda, 1988). One and a half MAC is generally accepted

as the standard to allow most surgical interventions. However, some cases require a higher MAC when no supplementary analgesics or related drugs are administered during anaesthesia.

Basically, sevoflurane produces a dose dependent cardiopulmonary depression with systemic hypotension what is partly explained by an occuring peripheral vasodilatation. The influences of sevoflurane without premedication on the cardiopulmonary parameters were already intensively studied, whereby different MAC values were compared with the awake status in experimental dogs (Bernard et al., 1990; Frink et al., 1992; Harkin et al., 1994; Mutoh et al., 1997). In the present study only the changes induced by an increase in MAC were investigated. Fentanyl and propofol are relatively fast acting and short lasting agents. Interactions of these drugs after the instrumentation period of one hour with the sevoflurane protocol in the present study were not expected. On the other hand, although these drugs have a short half-life, it could not be excluded that their interfering effects were of longer duration. Droperidol has relatively long lasting effects. A possible influence of droperidol can therefore not be ruled out (Bissonnette et al., 1999). A fluid rate of 4 to 8 ml/ kg/ hour is generally accepted for the maintenance of a stable water balance during anaesthesia (Giesecke and Egberth, 1985). No fluids were administered in the present study. Nevertheless, the thermodilution method includes the administration of different boli of saline. Overall, an estimated quantity of 2 to 4 ml/ kg/ hour was administered during the whole experimental period. The influences of this relatively low fluid administration in this study can probably be neglected.

Two papers reported the cardiopulmonary influences of sevoflurane when increasing the MAC in spontaneous breathing dogs

(Harkin et al., 1994; Mutoh et al., 1997). Overall, the cardiopulmonary depression was characterized with non-significant decreases in cardiac output and index, stroke volume and index and pressure work index and a significant decrease in left ventricular stroke pressure. The decrease in mean and systolic arterial blood pressure only changed significantly in the study of Mutoh et al. (1997). All these findings were similar in the present study, although significant changes were observed or calculated mainly in the pulmonary pressures, the cardiac output and stroke volume and the LVSWI. Surprisingly, a significant increase in HR was also observed in the present study. This is in contrast to the literature, where a constant or a slight decrease in HR was reported (Harkin et al., 1994; Mutoh et al., 1997). The reason for this is not clear. Although the observed increase in HR was not very high, it was obvious and constant (about 10 %) in all dogs. Most likely the increased HR might be related to different factors. First of all, Mutoh et al. (1997) reported that sevoflurane in dogs induced a stimulation of the baroreceptor-reflex due to a dose dependent decrease in blood pressure. Secondly, the increase in $PaCO_2$ in men resulted in a sympathic stimulation (Cullen and Eger, 1974). Both factors might explain the observed slight, but significant increase in HR.

In our study significant decreases in SI, CI, and LVSWI with an increasing MAC value were seen. The decrease in SV and SI could be related to a decreased preload, an increased afterload, a decreased contractility or a combination of those (Suga et al., 1985). PCWP and SVR can be used as measures for preload and afterload, respectively (Muir and Mason, 1996; Suga et al., 1985). In the present study PCWP increased significantly, while the SVR remained constant. Mutoh et al. (1997) only found non-significant increases in RAP and PCWP, while PAP and SVR remained constant by

increasing the sevoflurane MAC. Thus, decreased contractility is the most obvious explanation for the depression of cardial function by increasing the MAC value. A reduced myocardial contractility is often compensated by an increase in end diastolic pressure (Kittleson, 1988). This phenomenon most likely occurred in the present study since PCWP and PAP's which are good reflections of the end diastolic pressure, increased (Brutsaert et al., 1985). PVR and RVSWI reflect the right ventricular afterload (Kaplan, 1986). Little changes occurred in the spontaneous breathing dogs by increasing the sevoflurane concentration.

Cardiopulmonary influences of sevoflurane were investigated in chronically instrumented dogs ventilated with IPPV (Bernard et al., 1990; Frink et al., 1992). Several MAC multiples (1.2, 1.5 and 2 MAC) were compared with the awake values in these studies. Bernard et al. (1990) reported significant decreases in CO, arterial pressures and SV by increasing the MAC from 1.2 to 2 MAC. The systemic vascular resistance remained constant. The same trend was noticed by Frink et al. (1992) when increasing the MAC from 1.5 to 2 MAC; although no significancy was observed. This is in agreement with the findings in the present study. An increase in MAC from 1.5 to 2 MAC in IPPV ventilated dogs induced a severe cardiopulmonary depression. Arterial pressures were significantly lower during the high MAC protocol. This decrease was more pronounced compared to the same MAC protocol in spontaneously ventilated dogs. The CO, CI, SV, SI, LVSWI and RVSWI decreased significantly. These observed decreases were more accentuated but not significantly different from the spontaneously breathing dogs. Right cardiac pressures increased also with increasing anaesthetic concentration; although only the RAP and PCWP were significantly different in the IPPV protocol.

Changing from SpV to IPPV using 1.5 MAC in our study surprisingly induced a small increase of arterial blood pressures and HR. In the same low MAC protocol little to no influences on the other cardiac parameters were observed by using IPPV. Data concerning the influences of AR on arterial blood pressure and vascular resistance in animals are conflicting. In horses a severe impact on the cardiopulmonary system using IPPV was reported (Aida et al., 1996). However, experiments in rats demonstrated a significant rise in arterial blood pressure and systemic vascular resistance when artificial respiration was applied (Sellden et al., 1986). Apparently, the influences of IPPV in smaller body weights were almost non-existing whereby a clear reason for our findings were not obvious. The same tendency was observed when changing from IPPV to PEEP ventilation. Right cardiac pressures increased when changing from SpV to IPPV at 1.5 MAC sevoflurane; but only the increase in MPAP was significant. During PEEP ventilation at 1.5 MAC the increases in right cardiac pressures were even more pronounced and only the increase in RAP was not significant. Overall, the existing cardiopulmonary depression was only slightly influenced by the different pressure ventilation patterns in the 1.5 MAC protocols.

The situation changed completely when MAC was increased from 1.5 to 2. Artificial respiration with 2 MAC induced a severe impact on the arterial pressures and most of the cardiac related parameters. CO, CI, SV, SI, LVSWI and RVSWI decreased significantly. PEEP induced a more pronounced negative impact than IPPV, but the difference between both ventilation patterns was not significant. The right cardiac pressures increased while the arterial pressures were clearly lowered. These findings were according to those reported in the literature (Cassidy et al., 1978; Pinsky, 1990; Smiseth et al., 1996). The main patho-physiologic mechanism for these

cardiovascular side effects of PEEP is a decreased venous return due to the increased intrathoracic pressure (Versprille, 1990) and a decreased coronary blood flow inversely related with the PEEP level (Jacobs and Venus, 1983). We did not find significant differences in CO, CI, SV, SI, LVSWI and RVSWI between IPPV and PEEP in this study.

In the present study, pulmonary vascular resistance increased during AR compared to spontaneous ventilation at both anaesthetic concentrations, the difference was only significant for the PEEP ventilation mode. On the contrary, systemic vascular resistance decreased when changing from spontaneous to controlled ventilation at 2 MAC. Apparently, the reported vasodilating properties of sevoflurane were more pronounced at the higher anaesthetic concentration when combined with artificial breathing. An analogue slight influence was reported in men using 3 cm H_2O PEEP; a steeper fall was observed when PEEP was increased to 10 cm H_2O. Increasing PEEP above 10 cm H_2O had only minor effects (Schreuder et al., 1982). The same tendancy was observed in dogs under controlled ventilation whereby a stepwise increase in PEEP induced a proportional decrease in CO (Sykes et al., 1970; Scharf et al., 1977). In the present study AR was applied during a relatively short period of 20 minutes. The influence on the cardiopulmonary parameters was also reported to be proportionally depending on the length of the period in which positive pressure was applied (Shawley, 1987). Therefore, to lessen cardiovascular compromise, the amount of time either inspiratory or expiratory pressure is applied must be minimized. It could have been possible that significant changes occurred if the length of the observation period was enlarged.

Arterial carbon dioxide pressure is the most frequently used index of respiratory system response to general anaesthetics. All contemporary inhalation anaesthetics depress alveolar ventilation and as a consequence increase $PaCO_2$ in a dose-related fashion (Green, 1995). Sevoflurane is a more potent ventilatory depressant than halothane (Green, 1995), and the characteristics of the ventilatory depression associated with sevoflurane are similar to that of isoflurane (Fourcade et al., 1971). As expected, in our study a significant rise in $PaCO_2$ and CO_2ET % occurred when increasing Sevo concentration in spontaneous breathing dogs. This is consistent with the results of Mutoh et al. (1997).

The present study showed that in anaesthetized spontaneously ventilating dogs increasing MAC values of sevoflurane from 1.5 to 2 induced a pronounced cardiopulmonary depression together with a significant increase in HR. However, this increase had little clinical consequence. The increased HR could be explained by the baroreceptor-reflex and/ or by sympathetic stimulation. The influences of artificial respiration on cardiopulmonary parameters at 1.5 MAC anaesthetic concentration were relatively minimal. On the other hand, AR during 2 MAC sevoflurane anaesthesia had severe negative influences, especially on all cardiac parameters. PEEP ventilation had a greater impact than IPPV.

In conclusion, sevoflurane anaesthesia at 1.5 MAC in premedicated healthy dogs induced a relatively moderate cardiopulmonary depression during spontaneous and controlled ventilation (IPPV and PEEP of 5 cm H_2O) and can be used safely. Increasing the MAC from 1.5 to 2 caused a marked cardiopulmonary depression. Higher concentrations of sevoflurane should better be avoided during all ventilation modes in dogs.

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INTRODUCTION TO CHAPTER 5

Since the application of thoracoscopy for diagnostic procedures is under development in veterinary clinical practice, the search for an adequate anaesthetic technique has a high priority. Anaesthesia during thoracoscopy has to deal with several specific problems such as ventilation-to-perfusion mismatches, lung atelectasis, hypoxemia, reduced hypoxic pulmonary vasoconstriction, etc.

During thoracoscopy one lung is entirely collapsed to create an optimal visualization and working space in the hemi-thorax. This can be achieved by two possible ventilation techniques: one lung ventilation (OLV) with passive lung collapse or two lung ventilation (TLV) with active lung collapse by gas insufflation. During OLV selective ventilation of one lung is applied using specific intubation techniques and materials such as double-lumen tubes, endobronchial intubation or bronchial blockers. During TLV the lung collapse is induced by gas insufflation in the hemi-thorax and can be performed with a standard endotracheal intubation technique.

Both ventilation techniques induce hypoxemia since one lung is entirely collapsed and regions of atelectasis develop in the ventilated lung. The atelectasis creates ventilation-to-perfusion mismatches due to intra-pulmonary shunting. However, active vasoconstrictive mechanisms in the non-ventilated lung reduce the blood flow and minimize the shunt. This is the so-called “hypoxic pulmonary vasoconstriction” reflex (HPV). Another problem arises since the majority of inhalation anaesthetics inhibit HPV. Sevoflurane, was reported to not inhibit HPV in dogs.

This absence of HPV inhibition justifies the use of sevoflurane in the examined anaesthetic protocol applying two lung ventilation with different levels of CO_2-insufflation. TLV was chosen since numerous technical problems arise using bronchial blockers or double lumen tubes during the one lung ventilation technique. Different levels of CO_2-insufflation were investigated in search for the insufflation pressure with the least pronounced influence on cardiopulmonary parameters in combination with an adequate visualization of the hemi-thorax.

CHAPTER 5

THE EFFECTS OF INTRATHORACIC PRESSURE DURING CONTINUOUS TWO-LUNG VENTILATION FOR THORACOSCOPY ON THE CARDIORESPIRATORY PARAMETERS IN SEVOFLURANE ANAESTHETIZED DOGS.

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SUMMARY

The cardiopulmonary effects of different levels of carbon dioxide insufflation (3, 5 and 2 mm Hg) under two-lung ventilation were studied in 6 sevoflurane (1.5 MAC) anaesthetized dogs during left sided thoracoscopy.

An arterial catheter, Swan-Ganz catheter and multi-anaesthetic gas analyser were used to monitor the cardiopulmonary parameters during the experiment. Baseline data were obtained before intrathoracic pressure elevation and the measurements were repeated at several intervals after left lung collapse induced by insufflation with carbon dioxide gas. The used intrapleural pressure levels were 3, 5 and 2 mm Hg.

Arterial blood pressures, cardiac index, stroke index, left and right ventricular stroke work index, arterial haemoglobin saturation, arterial oxygen tension and systemic vascular resistance decreased significantly during hemithorax insufflation, whereas heart rate, right atrial pressure, mean, systolic and diastolic pulmonary arterial pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance and arterial carbon dioxide tension significantly increased during intrapleural pressure elevation.

Although carbon dioxide insufflation into the left hemithorax with an intrapleural pressure of 2 to 5 mm Hg compromises cardiac functioning in 1.5 MAC sevoflurane anaesthetized dogs, it can be an efficacious adjunct for thoracoscopic procedures. Intrathoracic view was satisfactory with an intrapleural pressure of 2 mm Hg. Therefore, the intrathoracic pressure rise during thoracoscopy with two-lung

ventilation should be kept as low as possible. Additional insufflation periods should be avoided, since a more rapid and more severe cardiopulmonary depression can occur.

INTRODUCTION

Compared with traditional surgery, the advantages of minimally invasive techniques for diagnosis and treatment of intrathoracic lesions have been well established in humans (Rodgers and Talbert, 1976; Toy and Smoot, 1992; Marchandise et al., 1993; Miller, 1993; Perrault et al., 1993; Tanguilig et al., 1993). Thoracoscopy is the examination of the chest cavity with an endoscope. A lot of diagnostic and therapeutic applications of thoracoscopy have been described and are presently used in human medicine. The use of thoracoscopy in veterinary medicine is only gradually starting. Although the technique can be performed in sedated standing horses, this is not possible in small animals such as dogs, pigs and sheep (Vachon and Fischer, 1998; Peroni et al., 2000). General anaesthesia is necessary to perform thoracoscopy in these smaller animals (Fujita et al., 1993; Jones et al., 1993; Faunt et al., 1998).

Specific problems in particular compromised ventilation occur during general anaesthesia for thoracoscopy. Thoracoscopic procedures require an immobilized and collapsed lung, facilitating intrathoracic viewing and working space. This can be achieved by two methods: the so-called one lung ventilation (OLV) with passive lung collapse or two lung ventilation (TLV) with lung compression induced by gas insufflation in one hemithorax. In the one-lung ventilation technique only one lung is selectively ventilated. This technique is

intensively used in human anaesthesia and needs specific intubation techniques with double-lumen tubes, endobronchial intubation or bronchial blockers. In all techniques bronchoscopic confirmation of an adequate tube placement is strongly recommended and can be considered as a disadvantage (Smith et al., 1986; Benumof, 1993). Gas (mostly carbon dioxide) insufflation is routinely used for laparoscopy and has been proved to be a safe, effective technique allowing the creation of intra-abdominal space for surgical interventions (Ishizaki, 1993). The same technique can be used for thoracoscopy.

Both techniques (OLV and TLV) include significant risks for the patient and require intensive attention from the anaesthetist. The greatest risk during thoracoscopy is hypoxaemia, because one entire lung is collapsed and non functional. Even more, atelectasis can develop in the ventilated lung (Cohen et al., 1988). This complex phenomenon leads to significant ventilation-to-perfusion mismatches due to intrapulmonary shunting. Hypoxic pulmonary vasoconstriction (HPV) is a physiologic response in the lung that decreases the shunt fraction. Many factors, including the use of volatile anaesthetic agents, can reduce the magnitude of HPV (Ishibe et al., 1993).

In veterinary medicine only two papers describe the technique of TLV with gas insufflation in experimental dogs and pigs (Jones et al., 1993; Faunt et al., 1998). In the present study several items were investigated. First of all, the possible use of sevoflurane as anaesthetic agent for thoracoscopy was evaluated. Furthermore, the influence of low-pressure (2, 3, and 5 mm Hg) intrathoracic insufflation of CO_2 on cardiorespiratory parameters during non-selective intubation with TLV was examined.

MATERIALS AND METHODS

The study was approved by the Ethical Committee of the Faculty of Veterinary Medicine, Ghent University (filenumber: 97/12). Six ASA I mongrel male dogs weighing 31.5 ± 5.8 kg (mean ± standard deviation) aged 3 to 7 years were used in the study. The dogs were vaccinated and dewormed on a regular basis. Clinical examination and a blood analysis (blood chemistry and haematology) confirmed the health status of the animals before the study. Chest radiographs revealed no abnormalities. No specific medication altering anaesthetic or analgesic requirements were administered at least 1 month before the experiments.

Food but not water was withheld for 12 hours before each experiment. The dogs were premedicated with 5 micrograms fentanyl/kg and 0,25 mg droperidol/kg of body weight (Thalamonal®, Janssen-Cilag, Berchem, Belgium) 30 minutes before induction of anaesthesia. Induction of anaesthesia was performed using propofol (6 mg/kg of BWT) (Rapinovet®, Mallinckrodt Veterinary, Stockholm, Sweden) intravenously over 15 to 20 seconds. After loss of the swallow reflex the dogs were orally intubated (endotracheal tube 12 mm ID, Rüsch, Germany).

An anaesthesia machine (Titus®, Dräger, Lübeck, Germany) with a circle system and a precision out of circuit vaporiser (Vapor 19,3®, Dräger, Lübeck, Germany) was used in the study. The soda lime (Dräger Sorb 800®, Dräger, Lübeck, Germany) was renewed before each experiment. The whole system was air dried between the experiments. The anaesthetic circuit was flushed with 100% oxygen for 5 minutes before the experiment. Sevoflurane (Sevorane®, Abbott, Ottignies, Belgium) (1.5 MAC x 2.36 vol%) (Kazama and Ikeda, 1988)

and 2 L oxygen/min fresh gas flow was used. The dogs were mechanically ventilated (IPPV) using a time-cycled ventilator (Ventilog 3®, Dräger, Lübeck, Germany) and a tidal volume of 10 mL/kg. The respiratory rate was adjusted to maintain end-tidal CO_2 concentration between 5 and 6.5 %. No intravenous infusions were administered during the trial. The dogs were placed in right lateral recumbency.

Monitoring included a calibrated (Quick Cal™ Calibration Gas, Datex-Ohmeda Corp., Helsinki, Finland) multi anaesthetic gas analyser (Capnomac Ultima®, Datex Engstrom Instrumentation Corp., Helsinki, Finland) for determination of the following parameters: inspiratory anaesthetic agent concentration (FiAA %), inspiratory oxygen fraction (FiO_2), end tidal CO_2 concentration (ET CO_2 %) and respiratory rate (RR). Samples were taken at the Y-piece with a rate of 200 mL/min and were scavenged. Tidal volume was monitored with a respirometer (Volumeter®, Dräger, Lübeck, Germany). The vaporizer settings were adjusted throughout the experiment to maintain an end-tidal anaesthetic concentration of 1.5 MAC sevoflurane. Heart rate (HR) and haemoglobin saturation (SpO_2 %) were monitored continuously using a pulse oximeter (N-20PA Portable Pulse Oximeter®, Nellcor Puritan Bennett Inc., Pleasanton, CA, U.S.A.) with the probe placed on the tongue.

During the first hour of anaesthesia the dogs were instrumented for cardiopulmonary monitoring. A thermodilution catheter (Swan-Ganz® catheter, 7.5 french, American Edwards Laboratories, Santa Ana, U.S.A.) was placed in the left jugular vein through an introducer (Percutaneous Sheath Introducer Set®, Arrow, Reading, U.S.A.). The thermodilution catheter was advanced into the pulmonary artery using the characteristic pressure waveforms on the display of the haemodynamic monitor (Hellige Servomed SMV 104®,

Germany). The proximal port of the thermodilution catheter was positioned in the right atrium. The distal port and thermistor were positioned in the pulmonary artery in a way that by inflating the balloon at the catheter tip the wedge position was reached. The thermodilution catheter was connected to the pressure transducer (Monitoring-set®, Vascumed N.V., Ghent, Belgium) with an extension tube (Lectrocath®, 150 cm, cap. 1.60 mL, Vygon, Ecouen, France) filled with heparinised saline (5 I.U. heparin per ml) to measure mean (MPAP), systolic (SPAP), diastolic (DPAP) pulmonary artery pressure, right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP). The pressure transducer was placed at the heart level of the dog.

The thermodilution catheter was connected to the cardiac ouput computer (COM-1®, American Edwards Laboratories, Santa Ana, U.S.A.) and a closed injectate delivery system (CO-set®+, Model 93-610, Baxter Healthcare Corporation, Edwards Critical Care Division, Irvine, U.S.A.). Several cardiac output (CO) determinations were performed using 5 ml of a saline 0.9% solution at room temperature injected into the right atrium. The mean value of 3 measurements close to each other was regarded as actual value. Blood temperature of the dog and injection temperature of the saline solution were measured using the cardiac output computer.

A catheter (Vasocan®Braunüle, 22 gauge, B.Braun, Melsungen, Germany) was surgically placed into the right femoral artery. The catheter was connected to the pressure transducer (Monitoring-set®, Vascumed N.V., Ghent, Belgium) by an extension tube filled with heparinised saline. The mean (MAP), systolic (SAP) and diastolic arterial blood pressure (DAP) were monitored using a calibrated haemodynamic monitor (Hellige Servomed SMV 104®,

Germany). Arterial blood was collected in heparinised syringes and stored on ice (maximum during 15 minutes) for measurement of blood gas tensions (pCO_2, pO_2) and acid-base parameters (pH, standard bicarbonate (HCO_3^-), standard base excess (SBE)) and PVC with a blood gas analyser calibrated at 37°C (ABL 5®, Radiometer Copenhagen, Denmark).

Experimental Design

The type of intervention and timing are given in Table 1. The dogs were anaesthetized for 1 hour at a concentration of 1.5 MAC sevoflurane with controlled ventilation (IPPV) before base line measurements were recorded (control 1). Afterwards intrathoracic pressure was raised to 3 mm Hg by intrapleural insufflation of CO_2 (4 L/min) through a 10-mm cannula (Thoracoscopic cannula®; Richard Wolf GmbH, Knittlingen, Germany) placed in the dorsal third of the eight intercostal space. A high-flow, pressure-limited insufflating device (Insufflator®; Richard Wolf GmbH, Knittlingen, Germany) was connected to the cannula and maintained a constant pressure. Measurements were done after 5, 10 and 15 minutes (measurements 2, 3 and 4). After 20 minutes both lungs were expanded and a stabilisation period of 10 minutes was respected. For the following measurements intrathoracic pressure was increased to 5 and 2 mm Hg; measurements of the different parameters were recorded 5 minutes after reaching intrathoracic pressure (measurements 6 and 8). Between each intrathoracic pressure a stabilisation period of 10 minutes was respected followed by a control measurement (control 2 and 3). After final lung re-expansion, the dogs were ventilated during 15 minutes with positive end expiratory pressure ventilation (PEEP to 5 cm H_2O) and final recordings were performed (control 4) (Table 1). All instruments and catheters were removed during this period.

Table 1 : Time Schedule used for thoracoscopy with two lung ventilation in 6 sevoflurane (1.5 MAC) anaesthetized dogs

TIME (minutes)	INTRATHORACIC PRESSURE + VENTILATION PATTERN	ACTION
T0	0 mm Hg IPPV	induction of anaesthesia instrumentation
T60	0 mm Hg	measurement 1 control 1
T65	3 mm Hg	measurement 2
T70	3 mm Hg	measurement 3
T75	3 mm Hg	measurement 4
T80	0 mm Hg	lung re-expansion
T90	0 mm Hg	measurement 5 control 2
T100	5 mm Hg	measurement 6 followed by lung re-expansion
T110	0 mm Hg	measurement 7 control 3
T115	2 mm Hg	measurement 8 followed by lung re-expansion
T130	0 mm Hg PEEP 5 cm H2O	measurement 9 control 4

IPPV: intermittent positive pressure ventilation
PEEP: positive end expiratory pressure.

Remaining gas in the pleural space was evacuated through the trocard by applying positive pressure to the rebreathing system. The extent of lung expansion was checked with the endoscope. When re-

expansion was nearly complete a thorax drain was placed. Postoperative analgesia was provided with buprenorphine 10 µg/kg IM q6h (Temgesic®, Schering-Plough, Hull, England) and 0.5 mg/kg bupivacaine (Marcaine 0.5 %, Astra Pharmaceuticals, Södertälje, Sweden) intrapleurally. The dogs received amoxycillin clavulanate (8.75 mg/kg/day SC, Synulox® Ready-To-Use, Pfizer Animal Health) during 5 days to prevent wound infection.

Calculations

Calculated parameters were determined as follows: (Gross et al., 1990; Davis et al., 1995)

Body surface area (BSA; m^2)

$$BSA = \frac{\text{Body Weight (g)}^{2/3} \times 10.1}{10^4}$$

Cardiac index (CI; L/min/m^2)

$$CI = \frac{CO}{BSA}$$

Stroke volume (SV; mL/beat)

$$SV = \frac{CO}{HR} \times 1000$$

Stroke index (SI; mL/beat/m^2)

$$SI = \frac{SV}{BSA}$$

Systemic vascular resistance (SVR; dynes.sec/cm^5)

$$SVR = \frac{MAP - RAP}{CO} \times 80$$

Pulmonary vascular resistance (PVR; dynes.sec/ cm^5)

$$PVR = \frac{MPAP - PCWP}{CO} \times 80$$

Left ventricular stroke work index (LVSWI; g.m/m²)

$$LVSWI = \frac{1.36\ (MAP - PCWP)}{100} \times SI$$

Right ventricular stroke work index (RVSWI; g.m/m²)

$$RVSWI = \frac{1.36\ (MPAP - RAP)}{100} \times SI$$

End tidal CO_2 content (CO_2 ET; mm Hg)

$$CO_2\ ET = \frac{(750\text{-}47) \times CO_2\ ET\ \%}{100}$$

Statistical Analysis

Analysis of the data was done with repeated measures analysis of variance. Continuous dependent variables were analysed with Proc Mixed (SAS v8, SAS Institute Inc., SAS Campus Drive, Cary, NC, USA). Dependent variables expressing a proportion were analysed with Glimmix Macro (SAS v8) using a logit link function and a binomial error term. Ventilation, dose and the 'ventilation by dose' interaction term were the fixed factors in the model. Time was considered a repeated measure, and dog a random effect. An autoregressive covariance structure of order 1 was included in the analyses to take into account correlations between measurements at different time point intervals.

RESULTS

Initially, there was a significant increase in HR 5 minutes after increasing intrathoracic pressure (ITP) to 3 mm Hg (p=0.03), followed by a normalisation at 10 and 15 minutes later (p= 0.001 and p=0.03). After each lung re-expansion and at the end of anaesthesia HR differed significantly from control 1 (p=0.02) (Table 2).

Table 2 : The influences of increased intrathoracic pressure (ITP: 3, 5 and 2 mm Hg) on cardiovascular parameters in 6 sevoflurane (1.5 MAC) anaesthetized dogs.

ITP mm Hg	0	3	3	3	0
Time	control 1	5 minutes	10 minutes	15 minutes	control 2
HR beats/min	104 ± 14.57	109 ± 22.17 °	101 ± 19.93 |	103 ± 15.86 |	114 ± 17.69 °
MAP mm Hg	75 ± 7.54	61 ± 17.68 °, *	55 ± 16.34 °, |	54 ± 15.31 °	80 ± 12.76
SAP mm Hg	106 ± 8.54	82 ± 24.71 °	78 ± 25.92 °	78 ± 25.5 °	111 ± 15.29
DAP mm Hg	59 ± 9.49	51 ± 14.42 °, *	45 ± 12.55 °	44 ± 12.19 °	66 ± 11.62
RAP mm Hg	4.75 ± 2.71	12.00 ± 2 °	12.13 ± 3.14 °	10.88 ± 3.68 °	5.38 ± 2.13
MPAP mm Hg	12.63 ± 2.39	19.63 ± 2.45 °	20.13 ± 3.64 °	21.75 ± 4.4 °	14.75 ± 2.82
SPAP mm Hg	20.75 ± 4.33	26.13 ± 3.48 °	27.75 ± 4.95 °	30.38 ± 6.44 °, |	21.88 ± 5
DPAP mm Hg	8.00 ± 2.33	15.88 ± 2.53 °	15.75 ± 2.55 °	16.75 ± 3.85 °	10.25 ± 2.25
PCWP mm Hg	7.50 ± 2.00	13.25 ± 2.05 °	13.00 ± 3.12 °	13.00 ± 2.27 °	7.88 ± 2.53
ITP mm Hg	5	0	2	0	
Time	5 minutes	control 3	5 minutes	control 4	
HR beats/min	109 ± 19.61	115 ± 18.56 °	112 ± 19.85	115 ± 18.25 °	
MAP mm Hg	54 ± 14.58 °	74 ± 12.47	57 ± 9.56 °, *	67 ± 7.97	
SAP mm Hg	78 ± 25.03 °	106 ± 16.03	81 ± 19.87 °	98 ± 12.31	
DAP mm Hg	44 ± 11.38 °	62 ± 10.81	47 ± 7.91 °	51 ± 4.71	
RAP mm Hg	11.38 ± 2.97 °	5.25 ± 2.25	10.38 ± 1.77 °, §	5.13 ± 2.23	
MPAP mm Hg	22 ± 4.31 °	13.5 ± 3.07	21.8 ± 2.82 °	14.8 ± 2.71	
SPAP mm Hg	29.1 ± 6.29 °	19.5 ± 3.66	28.6 ± 4.1 °	21.4 ± 3.38	
DPAP mm Hg	16.3 ± 3.06 °	10.3 ± 2.31	15.8 ± 3.11 °	9.88 ± 3.52	
PCWP mm Hg	13.1 ± 2.75 °	7.5 ± 2.33	12.1 ± 2.75 °	8.13 ± 1.96	

Data are expressed as mean ± standard deviation; ° significantly different from control 1 (p=0.05); | significantly different from 5 minutes after 3 mm Hg ITP (p=0.05); * significantly different from 5 mm Hg ITP (p=0.05); § significantly different from 3 mm Hg ITP (p=0.05); Abbreviations of variables: see text.

MAP, SAP and DAP decreased significantly when ITP increased to 3, 5 and 2 mm Hg compared to control 1($p<0.0001$). MAP continued to decrease during the 15-minute period of ITP of 3 mm Hg, but this was only significantly different between 5 and 10 minutes ($p=0.05$). The 5 mm Hg ITP induced the lowest MAP compared to 2 and 3 mm Hg at 5 minutes after ITP elevation ($p=0.007$ and $p=0.04$). There was no significant difference in SAP between 2, 3 and 5 mm Hg ITP; again 5 mm Hg ITP produced the lowest DAP. Ten minutes after lung re-expansion and the end of the experiment MAP, SAP and DAP returned to baseline values (control 1) (Table 2 and Figure 1).

RAP, MPAP, SPAP, DPAP and PCWP increased significantly during ITP rise to 3, 5 and 2 mm Hg compared to control 1. During 3 mm Hg ITP RAP, MPAP, DPAP and PCWP remained relatively constant during the entire period. SPAP increased significantly after 15 minutes of ITP 3 mm Hg compared to 5 minutes after pressure elevation ($p=0.03$). RAP was significantly lower at 2 mm Hg ITP compared to 3 mm Hg. MPAP, SPAP, DPAP and PCWP were not significantly different between the 3 ITP levels. There were no significant differences in these right heart parameters after lung re-expansion and at the end of anaesthesia compared to values before ITP rise (control 1) (Table 2 and Figure 1).

Initially, CO, CI, SV and SI decreased significantly during 3 mm Hg ITP compared to control 1. However, these parameters increased gradually afterwards. The differences in CO, SV and SI between 5 and 15 minutes of 3 mm Hg ITP were significant ($p=0.04$, $p=0.006$ and $p=0.02$). SV and SI were significantly lower at 5 and 2 mm Hg ITP compared to values before ITP elevation (control 1). There was no significant difference in CO, CI, SV and SI between the 3 ITP levels. On the contrary, these parameters returned to control

values (control 1) after ITP elevation to 5 and 2 mm Hg (control 3 and 4). There was a significant overshoot of CO and CI after the first lung re-expansion ($p=0.04$), but this was less pronounced after 5 and 2 mm Hg of ITP. SV and SI returned to baseline (control 1) after lung re-expansion. At the end of anaesthesia these parameters were not significantly different from values before starting ITP increase (control 1) (Table 2 continued and Figure 1).

LVSWI decreased significantly after ITP increase to 3, 5 and 2 mm Hg compared to control 1. There were no significant differences in LVSWI between 5 and 15 minutes in the 3 mm Hg protocol. On the other hand, RVSWI increased non-significantly at 5 and 2 mm Hg ITP compared to control 1; RVSWI increased significantly only between 5 and 15 minutes of 3 mm Hg ITP ($p=0.03$). LVSWI and RVSWI were not significantly different between the 3 pressure levels and returned to the start values (control 1) after lung re-expansion and at the end of anaesthesia (Table 2 continued).

PVR increased significantly after ITP of 3, 5 and 2 mm Hg compared to control 1 and remained constant during the entire period of 3 mm Hg ITP. There was no significant difference between the 3 mm Hg ITP levels. PVR decreased to base line values (control 1) after lung re-expansion and at the end of anaesthesia (Table 2 continued).

Five minutes after ITP 3 mm Hg SVR remained constant, but decreased significantly after 10 and 15 minutes compared to 5 minutes post and before pressure elevation (control 1) ($p<0.0001$). SVR was also significantly lower compared to control 1 during 5 and 2 mm Hg ITP. There was a significant difference between 3 and 5 mm

Table 2 (continued) : The influences of increased intrathoracic pressure (ITP: 3, 5 and 2 mm Hg) on cardiovascular parameters in 6 sevoflurane anaesthetized dogs

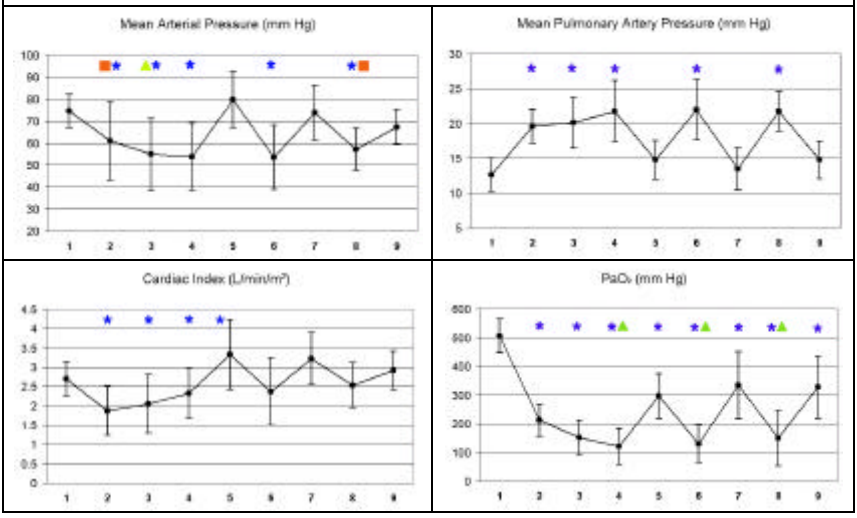
ITP mm Hg	0	3	3	3	0
Time	control 1	5 minutes	10 minutes	15 minutes	control 2
CO L/min	2.68 ± 0.38	1.85 ± 0.72 °	2.07 ± 0.88 °	2.35 ± 0.81 °, |	3.28 ± 0.7 °
CI L/min/m²	2.70 ± 0.45	1.87 ± 0.64 °	2.05 ± 0.76 °	2.33 ± 0.66 °	3.33 ± 0.91 °
SV mL/beat	26.11 ± 4.22	16.86 ± 3.87 °	19.96 ± 5.79 °	22.49 ± 5.51 °, |	28.88 ± 4.89
SI mL/beat/m²	26.72 ± 7.71	17.07 ± 4.84 °	20.02 ± 5.5 °	22.56 ± 5.19 °, |	29.63 ± 8.69
LVSWI g*m/m²	24.86 ± 10.22	11.50 ± 5.87 °	12.12 ± 7.62 °	12.91 ± 6.72 °	29.38 ± 12.23
RVSWI g*m/m²	2.89 ± 1.09	1.85 ± 0.96 °	2.26 ± 1.35 °	3.46 ± 2.58 |	3.92 ± 2.13
PVR dynes*sec/cm^5	156.7 ± 37.34	299.3 ± 93.2 °	293.4 ± 106 °	290.9 ± 85.9 °	167.4 ± 39.72
SVR dynes*sec/cm^5	2114 ± 323.7	2118 ± 353 °	1671 ± 194 °, |	1461 ± 267 °, |	1831 ± 169.8 °
SpO_2 %	98 ± 1.69	95 ± 2.14 °	94 ± 3.07 °	92 ± 4.75 °, |	96 ± 2.39
ITP mm Hg	5	0	2	0	
Time	5 minutes	control 3	5 minutes	control 4	
CO L/min	2.40 ± 1.03 °	3.19 ± 0.55	2.51 ± 0.54 °	2.91 ± 0.53	
CI L/min/m²	2.37 ± 0.87	3.22 ± 0.67	2.54 ± 0.58	2.92 ± 0.49	
SV mL/beat	21.30 ± 5.62 °	27.87 ± 3.29	22.39 ± 5.97 °	25.52 ± 3.72	
SI mL/beat/m²	21.33 ± 5.00 °	28.49 ± 6.81	23.33 ± 7.52 °	25.97 ± 5.89	
LVSWI g*m/m²	12.47 ± 6.79 °	25.76 ± 7.91	14.37 ± 5.24 °	21.00 ± 3.59	
RVSWI g*m/m²	3.34 ± 2.25	3.28 ± 1.43	3.61 ± 1.39	3.46 ± 1.22	
PVR dynes*sec/cm^5	298.0 ± 77.67 °	154.2 ± 38.8	305.7 ± 72.7 °	185.3 ± 37.4	
SVR dynes*sec/cm^5	1440 ± 179.5 °, §	1719 ± 102 °	1501 ± 143 °	1724 ± 308 °	
SpO_2 %	92 ± 4.28 °	97 ± 1.92	91 ± 4.41 °	97 ± 1.92	

Data are expressed as mean ± standard deviation; ° significantly different from control 1 (p=0.05); | significantly different from 5 minutes after 3 mm Hg ITP (p=0.05); § ignificantly different from 3 mm Hg ITP (p=0.05); Abbreviations: see text

Hg ITP (p=0.004). SVR values did not return to baseline values (control 1) after lung re-expansion and at the end of anaesthesia, but remained significantly lower (Table 2 continued).

SpO_2 % decreased significantly during ITP rise of 3, 5 and 2 mm Hg compared to control 1 (p<0.0001) and continued decreasing significantly between 5 and 15 minutes of ITP of 3 mm Hg. There were no significant differences between the 3 pressure levels. SpO_2 % returned to normal values (control 1) after lung re-expansion and at the end of anaesthesia (Table 2 continued).

Fig. 1a : The influences of increased ITP (3, 5 and 2 mm Hg) on PaO_2 and cardiovascular parameters in 6 sevoflurane (1.5 MAC) anaesthetized dogs. ✱ significantly different from control value 1; ▲ significantly different from 5 minutes after 3 mm Hg ITP; ■ significantly different from 5 mm Hg ITP. Values are expressed as mean ± standard deviation.



Blood temperature decreased slightly but significantly in time (p<0.0001). PCV changed significantly over time with a significant decrease at the end of anaesthesia (p=0.003). The pH decreased significantly from control 1 during the whole anaesthesia duration

($p<0.0001$). There were no significant differences between the 3 ITP levels. $PaCO_2$ increased significantly during 3, 5 and 2 mm Hg ITP compared to control 1 ($p<0.0001$) and continued increasing progressively during 3 mm Hg ITP. There were no significant differences between the 3 different ITP levels. $PaCO_2$ decreased after lung re-expansion. However, $PaCO_2$ at the end of anaesthesia was significantly higher compared to control 1 ($p=0.008$) (Table 3).

PaO_2 decreased significantly during the 3 pressure levels ($p<0.0001$) compared to control 1. The decrease in PaO_2 during 3 mm Hg ITP was significant between 5 and 15 minutes after elevation of intrathoracic pressure ($p=0.02$). PaO_2 was significantly lower at 5 and 2 mm Hg compared to PaO_2 after 5 minutes of 3 mm Hg ITP ($p=0.01$ and $p=0.03$). There was no significant difference in PaO_2 between 5 and 2 mm Hg ITP elevation. After lung re-expansion and at the end of anaesthesia PaO_2 still remained significantly lower compared to control 1 ($p<0.0001$) (Table 3 and Figure 1).

Inspiratory pressure (Pinsp.) in dogs significantly increased with IPPV and addition of ITP at 3, 5 and 2 mm Hg of CO_2 -insufflation. There were no significant differences between the 3 different ITP levels. Pinsp. returned to base line values (control 1) after termination of lung re-expansion of dogs in the 3 and 5 mm Hg ITP group but not in dogs treated with 5 cm H_2O PEEP ($p=0.04$). There were no significant changes in TV, CO_2 ET % and RR during the entire protocol. Standard bicarbonate concentration (SBC) decreased significantly from before ITP elevation (control 1) at 3, 5 and 2 mm Hg. There were no significant differences between the 3 different pressure levels. SBC returned to base line value (control 1) after 5 and 2 mm Hg ITP, but remained low after the longer period of 3 mm Hg ITP elevation ($p=0.008$) (Table 3).

Table 3 : The influences of increased intrathoracic pressure (ITP: 3, 5 and 2 mm Hg) on cardiovascular parameters in 6 sevoflurane anaesthetized dogs

ITP mm Hg	0	3	3	3	0
Time	control 1	5 minutes	10 minutes	15 minutes	control 2
BLOODT. (°C)	37.24 ± 0.55	36.95 ± 0.69	36.95 ± 0.75	36.91 ± 0.74	36.70 ± 0.77
PCV	31.01 ± 3.52	32.16 ± 4.69	32.16 ± 4.36	32.20 ± 3.89	31.86 ± 4.19
pH	7.30 ± 0.02	7.23 ± 0.06 °	7.18 ± 0.05 °, |	7.14 ± 0.06 °, |	7.23 ± 0.05 °
$PaCO_2$ (mm Hg)	40.38 ± 3.16	50.38 ± 6.19 °	59.75 ± 13.77 °	67.13 ± 10.95 °	47.13 ± 5.51
PaO_2 (mm Hg)	507 ± 58.37	212 ± 56.31 °	153 ± 60.66 °	122 ± 62.26 °, |	296 ± 78.64 °
RR (breaths/min)	12.50 ± 1.85	13.25 ± 2.31	13.25 ± 2.12	14.13 ± 4.05	13.13 ± 2.42
TV (mL)	336 ± 30.68	338 ± 51.27	359 ± 27.48	346 ± 51.23	341 ± 31.37
Pinsp. (mm Hg)	9.13 ± 1.55	21.00 ± 2.78 °	21.38 ± 3.54 °	22.38 ± 2.00 °	8.88 ± 2.30
CO_2% ET	5.53 ± 0.32	5.74 ± 0.97	5.98 ± 1.31	6.24 ± 1.06	5.46 ± 0.41
SBC (mEq/L)	19.13 ± 1.46	18.25 ± 1.16 °	17.88 ± 1.13 °	17.75 ± 1.58 °	17.75 ± 1.58 °

ITP mm Hg	5	0	2	0
Time	5 minutes	control 3	5 minutes	control 4
BLOODT. (°C)	36.78 ± 0.83	36.6 ± 0.82	36.6 ± 0.83	36.45 ± 0.92
PCV	32.28 ± 4.66	33.01 ± 4.6	29.96 ± 1.81	30.39 ± 2.32 °
pH	7.17 ± 0.05 °	7.24 ± 0.04 °	7.17 ± 0.04 °	7.23 ± 0.07 °
$PaCO_2$ (mm Hg)	61.38 ± 7.11 °	47.5 ± 6.23	60.29 ± 5.82 °	50.43 ± 7.76 °
PaO_2 (mm Hg)	131 ± 63.94 °, |	334 ± 116.9 °	150 ± 95.75 °, |	328 ± 109.1 °
RR (breaths/min)	14.25 ± 5.09	13.13 ± 2.42	14.13 ± 2.47	13.38 ± 2.92
TV (mL)	324 ± 100.3	348 ± 40.27	358 ± 30.59	330 ± 37.03
Pinsp. (mm Hg)	22.50 ± 2.88 °	9.38 ± 2.26	21.63 ± 2.77 °	11.50 ± 3.02 °
CO_2% ET	5.71 ± 0.52	5.41 ± 0.41	5.51 ± 0.94	5.73 ± 0.66
SBC (mEq/L)	17.88 ± 1.46 °	18.75 ± 1.58	18.00 ± 1.41 °	18.71 ± 1.8

Data are expressed as mean ± standard deviation; ° significantly different from control 1 (p=0.05); | significantly different from 5 minutes after 3 mm Hg ITP (p=0.05);
Abbreviations of variables: see text.

DISCUSSION

Minimally invasive surgery techniques, including thoracoscopy are quickly gaining ground in human and veterinary medicine. Until recently, few studies were available about the applicable ventilation techniques for anaesthesia of dogs, pigs, sheep and horses during thoracoscopy (Fujita et al., 1993; Jones et al., 1993; Faunt et al., 1998; Vachon and Fischer, 1998; Peroni et al., 2000). Thoracoscopy requires general anaesthesia in dogs, sheep and pigs, whereas the technique can be performed in sedated standing horses. The basic procedure involves the introduction of a rigid or flexible fibreoptic endoscope into the thoracic cavity, and the use of air or another gas to create a pneumothorax allowing visualization of intrathoracic structures. If the animals are placed in lateral recumbency, it is necessary to collapse the upper lung. This can be achieved by two possible ventilation techniques: one lung ventilation (OLV) with passive lung collapse or two lung ventilation (TLV) with active lung collapse by gas insufflation.

During OLV selective ventilation of one lung is applied for which specific intubation including double-lumen tubes, endobronchial intubation or bronchial blockers is necessary. Positioning is technically difficult in dogs and sheep (Muneyuki et al., 1983; Fujita et al., 1993; Cantwell et al., 2000). Due to malpositioning (up to 30 %) in men routine bronchoscopy after double-lumen tube or bronchial blocker placement is certainly recommended. However, bronchoscopy is expensive, time consuming and not universally available (Kleine et al., 1998). Another technical problem is the limited use of commercially available tube systems for animals with smaller body weights such as cats and toy breed dogs. Furthermore, the potentially more

pronounced cardiopulmonary impact of OLV and TLV with gas insufflation in animals with smaller body weights has not yet been investigated.

Abdominal insufflation with gas is routine for laparoscopic procedures to produce the required viewing space. This insufflation has certainly adverse cardiopulmonary effects. The effects vary with the gas used, the presence or absence of mechanical ventilation, and the pressure and duration of insufflation (Johannsen et al., 1989; Windberger et al., 1994). With TLV for thoracoscopy insufflating the thorax minimally enhances the optical cavity; however, it must be applied with extreme caution. TLV with gas insufflation is seldom used in human anaesthesia for thoracoscopy because of occurring haemodynamic impairment (Brock et al., 2000).

Both ventilation techniques induce hypoxaemia since one lung is entirely collapsed and regions of atelectasis develop in the ventilated lung (Cohen et al., 1988). This induces ventilation-perfusion mismatches due to intra-pulmonary shunting. However, active vasoconstrictive mechanisms in the non-ventilated lung reduce the blood flow and minimize the shunt. This is the so-called hypoxic pulmonary vasoconstriction reflex. Several techniques can be applied to improve oxygenation during thoracoscopy: selective continuous airway pressure (CPAP) to the non-ventilated lung, positive end expiratory pressure (PEEP) to the ventilated lung, a combination of both or the use of high frequency ventilation to the non-dependent lung (Alfery et al., 1981; Benumof, 1982; Nakatsuka et al., 1988; Fujita et al., 1993).

Until now only two studies described TLV with gas insufflation in smaller animals. Faunt et al. (1998) examined the cardiopulmonary effects of TLV with N_2O insufflation for thoracoscopy in isoflurane anaesthetized dogs. In this study intrathoracic pressures were not measured, but were stated to be below 10 mm Hg. TLV with sustained pneumothorax was well tolerated in these clinically healthy dogs. In another study the effects on haemodynamic parameters of 5, 10 and 15 mm Hg of CO_2 insufflation during TLV were evaluated in isoflurane anaesthetized pigs (Jones et al., 1993). Routinely used positive pressure insufflation during thoracoscopy was not recommended because of the significant haemodynamic compromise in this experiment.

In the present study the cardiopulmonary effects of varying degrees of intrathoracic pressure elevation after CO_2-insufflation during 1.5 MAC sevoflurane anaesthesia in continuous two-lung ventilated dogs were examined. Conventional intubation was chosen to avoid the laborious difficulties of endobronchial intubation or bronchial blocker placement and to skip the need for specialized equipment. Three different levels of intrathoracic pressure elevation of the left hemi-thorax (3, 5 and 2 mm Hg) after CO_2-insufflation were evaluated during IPPV. The intrathoracic pressure level that induced a sufficient visualisation into the thorax and the least pronounced cardiopulmonary side effects was tested, since only one short communication about the maximum intrathoracic pressure increase (3 to 10 mm Hg) during thoracoscopy in dogs is available (Daly et al., 1999).

Inhalation anaesthetics including sevoflurane induce a dose-dependent cardiopulmonary depression in all animals (Bernard et al.,

1992; Aida et al., 1996; Grosenbaugh and Muir, 1998). The MAC of sevoflurane in dogs has been established to be 2.36 volume % (Kazama and Ikeda, 1988). One and a half MAC is generally accepted as the standard to allow most surgical interventions. However, some cases require a higher MAC when no supplementary analgesics or related drugs are administered during anaesthesia. Furthermore, several studies showed that 4% sevoflurane does not inhibit the hypoxic pulmonary vasoconstriction reflex in dogs (Domino et al., 1986; Okutomi and Ikeda, 1990). This specific characteristic might be justified in the present study because of the occurring ventilation-perfusion mismatches.

Fentanyl and propofol are relatively fast acting and short lasting agents. Interactions of these drugs after the instrumentation period of one hour with sevoflurane protocol were not likely to be present. However, although these drugs have a short half-life, it could not be excluded that their interfering effects were of longer duration. On the other hand, droperidol has relatively long lasting effects. A possible influence of droperidol can therefore not be ruled out (Bissonnette et al., 1999).

A fluid rate of 4 to 8 ml/ kg/ h is generally accepted for the maintenance of a stable water balance during anaesthesia (Giesecke and Egbert, 1985). No fluids were administered in the present study. Nevertheless, the thermodilution method includes the administration of different boli of saline. Overall, an estimated quantity of 2 to 4 ml/ kg/ h was administered during the whole experimental period. The influences of this relatively low fluid administration in this study were probably neglectable.

In the present study all direct cardiac parameters (blood pressures, CO, SV, SI, LVSWI) initially decreased significantly during ITP increase to 3, 5 and 2 mm Hg. Afterwards, there was a gradual correction of these parameters probably induced by the occurring hypercapnia (Walley et al., 1990). After lung re-expansion there was a clear overshoot in cardiac output and cardiac index related to the increased HR at that moment, since SV remained constant during this period. Heart rate, on the other hand, increased at the start of ITP increase at every level and increased even more after lung insufflation. The tachycardia could result from a sympathetic stimulation induced by a stress response related to the increase in $PaCO_2$ and/ or from stimulation of the baroreceptor-reflex due to a dose dependent decrease in blood pressure induced by sevoflurane in dogs (Cullen and Eger, 1974; Mutoh et al., 1997). These findings were in contrast with the results of Faunt et al. (1998). In this study an increase in CI, stroke volume index, MPAP and total peripheral vascular resistance was observed. Jones et al. (1993) and Daly et al. (1999), reported decreases in CO and arterial blood pressure in an analogue protocol, while HR remained relatively constant. The decrease in direct cardiac parameters in our study could be subsequent to the reduced venous return due to increased intrathoracic pressure, as described in humans, and/ or to a decreased myocardial contractility induced by sevoflurane anaesthesia (Mutoh et al., 1997; Brock et al., 2000; Polis et al., 2001). The reduced venous return is comparable with the one induced by a tension pneumothorax (Conolly, 1993; Light, 1994).

Right heart parameters (RAP, PAP, PCWP) and PVR increased significantly during intrathoracic pressure elevation at every level compared to values before CO_2-insufflation in the present study. This was consistent with previous studies (Jones et al., 1993; Faunt et

al., 1998). In contrast with the other right heart parameters, RVSWI decreased significantly during the first 10 minutes of 3 mm Hg ITP and then increased significantly after 15 minutes compared to 5 minutes after ITP rise. RVSWI increased at 5 and 2 mm Hg IT pressure compared to before CO_2-insufflation. The initial decrease in RVSWI is difficult to explain, since an increase was expected. This finding might be related to the position of the Swan-Ganz catheter either in the left or the right lung. The exact position of the catheter in the lung (ventilated or collapsed) was not checked. The increase in RAP, PAP, PCWP and PVR can be explained by the rise in pulmonary tissue pressure that leads to a decrease in pulmonary perfusion after CO_2-insufflation, as well as by hypoxic vasoconstriction in the collapsed pulmonary parenchyma (Ohtsuka, 1999). Large increases in intrathoracic pressure are presumed to decrease venous return and increase pulmonary vascular pressures so that stroke work and cardiac output are compromised, leading to hypotension and hypoperfusion (Lenaghan et al., 1969; Conolly, 1993).

SVR decreased significantly after CO_2-insufflation and remained low during the entire procedure. This could be partly explained by the vasodilating properties of sevoflurane, but also by the occurring hypercapnia during thoracoscopy. In a previous study SVR remained constant in 1.5 MAC sevoflurane anaesthetized dogs. A significant decrease in SVR was observed only at 2 MAC sevoflurane (Polis et al., 2001). The decreased SVR is consistent with the study of Faunt et al. (1998) where a small decrease in SVR was found. Jones et al. (1993) observed a constant SVR at low ITP (5 mm Hg), an increased SVR at 10 mm Hg and a decreased SVR at 15 mm Hg.

SpO_2 and PaO_2 decreased significantly after CO_2-insufflation, whereby the decrease was more rapid and pronounced after

consecutive ITP elevations compared to the first pressure rise. SpO_2 returned quickly to base line value after lung insufflations, but PaO_2 remained significantly lower even at the end of anaesthesia. This was also reported in analogue studies (Faunt et al., 1998; Daly et al., 1999). The phenomenon might be explained by an increased amount of blood flow due to the effect of gravity in the underlying lung, while its lung volume is decreased by compression of the mediastinal weight. This results in inefficient oxygenation of circulating blood due to ventilation/perfusion mismatch and blood shunting.

$PaCO_2$ increased significantly during CO_2-insufflation and continued to increase during the 15-minute period of intrathoracic pressure of 3 mm Hg despite constant ventilator settings. The increase could be related to the induced capnothorax (Peden and Prys-Roberts, 1993). In the study of Faunt et al. (1998) $PaCO_2$ increased also, although insufflation was done with N_2O, there was found no evidence of N_2O resorption from the thorax. Hypercapnia causes acidemia, resulting in decreased pH. In the present study the calculated P(a-A) CO_2 -gradient did not increase. The use of capnography and pulse oximetry is certainly recommended during thoracoscopic interventions because indirect moment-to-moment indications of $PaCO_2$ and haemoglobin saturation with oxygen are provided.

In conclusion, thoracoscopic procedures in sevoflurane (1.5 MAC) anaesthetized dogs with low pressure (2 mm Hg) CO_2-insufflation into one hemithorax allows safe visualization of the intrathoracic space for short periods. The thoracoscopic procedure should be accomplished in one short episode of CO_2-insufflation since additional insufflation periods can lead to more rapidly occurring and more pronounced cardiopulmonary depression.

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INTRODUCTION TO CHAPTERS 6/ 7/ 8

The use of sevoflurane is still rather expensive for veterinary practice. Therefore, methods inducing a decreased consumption of inhalant anaesthetic agent can be indicated to reduce anaesthetic costs. This can be achieved by reduction of fresh gas flows and/or by combination of inhalation anaesthesia with analgesic drugs. A "balanced anaesthesia" regimen combining potent opioids with sevoflurane should result in a MAC reducing effect and less anaesthetic agent. During the last decade, treatment of animal pain, its recognition, alleviation and subsequent prevention has gained increasing attention. This trend provides a relevant argument in support of adequate pain relief and the application of "balanced anaesthesia" techniques in general practice.

In order to obtain a method for beneficial cost optimisation and adequate pain relief when using sevoflurane, premedication with a long-acting sufentanil formulation was investigated. Hence, 40 dogs were enclosed in a study combining sevoflurane with sufentanil LA administered at different time intervals before induction of anaesthesia. The emphasis in this study was put on the antinociceptive and sedative effects of sufentanil LA and the dosage reducing effect on sevoflurane anaesthesia in dogs, since "pre-emptive analgesia" is nowadays considered as the keystone for post-operative pain relief (Chapter 8). In addition, potential influences on cardio-respiratory parameters when using this drug combination were evaluated in chapter 7. The administration of a long-acting formulation of sufentanil should facilitate pre- per- and post-operative analgesia in veterinary practice, because a single intramuscular injection could provide satisfactory pain relief during 24 hours.

To perform the study repeated blood pressure measurements and arterial blood sampling were necessary. Multiple femoral artery punctures were unfeasible and therefore catheter and vascular access port implantation was imposed (Chapter 6). Two possible techniques were considered: conventional externalised or totally implantable catheter systems. Conventional externalised catheter systems have a rate of complications that limits its clinical and animal experimental use. These complications have led to the development of the totally implantable catheter system. The system consists of a titanium port and a poly-urethane catheter. The port is implanted subcutaneously and can be accessed by a hypodermic needle. The totally implantable system gives only limited infection risks compared to the use of externalised catheters and was therefore preferred in our study.

CHAPTER 6

ARTERIAL CATHETERISATION AND VASCULAR ACCESS PORT IMPLANTATION FOR BLOOD SAMPLING AND CONTINUOUS BLOOD PRESSURE MEASUREMENT IN DOGS.

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SUMMARY

In the present study a modified method using coated polyurethane catheters into the femoral artery and a titanium vascular access port (VAP) with a silicone membrane was described in forty dogs. This device allowed repeated arterial blood pressure measurement and blood sampling in conscious and anaesthetised dogs for an average period of 2 weeks. Minor clinical influences nor catheter extraction were observed. On the other hand, infection with *Pseudomonas aeruginosa* induced by a contaminated flush solution was diagnosed in 4 dogs. These dogs recovered rapidly after an appropriate antibiotic therapy.

It was concluded that the described arterial catheterisation technique with vascular access port over a two weeks period was suitable and technically feasible for experimental protocols in dogs.

INTRODUCTION

Anaesthetic studies in experimental dogs often require repetitive blood sampling and blood pressure monitoring in unrestrained animals over a relatively long period of time. The repetitive puncture of arteries and veins or multiple consecutive peripheral catheter placement is accompanied by technical problems and stress responses, but also by iatrogenically induced damage of the blood vessels including thrombosis and sclerosis (Mesfin et al., 1988; Bagley and Flanders, 1990; Endres et al., 1990; Grosse-Siestrup and Lajous-Petter, 1990). Therefore, these methods are only suitable for the prelevation of a limited number of blood samples.

A potential option is the placement of a permanent intravenous or intra-arterial catheter combined with an implant, as mentioned in literature (Hai, 1982; Garner and Laks, 1985; Béliveau et al., 1990; Abrams-Ogg et al., 1992; Evans et al., 1994). However, maintaining chronically indwelling catheters and avoiding destruction, dislodgement, or infection of the catheters is often a challenge. Local infection, sepsis, migration, extravasation and early occlusion of the catheter are major complications of commonly used catheter implants (Evans et al., 1994). Therefore, antibiotics are essential to prevent infection after implantation. Furthermore, as in humans, aseptic conditions during surgery and blood sampling are also of major importance (Burrows, 1982; Vazques and Jarrad, 1984). The catheter and vascular access port patency demands frequent flushing with heparinised saline.

The aim of the present study was to describe a modified surgical arterial catheterisation technique in combination with the use of a vascular access port for repetitive blood sampling and blood pressure measurement during and after experimental anaesthetic protocols in dogs (Fig. 1).

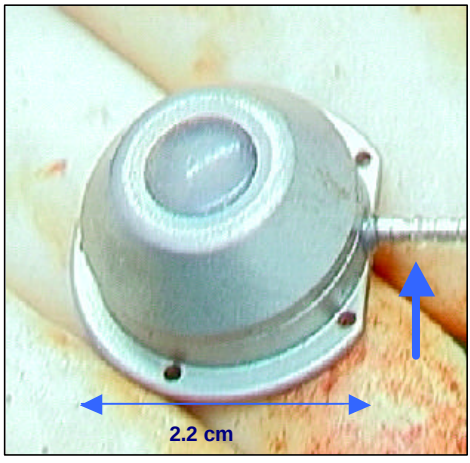


Fig.1. Vascular access port (Access™ Technologies, Skokie, USA)

→ Connection to the coated polyurethane catheter

Materials and Methods

The study was approved by the Ethical committee of the Faculty of Veterinary Medicine, Ghent University (filenumber: 39/2000). Forty adult female Beagles weighing 11.97 ± 1.40 kg (mean ± SD) from 1 to 2 years old were used in the study. The dogs were dewormed and vaccinated before the experiment. Clinical and blood examination one week before and the day of the experiment confirmed the good health status of the animals. Animals had free access to tap water and commercial dog food (Advance ™ Adult, Master Foods N.V., Belgium).

Anaesthetic protocol

The dogs were fasted 12 hours before surgical intervention. Acepromazine (0.05 mg/kg Placivet® 2%, Codifar N.V., Wommelgem, Belgium) was administered intramuscularly as premedication. Anaesthesia was induced 30 minutes later using propofol (4-6 mg/kg Rapinovet®, Mallinckrodt Veterinary, Aalst, Belgium) administered intravenously to effect. The dogs were intubated (endotracheal tube 6 mm ID, Rüsch, Germany) and connected to a commercial anaesthetic machine (Titus®, Dräger, Lübeck, Germany) with a circle system delivering 1 L/min of oxygen. The dogs breathed spontaneously throughout the surgical procedure. An anaesthetic gas analyser (Capnomac Ultima®, Datex Engstrom Instrumentation Corp., Helsinki, Finland) and pulse oximeter (N-20PA Portable Pulse Oximeter®, Nellcor Puritan Bennett Inc., Pleasanton, CA, U.S.A.) were used for non-invasive monitoring. No intravenous infusions were administered during anaesthesia.

Anaesthesia was maintained with propofol administered intravenously by an infusion pump (Ohmeda 9000 Syringe pump®,

Ohmeda, West Yorkshire, UK) at a dosage of 0.5 mg/kg/min. Analgesia and anaesthesia of the hind quarters was assured with an epidural technique using a 50/50 (v/v) mixture of lidocain 2% (Xylocaine® 2%, Astra Zeneca, Brussels, Belgium) and bupivacain 0.5% (Marcaine® 0.5%, Astra Zeneca, Brussels, Belgium) at a dosage of 1 ml/4 kg of body weight. Two dogs received half of the epidural dosage because the subarachnoidal space was punctured. For additional postoperative analgesia, the dogs were treated with carprofen (4 mg/kg PO) during 3 days, starting the day before surgery. The dog received a single injection of amoxicillin long acting (15 mg/kg SC) (Duphamox LA, Fort Dodge Animal Health Benelux, Brussel, Belgium) the day of catheter implantation.

Surgical procedure

After the dogs had been placed in left lateral recumbency, the right inguinal area, the medial side of the right knee and the backside of the dogs were surgically prepared. A 60 cm coated polyurethane catheter (Hydrocoat ™ Catheter 3.5 Fr; Access ™ Technologies, Skokie, USA) with a bead at 8 cm from the catheter tip and filled with heparinised saline (5 IU/ ml of Heparine®, Leo, Belgium) was used for arterial catheterisation. The catheter tip was transected obliquely and was grasped with a forceps (Semkin dressing forceps) for better handling. The catheter was occluded at the free end with a haemostatic clamp to prevent bleeding when inserting it to the femoral artery. A 4 cm incision was made through skin and subcutis above the femoral groove. The femoral artery was exposed by separation of the sartorius and gracilis muscles starting in the femoral triangle. The artery was freed from the femoral nerve and vein by blunt dissection (Fig. 2). Hence, the femoral artery was elevated and occluded during the surgical handling by gentle pulling on 2 sutures (Safil® green 3/0, B/Braun, Melsungen, Germany) positioned under the artery (Fig. 3).

Topical lidocain was administered to counteract the induced iatrogenic vasospasm of the femoral artery during handling. A small hole was made into the artery with a 19 gauge needle (19 G x 1"; 1.1 x 25 mm; Terumo Europe N.V., Leuven, Belgium) and the catheter tip was inserted into the artery towards the aorta for about 8 cm (Fig. 4). The proximal suture was used to fix the artery around the inserted catheter (Fig. 5). An additional suture was placed immediately behind the bead to assure an adequate ligation of the artery and the distal suture was used to ligate the femoral artery to the bead.

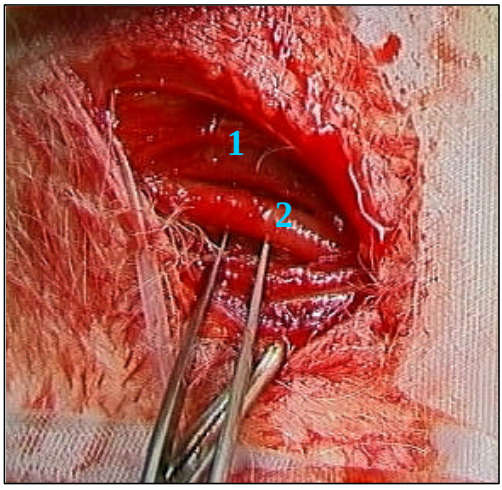


Fig.2. Surgical exposition of the femoral artery

1/ femoral vein and nerve

2/ femoral artery

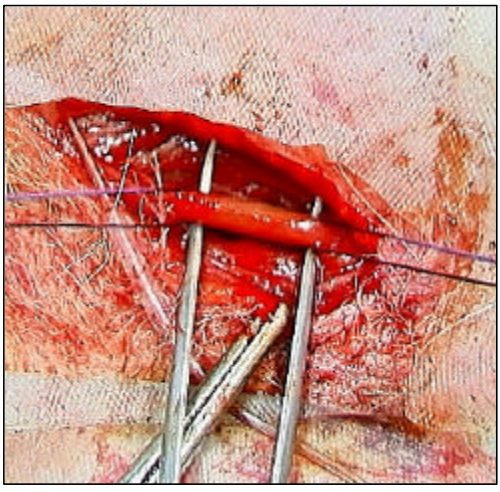


Fig.3. Elevation of the femoral artery by 2 stay sutures

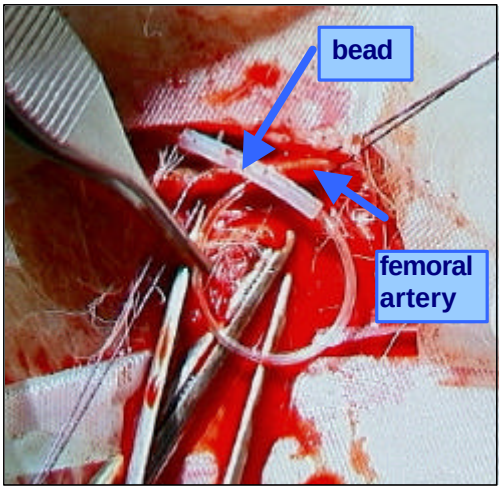


Fig.4. Insertion of the catheter into the femoral artery

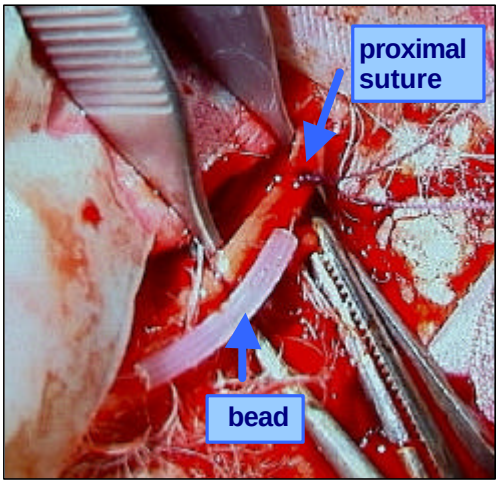


Fig.5. Ligation of the femoral artery around the inserted catheter

A second skin incision was made medial of the knee. The catheter was pulled subcutaneous from the femoral triangle to the knee with an atraumatic forceps (straight Rochester-Carmalt Haemostatic forceps). The catheter was secured using a single subcutaneous suture at the medial level of the knee. Finally a paramedian incision was made proximal from the ilium on the back of the dog. A small amount of subcutaneous fat was prelevated allowing

the formation of a suitable pocket for the titanium vascular access port (Access ™ Technologies, Skokie, USA). The catheter was tunnelled further subcutaneously from the knee to the backside of the dog with the same atraumatic forceps (Fig. 6). The vascular port was attached to the catheter allowing enough length for a so called tension loop around the port (Fig. 7-8). Catheter patency was tested using heparinised saline and a Huber point needle (Posi-Grip Huber Point Needle 22 gauge x 0-3/4'', Access ™ Technologies, Skokie, USA) placed through the silicone membrane of the vascular access port. The vascular access port was sutured with 3 single sutures (Safil® green 3/0, B/Braun, Melsungen, Germany) into the subcutaneous tissue.

After a final control of permeability, the catheter was filled with heparinised saline (200 IU/ml) and all skin incisions were closed with Safil® (fig. 9). The catheters and implants were removed 17.9 ± 8.7 days after implantation (mean ± SD) under a standardised isoflurane anaesthesia.

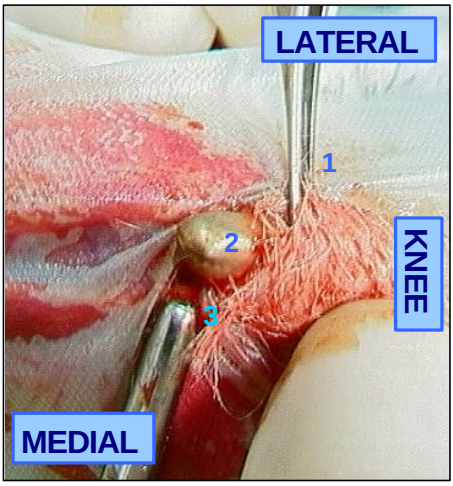


Fig. 6. Subcutaneous tunneling from the medial knee incision to the lumbar incision

1/ Subcutaneous tunnelling

2/ Top of the atraumatic forceps

3/ Katheter

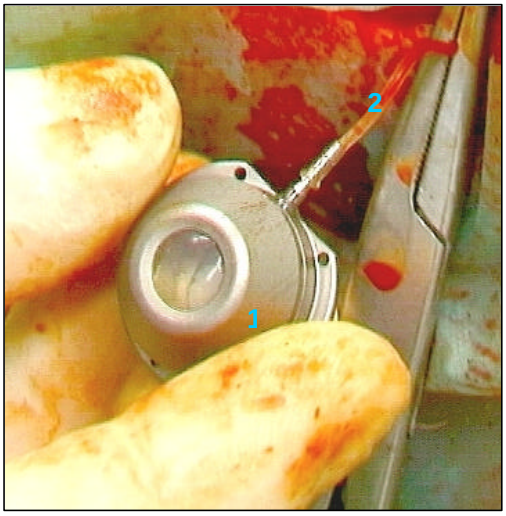


Fig.7. Attaching the vascular access port to the catheter

1/ vascular access port

2/ coated polyurethane catheter

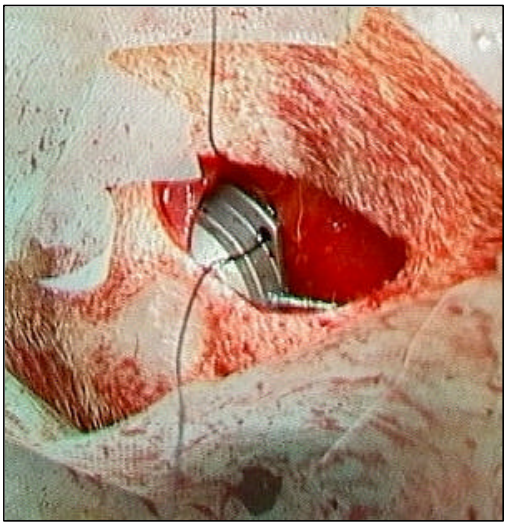
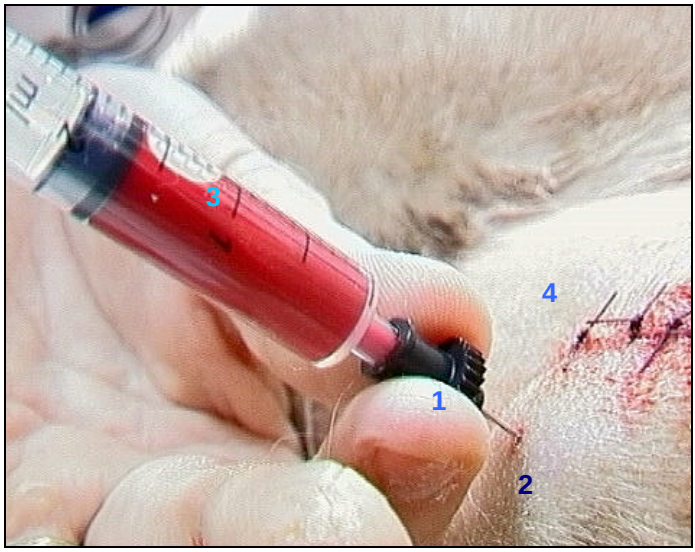


Fig. 8. Insertion of the vascular access port in a subcutaneous pocket

Fig.9. Testing of catheter patency



1/ Huber point needle 2/ Vascular access port 3/ Arterial blood sample

4/ Lumbar incision site

Experimental design

A haemodynamic study was carried out 2 to 6 days after catheter and vascular access port implantation. Measurements were performed during 24 hours. The arterial catheter was flushed percutaneously through the silicone membrane of the VAP every two days before the experiment with 1 ml of heparinised saline (200 IU/ml). The vascular access port was used for arterial blood pressure measurement at several time points. This was done by perforating the membrane of the port through the skin with a Huber point needle. The needle was connected to an extension tube filled with heparinised saline and a pressure transducer (Vascumed N.V., Gent, Belgium) placed at the level of the heart. Mean, systolic and diastolic blood pressure was measured (Hellige Servomed SMV 104®, Germany).

Arterial blood for blood gas analysis was sampled using the same method.

Clinical observation and examination

A clinical examination was done and rectal temperature of the dogs was recorded on a daily basis.

RESULTS

Anaesthesia and surgery were uneventful. The surgical implantation time ranged from 35 to 75 minutes. All 40 dogs tolerated the sampling procedures (14 samples in 24 hours) well without external signs of discomfort. Blood sampling and blood pressure measurement were successful and easy to perform in all dogs.

Several complications were encountered. An inadvertent implantation of the catheter into the femoral vein was diagnosed in one dog. This dog had a swelling of the hind leg and venous blood (PaO_2: 33 mm Hg) could be sampled from the vascular access port. The catheter was removed and a period of one month was respected before a new catheter could be implanted into the femoral artery of the same side without problems. Another dog was lame in the surgically treated hind leg the day of the experiment, however without pain or swelling. Lameness disappeared spontaneously within 4 days without therapy. One dog removed the sutures of the inguinal wound without damaging the arterial catheter. The wound was sutured again under local anaesthesia with lidocain (Xylocaine® 2%, Astra, Brussel, Belgium). Finally, a seroma occurred around the VAP in one of the dogs and was surgically treated by placing a Penrose drain (Penrose Tubing, Sherwood Medical, Tullamore, Ireland) after removal of the

VAP. The swelling caused no difficulties for blood sampling or blood pressure measurement.

Mean rectal temperature of all dogs was 39.3 ± 0.48°C on the day of the experiment (2 to 6 days after catheter implantation). Four dogs had fever (more than 40.0°C) one to two days after catheter implantation. However, on clinical examination no signs of lameness or inflammation on the catheter site were observed in these dogs. Samples for bacteriologic examination were taken from the heparinised flush solution used in these dogs. Contamination of the solution with *Pseudomonas aeruginosa* was found by a bacteriologic culture. An appropriate antimicrobial therapy guided by an antibiogram was done for 5 to 10 days with enrofloxacine SC (5 mg/kg/day, Baytril® 5%, Bayer, Leverkusen, Germany) and resulted in full clinical recovery. The arterial catheter and vascular access port of one of these dogs showed no bacteriological growth after surgical removal.

The catheters remained patent in all animals for at least 4.2 ± 2.2 days (mean ± SD). After the experiment the catheters were not further flushed in order to have an obstructed catheter by time of removal 17.9 ± 8.7 days after implantation (mean ± SD). This facilitated catheter removal, which could be done without an additional ligation of the femoral artery. After removal of catheters and vascular access ports skin incisions healed rapidly. No specific problems induced by the ligation of the femoral artery were encountered over time.

DISCUSSION

In the present study a permanent arterial catheter and totally implantable vascular access port system were inserted into the femoral artery of dogs for repetitive arterial blood sampling and invasive arterial blood pressure measurement at several time intervals during experimental procedures. The surgical technique was slightly modified from previously published studies (Garner and Laks, 1985; Grosse-Siestrup and Lajous-Petter, 1990; Evans et al., 1994).

Coated polyurethane catheters in combination with titanium vascular access ports were used in the present study. Compared to polyvinyl chloride, silicone and Teflon catheters, heparinised polyurethane were proven to be the least thrombogenic of all materials (Solomon et al., 1987). Moreover, silicone carries a greater risk for subcutaneous infection and induces a greater inflammation and kinking risk (Sheretz et al., 1995). In the present study, the catheter was inserted for about 8 cm into the femoral artery. Immediately after surgical handling of the artery a marked collapse of the vessel was observed making the insertion of the catheter difficult. Topical lidocain was administered to counteract the iatrogenically induced vasospasm (Wadstrom and Gerdin, 1991; Kim et al., 1996). To facilitate catheter implantation the catheter tip was cut off obliquely in combination with an opening in the vessel wall. Efficiency of catheter placement improved with experience. No problems of the hind limb vascularisation were observed after occlusion of the distal part of the femoral artery. Most likely a sufficient amount of collateral vessels assured an adequate circulation of the hind limb rapidly (Schaper and Ito, 1996). All catheters remained patent during the experiment. The incision wounds healed rapidly in the majority of the

dogs, particularly the femoral wound. This was also reported in similar studies (Hai, 1982).

The vascular access port consisted of a titanium base with multiple holes for securing it to the surrounding tissue and a central silicone diaphragm for puncturing. Multiple membrane punctures are guaranteed without vascular access port leakage when using Huber point needles with off-centre tips. The port was secured on the lumbar region away from the femoral incision in a separate pocket to minimize the potential for incisional swelling, pain or inflammation from interfering with multiple port punction. The lumbar port position was also facilitating blood sampling. In other studies the vascular access port was implanted in the right hemi-cervical region of the dogs facilitating access to the jugular vein (Evans et al., 1994).

Blood sampling and blood pressure measurement was easy requiring only minimal restraint. In most trained animals one person could do the blood sampling; the assistance of a second person was only necessary in nervous dogs. For blood pressure measurement previous flushing with heparinised saline was advisable to get a sharp blood pressure waveform on the haemodynamic monitor.

The rectal temperature remained within acceptable ranges in most dogs. However, some dogs had a transient slightly increased temperature after catheter implantation. The impact of anaesthesia and surgery and the implantation of a foreign body (catheter and VAP) had certainly an impact on the body temperature. A slight transient increase in body temperature was also observed in similar studies after intravenous catheterisation in pigs (Van Leengoed et al., 1987; Pijpers et al., 1989). Four dogs had an abnormal and persistent

increase in body temperature (> 40°C) without signs of lameness or local infection around the femoral artery or vascular access port. In human studies the most likely mechanism for catheter infection was reported to be caused by the normal bacterial skin flora, which can gain access during implantation of the catheter (Eykeyn, 1984). The aetiology of the infection in the present study was a contamination of the heparinised saline solution with *Pseudomonas aeruginosa*, although the flush solution was prepared weekly and stored aseptically. After an appropriate antibiotic treatment with enrofloxacine complete recovery was obtained. However, the anaesthetic experiment was postponed for several days until the body temperature of the dogs returned to normal values. Heparin solution was renewed daily to prevent this phenomenon. Occasionally and successfully treated bacteraemia were also observed in similar studies describing totally implantable catheter systems in dogs (Grosse-Siestrup and Lajous-Petter, 1990).

Other problems such as suture removement and seroma formation were of minor clinical importance and were easily treated using standard techniques (Garner and Laks, 1985). Since the distal part of the femoral artery was occluded, the artery could probably not be reused for the same purpose afterwards.

In conclusion, the above described modified arterial catheterisation technique with vascular access port is suitable and technically feasible for experimental haemodynamic protocols in dogs. This catheter system can be applied to improve the well-being of experimental animals, to facilitate experimental work, to simplify serial blood sampling. However, proper handling and aseptic blood sampling procedures are prerequisites.

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CHAPTER 7

PERIANAESTHETIC CARDIOPULMONARY, SEDATIVE AND ANTINOCICEPTIVE EFFECTS OF A LONG ACTING FORMULATION OF SUFENTANIL ADMINISTERED BEFORE SEVOFLURANE ANAESTHESIA IN DOGS.

PART I. CARDIOPULMONARY EFFECTS

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SUMMARY

The purpose of the present study was to evaluate the haemodynamic effects of sufentanil long acting premedication in sevoflurane anaesthetized dogs in an open randomised study. Forty dogs were divided over 5 parallel groups of 8 dogs each. Two control groups were used: one group of dogs (A) received sufentanil long acting (50 µg/kg IM) and a second group (B) the sufentanil vehicle followed by a standard inhalation anaesthesia of 90 minutes. After premedication with sufentanil long acting immediately before (C^0), 15 minutes (D^{15}) or 30 minutes (E^{30}) before induction with thiopental (IV) the dogs were anaesthetized for 90 minutes with sevoflurane in oxygen.

Heart rate (HR), direct mean arterial blood pressure (MAP), respiration rate (RR), arterial oxygen haemoglobin saturation (SaO_2) and sevoflurane concentration were measured every 10 minutes during anaesthesia and at 2, 4 and 24 hours after initiation of anaesthesia. Acid-base and blood gas analyses were performed at the same time points.

The present study showed that premedication with sufentanil LA followed by sevoflurane anaesthesia enhanced moderately some cardiopulmonary side effects accompanying clinically adjusted sevoflurane anaesthesia. The addition of sufentanil LA as premedication caused a decrease in heart rate and an increase in $PaCO_2$, while MAP was well maintained. The clinical importance is probably limited during inhalation anaesthesia where a high inspired oxygen fraction resulted in high PaO_2 and SaO_2 levels. Temporary support of ventilation with IPPV however might be occasionally necessary. Thirty minutes between sufentanil LA premedication and

induction of anaesthesia might be preferable, since less respiratory depression occurred in group E^{30}. In the post-anaesthetic period the bradycardia persisted and was still present after 24 hours. Although RR was lower then the control group without sufentanil pretreatment, $PaCO_2$ and PaO_2 were within an acceptable range in the postanaesthetic period up to 24 hours.

INTRODUCTION

The search for an optimal method to control acute pre-, per- and post-operative pain in veterinary medicine is still ongoing. Opioids are still of enormous therapeutic importance as the drug of choice for the treatment of moderate to severe pain. The major action of opioids is analgesia by binding to specific receptors (µ, ?, d, s, e) localised mainly in the brain and spinal cord (Pert and Snyder, 1973; Stein, 1993). In general, the clinically most effective opioids act selectively at µ receptors (Nolan, 2000). Intermittent administration of short-acting opioids on an as-needed basis leads to peaks and troughs in drug plasma level. Coupled to an inadequate dosage or too lengthy dosing intervals this can lead to insufficient control of peri- and postoperative pain (Oden, 1989; Sinatra, 1991). Pre-anaesthetic drugs classically include anticholinergics, tranquilizers or a2-agonists, but nowadays opioids are often included in the premedication protocol because of their analgesic characteristics (Taylor, 1999). The clinical advantage is a dosage reduction of the drugs used for general anaesthesia which eventually leads to improved patient safety (Brunner et al., 1994; Moon et al., 1995). Furthermore administration of analgesics before the surgical stimulus arises (pre-emptive analgesia) is thought to be important for better control of postoperative pain (Lascelles et al., 1995).

The problems associated with intermittent administration of short-acting opioids might be overcome with the intramuscular administration of a potent opioid in a long-acting formulation. Such a drug could than be used as premedication, providing effective pre-emptive analgesia over an extended period of time including the postanaesthetic period. The opioid sufentanil is a short-acting thiamyl analogue of the μ-agonist fentanyl ($T_{1/2}$ = 2 - 2.5 hours), but it is 11.5 times more potent (Brunner et al., 1994). It is used as an anaesthetic supplement to provide analgesia in balanced anaesthesia protocols in men. The clinical use of a balanced anaesthetic protocol using sufentanil and midazolam in dogs has been reported (Hellebrekers and Sap, 1991).

A long acting formulation of sufentanil (on a medium chain triglyceride base) has been investigated in several preclinical studies (Engelen et al., 1996a; Engelen et al., 1996b; Engelen et al., 1996c; Short and Vlaminck, 1998; Verbeeck et al., 1998). The dosage and the pharmacokinetic profile were confirmed in a dose finding trial and the safety was assessed in a tolerance study (Verbeeck et al., 1998; Hoeben et al., 1999; Sterkens, 1999). After intramuscular administration of 50 μg/kg BWT plasma levels of sufentanil very rapidly increased and peak levels around 1.53 ± 0.45 ng/ml were observed around 6 hours after injection. After this peak, the plasma concentration of sufentanil slowly decreased. The $T_{1/2}$ was 15.8 ± 5.1 hours. A dosage of 50 μg/kg of sufentanil LA provided plasma levels between 0.85 and 1.5 ng sufentanil/ml for at least 12 hours (Short, 1996).

In these studies sufentanil LA induced not only sedation but also the typical opioid side-effects such as reductions in heart rate, arterial blood pressure, rectal temperature, respiratory rate, and an increase in arterial carbon dioxide tension (Abdul-Rasool et al., 1989;

Werner et al., 1991; Engelen et al., 1996a; Engelen et al., 1996b; Engelen et al., 1996c; Short, 1996; Short and Vlaminck, 1998; Verbeeck et al., 1998; Hoeben et al., 1999; Sterkens et al., 1999). A classic anaesthetic technique to provide surgical anaesthesia in veterinary medicine consists in an intravenous induction of anaesthesia and subsequent maintenance by delivering a volatile agent with oxygen.

Thiopental, a short acting barbiturate and a popular veterinary induction agent, is known to induce induction apnoea, respiratory acidosis and hypoxaemia (Rawlings and Kolata, 1983; Muir, 1998a; Muir, 1998b). It also affects the cardiovascular system with hypotension, bradycardia followed by reflex tachycardia, hypertension and arrhythmias (Muir, 1998a; Muir, 1998b). Sevoflurane is a halogenated hydrocarbon developed by Wallin et al. (1975). In Europe it is commercially available as an inhalant anaesthetic for men since the early nineties. It is also used as a volatile anaesthetic in animals and its use in this field is expected to increase in the future. Like all volatile anaesthetics it also affects the cardiovascular and respiratory system (Mutoh et al., 1997; Polis et al., 2001a; Polis et al., 2001b). In a previous study in sevoflurane anaesthetized dogs dose dependent decreases in blood pressure, cardiac output, stroke volume and respiration rate in combination with an increase in arterial carbon dioxide tension were observed (Polis et al., 2001a).

Because the proposed therapeutic dose of sufentanil LA (50 µg/kg) is known to depress several cardiovascular and respiratory parameters, the use of sufentanil LA premedication before thiopental induction and sevoflurane as anaesthetic maintenance is expected to enhance cardiovascular and respiratory side-effects of the general anaesthetics. The present study was done to evaluate cardiovascular

status and gas exchange during and following clinically conducted sevoflurane anaesthesia when sufentanil LA was used as a premedication administered at different time points before induction.

MATERIALS AND METHODS

The study was approved by the Ethical committee of the Faculty of Veterinary Medicine, Ghent University (filenumber: 39/2000). Forty adult female Beagles weighing 11.97 ± 1.40 kg (mean ± SD) from 1 to 2 years old were used in the study. The dogs were dewormed and vaccinated 1 month before the experiment. Clinical examination one week before the experiment confirmed the good health status of the animals.

Study Protocol

The present study was an open randomised study with 40 dogs divided over 5 parallel groups. The study was conducted in 40 phases; each phase consisted of 1 dog monitored 24 hours after the administration of the drugs. No blinding was performed.

Table 1: Study groups involved in the study of sufentanil LA followed by sevoflurane anaesthesia in dogs (n=40).

STUDY GROUP	No. of DOGS	SUFENTANIL (µg/kg)	Time interval between sufentanil/vehicle administration and initiation of inhalation anaesthesia
A (control suf)	8	50	*
B (control sevo)	8	0 (vehicle)	§
C^{0}	8	50	0
D^{15}	8	50	15
E^{30}	8	50	30

* Dogs receive no inhalation anaesthesia, but only sufentanil at T_0

§ Dogs receive sufentanil-vehicle and inhalation anaesthesia at T_0

Initiation of inhalation anaesthesia was defined as T_0; except for group A

Time expressed in minutes

The dogs in group A (control suf) received sufentanil LA at T_0 without inhalation anaesthesia. The dogs from group B (control sevo) received only the sufentanil-vehicle at T_0 followed by inhalation anaesthesia. In groups C^0, D^{15} and E^{30} a time interval of respectively 0, 15 and 30 minutes between sufentanil LA administration and anaesthesia induction was respected (Table 1).

Preparation of the dogs

A titanium vascular access port with a silicone membrane (Access Technologies, Skokie, IL, USA) connected to the femoral artery was surgically implanted 3 to 6 days before each experiment. This device was used for blood sampling and blood pressure measurement. Anaesthesia for this procedure consisted in a total intravenous protocol with propofol combined with epidural anaesthesia using lidocaine and bupivacaine. Analgesia was supplemented with carprofen given at a dosage of 4 mg/kg orally for 3 days, starting the evening before surgery. Patency of the vessel access port was controlled by daily flushing with 1 ml of heparinised saline (200-300 I.U. heparin per ml). Three to five days after the experiment the port was surgically removed under isoflurane anaesthesia.

Premedication and Induction of Anaesthesia

The dogs of groups A, C^0, D^{15} and E^{30} received sufentanil long acting formulation (sufentanil (0.5 mg/ml); Janssen Animal Health, Beerse, Belgium) at a dosage of 50 µg/kg of BWT administered IM in the lumbar muscles. The dogs of group B received only sufentanil-vehicle. Anaesthesia (group B, C^0, D^{15} and E^{30}) was induced with thiopental (Pentothal®, Abbott Laboratories Ltd., Queenborough, UK). Four mg/kg was injected as a bolus and further dosing was slowly done to effect. “Effect” was defined as the moment that eyeballs

rotated ventrally and that intubation could be easily performed. Mean injection dose was 13.3 ± 2.5 mg/kg of BWT.

Maintenance of Anaesthesia

The dogs were positioned in lateral recumbency and connected to an anaesthetic machine with a circle system (Titus®, Dräger, Lübeck, Germany) and a sevoflurane out of circuit vaporiser (Vapor 19.3®, Dräger, Lübeck, Germany). The anaesthetic circuit was flushed with 100% oxygen for 5 minutes before the experiment. During the first 5 minutes of anaesthesia, a fresh gas flow of 2 l/min O_2 was used which was subsequently reduced to 1 l/min. The dogs breathed spontaneously, but manual ventilation was performed when marked respiratory depression occurred ($PaCO_2$ > 55 mm Hg and/or RR< 15 breaths/min). During anaesthesia the percentage of sevoflurane was adjusted to obtain and maintain an anaesthetic depth suitable to perform surgical interventions much like it would have been done in clinical conditions. Such a level was thought to exist when the eye-lid reflex was absent and the eyeballs were ventrally rotated. Moreover a standardised pain stimulus was administered by clamping the tail for 5 seconds every 10 minutes at a distance of approximately 3 cm from its top with a straight Rochester-Carmalt haemostatic forceps (10 cm) closed to the first ratchet lock. If a reaction (a movement, and/or an increase in HR of more than 15%) was observed, vaporizer settings were adjusted upwards with 0.5% on the vaporizer scale. If no reaction occurred, vaporizer settings were decreased step wise. Depth of anaesthesia was also controlled by observation of eye-lid reflex and position of the eyeballs and if necessary adjusted. Anaesthesia was continued for 90 minutes. No intravenous infusions were administered during the study.

Measurements and monitoring

A calibrated multigas analyser including a pulse oximetry unit (Quick Cal TM calibration gas® and Capnomac Ultima®, Datex Engstrom Instrumentation Corp., Helsinki, Finland) was used to monitor heart rate (HR), respiratory rate (RR), end tidal CO_2%, inspiratory and end tidal sevoflurane concentration and peripheral oxygen haemoglobin saturation (SpO_2%). MAP was recorded using a blood pressure transducer (Vascumed N.V., Gent, Belgium) connected to a blood pressure measuring device (Hellige Servomed SMV 104, Germany) following standard calibration procedure. The pressure transducer was connected to the vascular access port using extension tubing filled with heparinised saline (200-300 I.U. heparin per ml) and fitted with a special Huber point needle (Access Technologies, Skokie, IL, USA) used to perforate the silicone membrane of the vascular access port. Arterial blood was sampled through the vascular access port. The arterial oxygen (PaO_2 in mm Hg) and carbon dioxide tension ($PaCO_2$ in mm Hg), pH and arterial oxygen saturation (SaO_2 in %) were measured immediately after sampling with a calibrated blood gas analyser and corrected for body temperature (ABL 5®, Radiometer Copenhagen, Denmark).

All parameters were measured immediately before intramuscular administration of sufentanil LA or the vehicle, immediately before inhalation anaesthesia (T_0; except group A), and every 10 minutes during 90 minutes of inhalation anaesthesia. The same measurements were continued in the post anaesthetic period at 120 minutes (T_{120}), 240 minutes (T_{240}) and 24 hours (T_{1440}).

At the end of inhalation anaesthesia, the dogs breathed oxygen until extubation was possible. The dogs were transferred to the recovery box. If the rectal temperature was lower than 36°C, an

infrared heating source was installed in the recovery box. The occurrence of critical events was recorded in the time period T_0 to T_{1440} when predetermined limits were surpassed. Critical values of each parameter are represented in Table 2.

Table 2: Limits of the presence of critical events in the study of sufentanil LA followed by sevoflurane anaesthesia in dogs (n=40).

PARAMETER	LIMIT CRITICAL VALUE
Heart Rate	< 45 beats/min
Mean Arterial Blood Pressure	< 75 mm Hg
Respiratory Rate	< 15 breaths/min
$PaCO_2$	> 55 mm Hg
PaO_2	< 75 mm Hg
pH	< 7.25
Arterial O_2 Saturation	< 90 %

Abbreviations : see text.

Statistical Analysis

The dogs were sorted according to decreasing body weight and divided into 8 classes of 5 dogs each. In each class, the body weights were comparable. Within each class the 5 dogs were randomly allocated to the five different study groups and the 40 phases by a computer randomisation program. The statistical tests were two-sided and used a 0.05 type I error (α=5%). The StatXact software (StatXact 3 For Windows (1995), Users Manual, CYTEL Software, Cambridge, MA 02139 USA) was used for the Kruskal-Wallis one-way analysis of variance tests, for the Wilcoxon Mann-Whitney U tests and for the Fisher's exact tests (Siegel,1977).

The treatment groups A (control suf) and B (control sevo) were control groups. No statistics were done for these groups, since the effects of sufentanil LA and sevoflurane are studied previously in dogs (Bernard et al., 1990; Engelen et al., 1996a; Engelen et al., 1996b; Engelen et al., 1996c; Short, 1996; Short and Vlaminck, 1998; Verbeeck et al., 1998; Hoeben et al., 1999; Sterkens et al., 1999). The body weights of the dogs were compared by means of the Kruskal-Wallis one-way analysis of variance test to check the randomisation procedure.

To evaluate the homogeneity of the several treatment groups, baseline comparisons (T_0) was also performed on HR, MAP, RR, pH and blood gases of each treatment group by means of the Kruskal-Wallis one-way analysis of variance test. For each parameter (HR, MAP, RR, $PaCO_2$, PaO_2, pH, SaO_2) the following tests were performed: statistical comparisons on the mean over time (T_0 to T_{90}) was performed between the treatment groups C^0, D^{15} and E^{30} by means of the Kruskal-Wallis one-way analysis of variance test followed by two-by-two Wilcoxon Mann-Whitney U tests. Each of the treatment groups C^0, D^{15} and E^{30} was compared with the control groups A and B by Wilcoxon Mann-Whitney U tests.

The individual time points after inhalation anaesthesia (T_{120}, T_{240} and T_{1440}) were analysed in the same way as the variable mean over time. The number of dogs with a critical event was calculated. The amounts of dogs with a critical parameter value were used to compare the treatment groups by means of the Fisher's exact test.

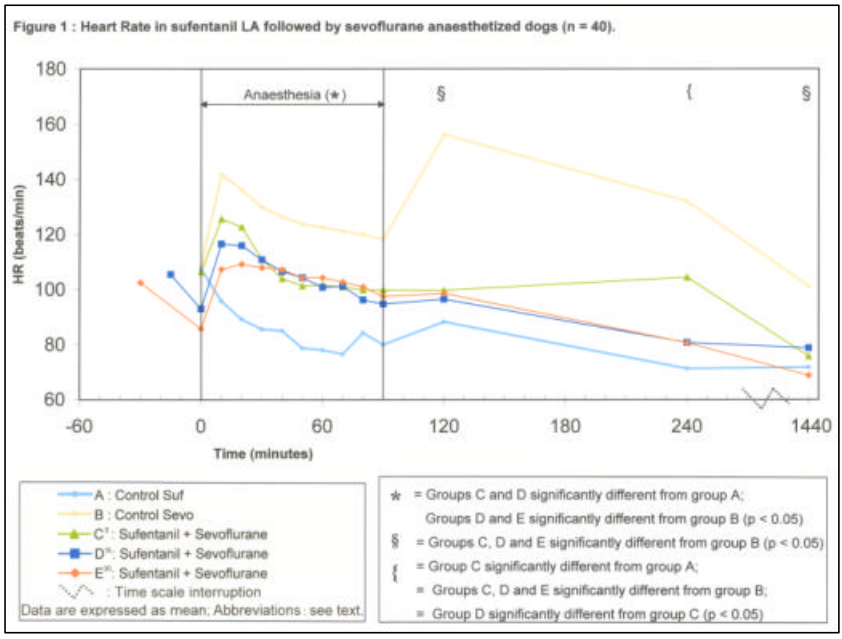
RESULTS

Results for different measured variables are given in Table 3 and 4 and Figures 1 to 6. No significant differences in baseline values per study group and per parameter were observed. The analgesic and sedative effects of sufentanil LA and the side effects which occurred in this experiment will be discussed in a second paper.

Anaesthesia period (T_0 to T_{90})

HR was significantly lower in sufentanil treated inhalation groups D^{15} and E^{30} compared to group B (control sevo) ($p<0.01$). HR was significantly lower in group A (control suf) compared to groups C^0 and D^{15} ($p<0.05$). Minimum and maximum (min-max) values for HR were 52 (group A at T_{60}) and 155 (group B at T_0) beats/minute respectively. MAP was similar in all inhalation groups (B, C^0, D^{15} and E^{30}). MAP was lower in all inhalation groups compared to group A and this difference was significant for groups C^0, D^{15} and E^{30} ($p<0.001$). Min-max values for MAP were 36 (group B at T_{90}) and 137 (group C^0 at T_0) mm Hg. RR was similar in all inhalation groups (B, C^0, D^{15}, E^{30}). RR was higher in group A compared to all inhalation groups and this difference was significant for groups C^0, D^{15} and E^{30} ($p<0.001$ and $p<0.01$). Min-max for RR were 2 (group D^{15} at T_{10}) and 160 (group A at T_{20}) breaths/minute. $PaCO_2$ was higher in the sufentanil treated inhalation groups compared to group B (control sevo) but this was significant for group C^0 and D^{15} only ($p<0.01$). $PaCO_2$ was also significantly higher in groups C^0 and D^{15} compared to group E^{30} ($p<0.01$). $PaCO_2$ was higher in all inhalation groups compared to group A and this difference was significant for groups C^0, D^{15} and E^{30} ($p<0.001$ and $p<0.01$). Min-max values of $PaCO_2$ were 21 (group C^0 at T_0) and 74 (group D^{15} at T_{10}) mm Hg. PaO_2 was similar in all inhalation

groups (B, C^0, D^{15} and E^{30}) and significantly higher compared to group A ($p<0.01$). No significant differences between sufentanil treated inhalation groups and group B (control sevo) occurred. Min-max values of PaO_2 were 63 (group B at T_0) and 605 (group B at T_{70}) mm Hg. SaO_2 values in the inhalation groups were similar. SaO_2 was higher in the inhalation groups compared to group A and this difference was significant for groups C^0, D^{15} and E^{30} ($p<0.001$); no differences were observed compared to group B (control sevo). SaO_2 values in the inhalation groups were similar. Min-max values of SaO_2 were 88 (group C^0 at T_0) and 100 (all groups) %. pH was significantly lower in groups C^0, D^{15} and E^{30} compared to groups A and B ($p<0.001$ and $p<0.01$). pH min-max values were 7.10 (group E^{30} at T_{10} and T_{20}; group C^0 at T_{10}) and 7.42 (group C^0 at T_0 and group A at T_{90}).



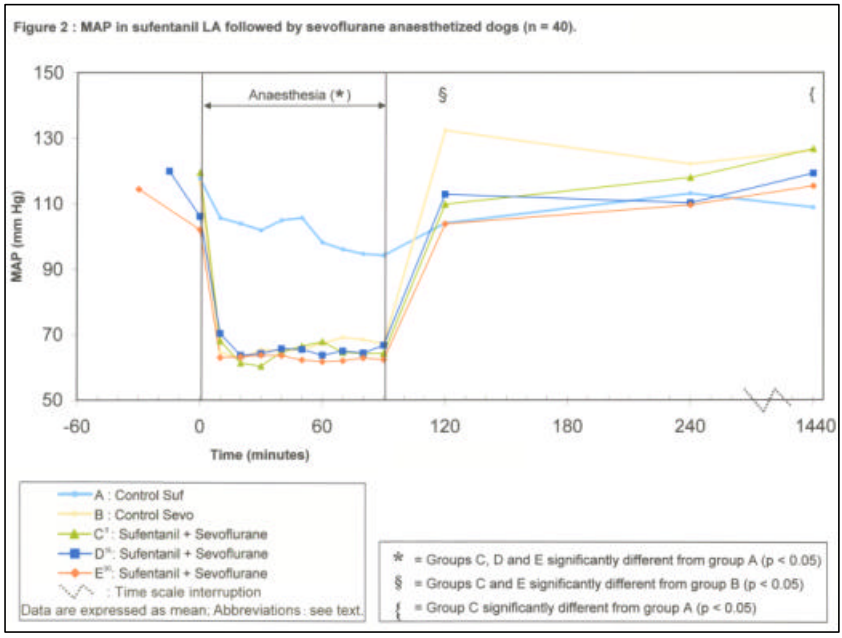


Figure 2 : MAP in sufentanil LA followed by sevoflurane anaesthetized dogs (n = 40).
MAP (mm Hg)
150
130
110
90
70
50
Anaesthesia (*)
§
{
-60
0
60
120
180
240
1440
Time (minutes)
A : Control Suf
B : Control Sevo
C¹ : Sufentanil + Sevoflurane
D¹ᵇ : Sufentanil + Sevoflurane
E¹ᵇ : Sufentanil + Sevoflurane
: Time scale interruption
Data are expressed as mean; Abbreviations : see text.
* = Groups C, D and E significantly different from group A (p < 0.05)
§ = Groups C and E significantly different from group B (p < 0.05)
{ = Group C significantly different from group A (p < 0.05)

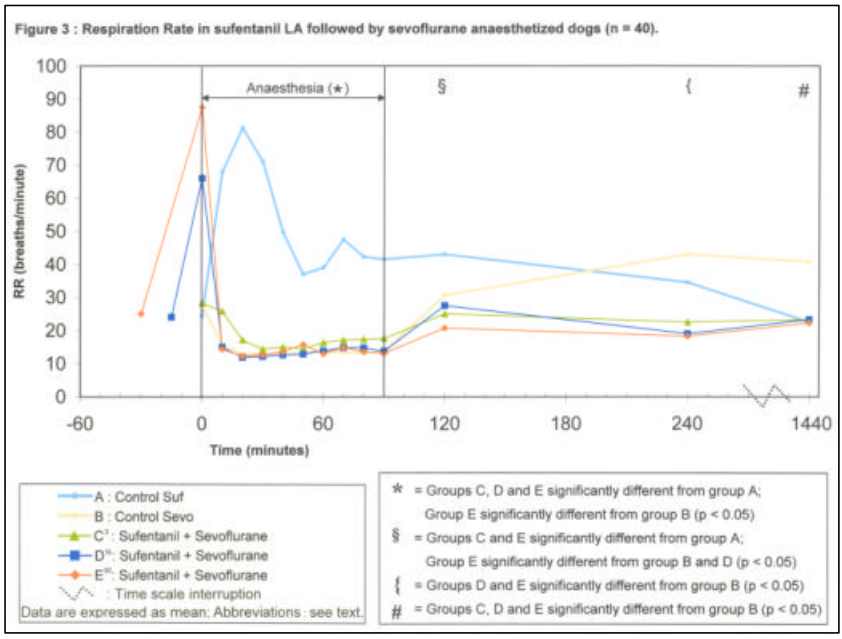


Figure 3 : Respiration Rate in sufentanil LA followed by sevoflurane anaesthetized dogs (n = 40).
RR (breaths/minute)
100
90
80
70
60
50
40
30
20
10
0
Anaesthesia (*)
§
{
#
-60
0
60
120
180
240
1440
Time (minutes)
A : Control Suf
B : Control Sevo
C¹ : Sufentanil + Sevoflurane
D¹ᵇ : Sufentanil + Sevoflurane
E¹ᵇ : Sufentanil + Sevoflurane
: Time scale interruption
Data are expressed as mean; Abbreviations : see text.
* = Groups C, D and E significantly different from group A;
Group E significantly different from group B (p < 0.05)
§ = Groups C and E significantly different from group A;
Group E significantly different from group B and D (p < 0.05)
{ = Groups D and E significantly different from group B (p < 0.05)
= Groups C, D and E significantly different from group B (p < 0.05)

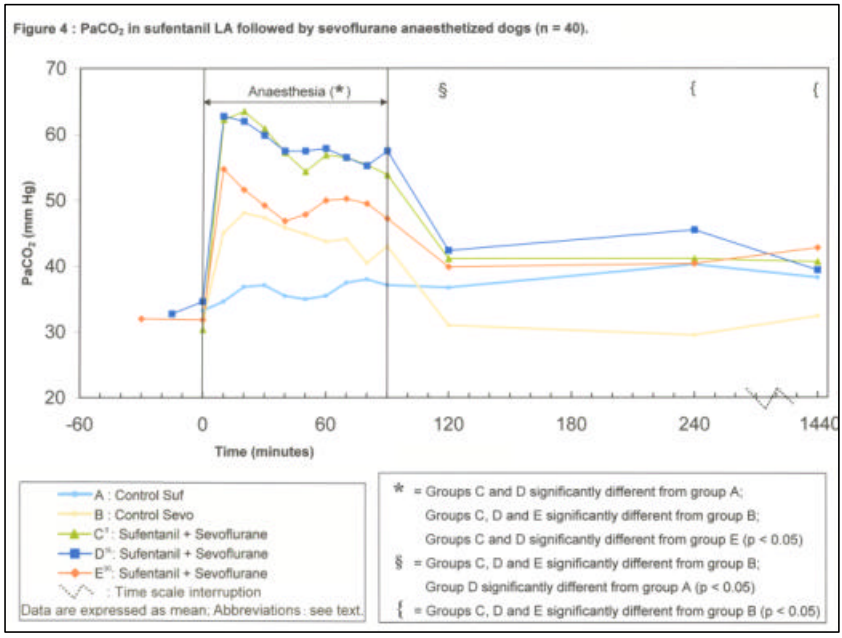


Figure 4 : PaCO2 in sufentanil LA followed by sevoflurane anaesthetized dogs (n = 40).
70
60
50
40
30
20
PaCO2 (mm Hg)
Anaesthesia (*)
§
{
{
-60
0
60
120
180
240
1440
Time (minutes)
A : Control Suf
B : Control Sevo
C†: Sufentanil + Sevoflurane
D‰: Sufentanil + Sevoflurane
E‰: Sufentanil + Sevoflurane
: Time scale interruption
Data are expressed as mean; Abbreviations : see text.
* = Groups C and D significantly different from group A;
Groups C, D and E significantly different from group B;
Groups C and D significantly different from group E (p < 0.05)
§ = Groups C, D and E significantly different from group B;
Group D significantly different from group A (p < 0.05)
{ = Groups C, D and E significantly different from group B (p < 0.05)

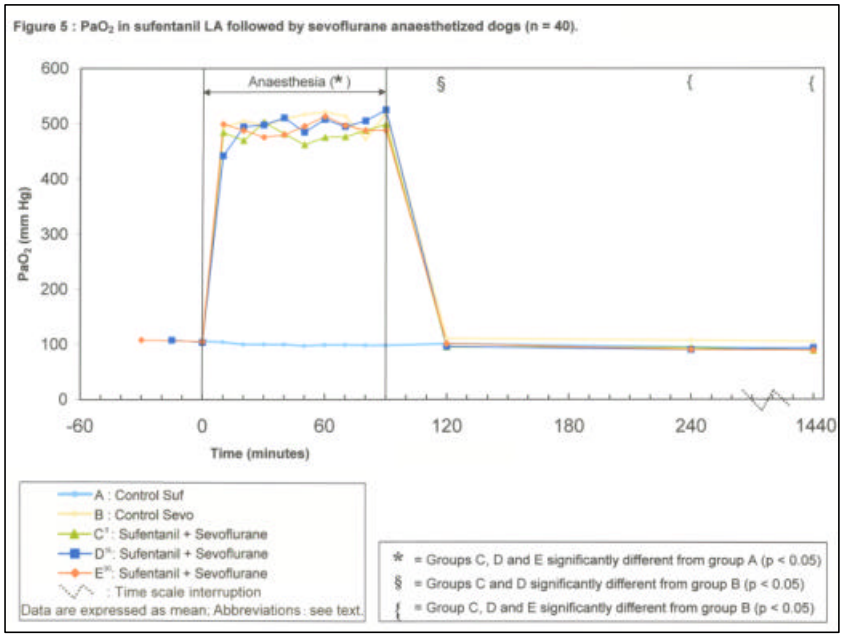
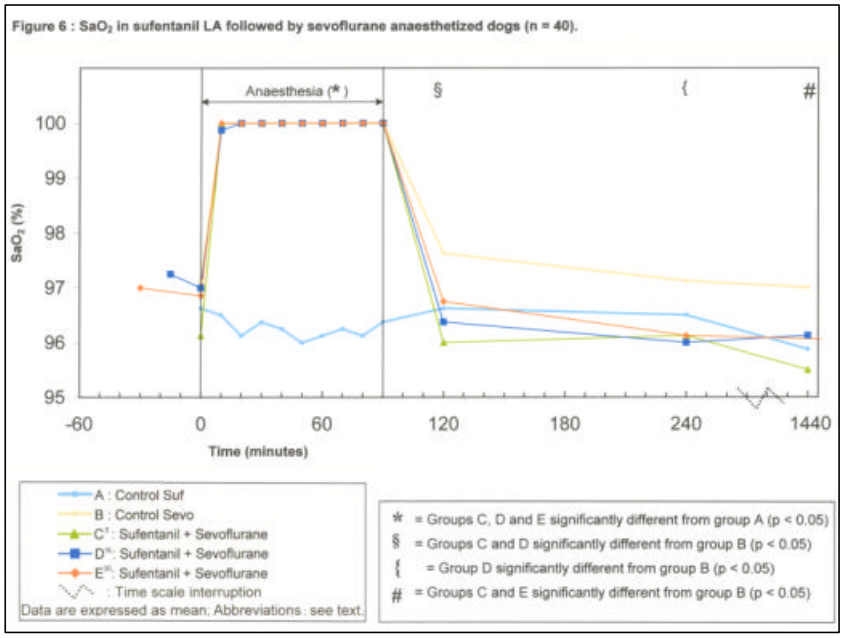


Figure 5 : PaO2 in sufentanil LA followed by sevoflurane anaesthetized dogs (n = 40).
600
500
400
300
200
100
0
PaO2 (mm Hg)
Anaesthesia (*)
§
{
{
-60
0
60
120
180
240
1440
Time (minutes)
A : Control Suf
B : Control Sevo
C†: Sufentanil + Sevoflurane
D‰: Sufentanil + Sevoflurane
E‰: Sufentanil + Sevoflurane
: Time scale interruption
Data are expressed as mean; Abbreviations : see text.
* = Groups C, D and E significantly different from group A (p < 0.05)
§ = Groups C and D significantly different from group B (p < 0.05)
{ = Group C, D and E significantly different from group B (p < 0.05)



Post-anaesthetic period (T_{120} to T_{1440})

HR was significantly lower at all time points in the sufentanil treated inhalation groups C^0, D^{15} and E^{30} compared to group B (control sevo) ($p<0.05$ to $p<0.001$). HR was not significantly different between these groups except in group D^{15}, where HR was significantly lower compared to group C^0 at time point T_{240} ($p<0.05$). HR was not significantly different between sufentanil treated inhalation groups C^0, D^{15} and E^{30} and group A (control suf) except for time point T_{240} where HR in group C^0 was significantly higher ($p<0.01$). Min-max values for HR were 44 (group E^{30} at T_{240}) and 170 (group B at T_{120}). MAP was lower in all sufentanil treated groups compared to group B (control sevo). At T_{120} this difference was statistically significant when compared with groups C^0 and E^{30} ($p<0.01$ and $p<0.001$). At T_{1440} MAP in group C^0 was significantly higher compared to group A (control suf). Min-max values for MAP were between 71 (group A at T_{120}) and 165 (group C^0 at T_{1440}) mm Hg.

Table 3A : Cardiopulmonary effects in sufentanil LA and sevoflurane anaesthetized dogs (n=40).

	Groups	T=presuf	T=0	T=10	T=20	T=30	T=40	T=50
HR beats per minute	Group A	107.5 ± 6.1	107.5 ± 6.1	95.9 ± 7.7	89.3 ± 3.9	85.6 ± 5.6	85.0 ± 6.6	78.8 ± 5.7
	Group B	109.0 ± 6.1	109.0 ± 6.1	141.8 ± 3.4	136.3 ± 3.3	129.9 ± 4.1	126.5 ± 3.7	123.8 ± 2.8
	Group C	106.5 ± 7.1	106.5 ± 7.1 *	125.6 ± 6.6 *	122.8 ± 6.5 *	111.0 ± 9.0 *	104.0 ± 8.4 *	101.4 ± 7.5 *
	Group D	105.5 ± 3.8	93.0 ± 4.4 *,|	116.6 ± 5.1 *,|	116.0 ± 6.5 *,|	110.9 ± 6.2 *,|	106.6 ± 5.9 *,|	104.4 ± 5.5 *,|
	Group E	102.5 ± 5.0	85.8 ± 4.8 |	107.4 ± 8.4 |	109.3 ± 8.6 |	108.0 ± 7.2 |	107.3 ± 6.1 |	104.4 ± 6.3 |
MAP mm Hg	Group A	117.8 ± 3.4	117.8 ± 3.4	105.8 ± 3.1	104.0 ± 4.2	102.0 ± 4.3	105.0 ± 2.3	105.8 ± 2.2
	Group B	116.4 ± 2.8	116.4 ± 2.8	64.6 ± 3.4	62.5 ± 3.7	65.5 ± 4.2	65.0 ± 3.8	65.5 ± 4.3
	Group C	119.6 ± 3.2	119.6 ± 3.2 *	68.1 ± 2.0 *	61.4 ± 3.6 *	60.4 ± 2.6 *	64.8 ± 1.6 *	66.5 ± 1.6 *
	Group D	120.0 ± 4.5	106.3 ± 2.8 *	70.4 ± 2.9 *	63.8 ± 3.1 *	64.3 ± 3.3 *	65.8 ± 3.4 *	65.5 ± 3.2 *
	Group E	114.5 ± 8.1	102.1 ± 5.6 *	63.0 ± 3.4 *	63.3 ± 2.8 *	63.8 ± 2.8 *	63.6 ± 3.4 *	62.3 ± 3.9 *
RR breaths per minute	Group A	24.3 ± 1.7	24.3 ± 1.7	68.0 ± 15.7	81.3 ± 14.9	71.0 ± 10.9	49.8 ± 7.2	37.0 ± 7.3
	Group B	27.8 ± 1.1	27.8 ± 1.1	15.6 ± 2.4	12.9 ± 0.6	13.1 ± 1.4	13.0 ± 1.3	13.4 ± 1.6
	Group C	28.3 ± 2.6	28.3 ± 2.6 *	25.8 ± 5.8 *	17.1 ± 4.8 *	14.4 ± 4.0 *	15.0 ± 3.9 *	14.5 ± 3.6 *
	Group D	24.0 ± 1.7	66.0 ± 19.7 *	15.0 ± 4.2 *	11.9 ± 2.3 *	12.1 ± 1.9 *	12.6 ± 2.3 *	12.9 ± 2.6 *
	Group E	25.0 ± 2.9	87.5 ± 13.9 *,|	14.4 ± 2.4 *,|	12.3 ± 1.9 *,|	12.6 ± 1.9 *,|	13.6 ± 2.2 *,|	15.8 ± 4.1 *,|

Data are expressed as mean ± standard deviation. * significantly different from group A ($p < 0.05$)

| significantly different from group B ($p < 0.05$); § significantly different from group D ($p < 0.05$).

Table 3B : Cardiopulmonary effects in sufentanil LA and sevoflurane anaesthetized dogs (n=40).

	Groups	T=60	T=70	T=80	T=90	T=120	T=240	T=1440
HR beats per minute	Group A	78.0 ± 6.4	76.5 ± 5.8	84.3 ± 8.3	80.0 ± 6.7	88.3 ± 6.3	71.3 ± 5.8	71.8 ± 4.3
	Group B	122.6 ± 3.5	121.3 ± 3.4	120.0 ± 3.6	118.3 ± 3.6	156.3 ± 3.7	132.0 ± 7.9	101.3 ± 7.5
	Group C	101.6 ± 7.5 *	101.0 ± 7.8 *	99.9 ± 7.9 *	99.9 ± 8.7 *	99.8 ± 9.2 |	104.5 ± 7.1 *,|	75.8 ± 5.3 |
	Group D	100.9 ± 5.4 *,|	101.3 ± 6.7 *,|	96.3 ± 4.7 *,|	94.8 ± 4.3 *,|	96.5 ± 9.0 |	80.8 ± 5.3 |	78.8 ± 8.4 |
	Group E	104.4 ± 6.1 |	102.8 ± 6.1 |	101.0 ± 5.3 |	97.5 ± 4.7 |	98.6 ± 7.2 |	80.6 ± 8.0 |	68.8 ± 5.5 |
MAP mm Hg	Group A	98.3 ± 2.7	96.1 ± 3.6	94.8 ± 3.3	94.3 ± 2.4	104.1 ± 6.9	113.1 ± 3.5	108.9 ± 4.4
	Group B	67.4 ± 4.4	69.1 ± 4.6	68.5 ± 5.0	67.1 ± 5.1	132.4 ± 4.0	122.1 ± 2.9	126.3 ± 2.4
	Group C	67.9 ± 2.4 *	64.6 ± 2.3 *	64.3 ± 2.9 *	64.3 ± 3.0 *	109.9 ± 4.5 |	118.0 ± 5.8	126.8 ± 6.4 *
	Group D	63.8 ± 3.4 *	65.0 ± 3.2 *	64.4 ± 3.3 *	66.8 ± 3.5 *	112.9 ± 7.4	110.3 ± 4.8	119.3 ± 7.1
	Group E	61.8 ± 2.5 *	62.0 ± 3.0 *	62.9 ± 3.2 *	62.4 ± 3.5 *	103.9 ± 4.1 |	109.6 ± 5.6	115.4 ± 8.0
RR breaths per minute	Group A	39.0 ± 5.7	47.5 ± 10.8	42.3 ± 10.4	41.5 ± 6.7	43.0 ± 9.1	34.5 ± 14.0	22.5 ± 2.4
	Group B	13.9 ± 1.3	13.4 ± 1.2	13.1 ± 1.0	13.6 ± 1.1	30.6 ± 3.1	43.0 ± 16.8	40.8 ± 6.5
	Group C	16.4 ± 3.0 *	17.1 ± 3.0 *	17.4 ± 3.3 *	17.6 ± 3.5 *	25.0 ± 3.7 *	22.5 ± 2.8	23.3 ± 2.5 |
	Group D	13.9 ± 2.4 *	14.9 ± 2.5 *	14.8 ± 2.7 *	13.8 ± 2.0 *	27.5 ± 3.0	19.0 ± 1.5 |	23.3 ± 1.6 |
	Group E	13.0 ± 2.5 *,|	14.9 ± 3.3 *,|	13.6 ± 2.8 *,|	13.1 ± 2.5 *,|	20.8 ± 2.1 *,|, §	18.3 ± 1.8 |	22.3 ± 1.6 |

Data are expressed as mean ± standard deviation. * significantly different from group A ($p < 0.05$)

| significantly different from group B ($p < 0.05$); § significantly different from group D ($p < 0.05$).

Table 4A : Acid-base balance and blood gas analysis in sufentanil LA and sevoflurane anaesthetized dogs (n=40).

		T=control	T=0	T=10	T=20	T=30	T=40	T=50
PaO_2	A	105.6 ± 3.8	105.6 ± 3.8	104.3 ± 3.5	100.0 ± 2.9	100.1 ± 2.1	99.9 ± 4.1	97.4 ± 2.4
mm Hg	B	107.3 ± 2.0	107.3 ± 2.0	493.5 ± 19.0	505.0 ± 20.3	497.4 ± 16.8	509.0 ± 14.7	516.8 ± 18.6
	C	105.4 ± 6.4	105.4 ± 6.4 *	484.5 ± 12.4 *	469.9 ± 15.7 *	503.3 ± 16.5 *	481.9 ± 20.9 *	462.1 ± 20.1 *
	D	107.8 ± 1.4	103.8 ± 2.2 *	442.3 ± 38.0 *	494.4 ± 11.5 *	498.1 ± 14.8 *	510.8 ± 10.2 *	484.9 ± 15.5 *
	E	108.0 ± 2.1	105.0 ± 2.4 *	499.5 ± 12.9 *	488.0 ± 24.2 *	475.9 ± 25.0 *	480.1 ± 26.5 *	495.8 ± 16.0 *
SaO_2	A	96.6 ± 0.3	96.6 ± 0.3	96.5 ± 0.4	96.1 ± 0.4	96.4 ± 0.3	96.3 ± 0.5	96.0 ± 0.3
%	B	97.1 ± 0.2	97.1 ± 0.2	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
	C	96.1 ± 1.2	96.1 ± 1.2 *	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *
	D	97.3 ± 0.2	97.0 ± 0.2 *	99.9 ± 0.1 *	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *
	E	97.0 ± 0.2	96.9 ± 0.3 *	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *
pH	A	7.37 ± 0.01	7.37 ± 0.01	7.35 ± 0.01	7.34 ± 0.01	7.33 ± 0.01	7.34 ± 0.01	7.34 ± 0.01
	B	7.34 ± 0.01	7.34 ± 0.01	7.26 ± 0.01	7.25 ± 0.01	7.25 ± 0.01	7.26 ± 0.01	7.27 ± 0.01
	C	7.36 ± 0.01	7.36 ± 0.01 *,|	7.17 ± 0.02 *,|	7.16 ± 0.02 *,|	7.18 ± 0.02 *,|	7.20 ± 0.01 *,|	7.20 ± 0.01 *,|
	D	7.36 ± 0.01	7.34 ± 0.01 *,|	7.17 ± 0.01 *,|	7.17 ± 0.01 *,|	7.19 ± 0.01 *,|	7.20 ± 0.01 *,|	7.21 ± 0.01 *,|
	E	7.34 ± 0.01	7.31 ± 0.02 *,|	7.17 ± 0.02 *,|	7.19 ± 0.02 *,|	7.20 ± 0.01 *,|	7.22 ± 0.02 *,|	7.22 ± 0.02 *,|
$PaCO_2$	A	33.3 ± 0.9	33.3 ± 0.9	34.6 ± 0.9	36.9 ± 1.4	37.1 ± 1.3	35.5 ± 1.2	35.0 ± 1.4
mm Hg	B	31.9 ± 0.7	31.9 ± 0.7	45.1 ± 3.2	48.1 ± 1.7	47.4 ± 1.9	45.9 ± 1.5	44.9 ± 1.7
	C	32.8 ± 1.0	32.8 ± 1.0 *,|,§	34.6 ± 0.6 *,|,§	62.8 ± 1.9 *,|,§	62.0 ± 1.9 *,|,§	59.9 ± 1.2 *,|,§	57.5 ± 1.7 *,|,§
	D	32.8 ± 1.0	34.6 ± 0.6 *,|,§	62.8 ± 3.1 *,|,§	62.0 ± 1.9 *,|,§	59.9 ± 1.2 *,|,§	57.5 ± 1.7 *,|,§	57.5 ± 1.7 *,|,§
	E	32.0 ± 1.1	31.9 ± 1.9 |	54.8 ± 1.6 |	51.6 ± 2.8 |	49.3 ± 2.8 |	46.9 ± 3.3 |	47.9 ± 3.3 |

Data are expressed as mean ± standard deviation. * significantly different from group A ($p < 0.05$)

| significantly different from group B ($p < 0.05$); § significantly different from group E ($p < 0.05$).

Table 4B : Acid-base balance and blood gas analysis in sufentanil LA and sevoflurane anaesthetized dogs (n=40).

		T=60	T=70	T=80	T=90	T=120	T=240	T=1440
PaO_2	A	98.9 ± 2.5	98.9 ± 2.5	98.3 ± 3.0	98.1 ± 4.4	101.0 ± 3.0	94.9 ± 2.8	91.5 ± 2.5
mm Hg	B	521.8 ± 14.4	513.6 ± 19.2	472.1 ± 27.2	519.9 ± 15.8	110.6 ± 1.3	107.3 ± 3.1	104.9 ± 2.6
	C	475.4 ± 32.8 *	476.4 ± 13.9 *	487.8 ± 25.0 *	498.8 ± 13.7 *	95.3 ± 2.5 |	93.6 ± 1.9 |	88.3 ± 2.4 |
	D	508.0 ± 12.1 *	494.9 ± 16.4 *	505.1 ± 15.8 *	525.0 ± 10.2 *	96.1 ± 2.4 |	90.0 ± 1.3 |	93.5 ± 3.4 |
	E	513.5 ± 18.4 *	497.0 ± 19.6 *	488.0 ± 21.6 *	487.8 ± 22.3 *	101.4 ± 4.1	90.3 ± 3.0 |	89.0 ± 1.5 |
SaO_2	A	96.1 ± 0.4	96.3 ± 0.3	96.1 ± 0.4	96.4 ± 0.4	96.6 ± 0.3	96.5 ± 0.3	95.9 ± 0.6
%	B	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	97.6 ± 0.2	97.1 ± 0.2	97.0 ± 0.2
	C	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *	96.0 ± 0.3 |	96.1 ± 0.4	95.5 ± 0.6
	D	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *	96.4 ± 0.3 |	96.0 ± 0.2 |	96.1 ± 0.4
	E	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *	100.0 ± 0.0 *	96.8 ± 0.5 |	96.1 ± 0.4	96.0 ± 0.3
pH	A	7.33 ± 0.01	7.33 ± 0.01	7.34 ± 0.01	7.34 ± 0.01	7.32 ± 0.01	7.31 ± 0.01	7.34 ± 0.01
	B	7.27 ± 0..01	7.28 ± 0.01	7.28 ± 0.02	7.28 ± 0.01	7.34 ± 0.01	7.35 ± 0.01	7.35 ± 0.01
	C	7.20 ± 0.01 *,|	7.20 ± 0.01 *,|	7.21 ± 0.01 *,|	7.21 ± 0.01 *,|	7.28 ± 0.02 |	7.28 ± 0.01 |	7.31 ± 0.01 |
	D	7.21 ± 0.01 *,|	7.21 ± 0.01 *,|	7.22 ± 0.01 *,|	7.21 ± 0.01 *,|	7.28 ± 0.01 |	7.26 ± 0.01 *,|	7.33 ± 0.01
	E	7.22 ± 0.02 *,|	7.22 ± 0.02 *,|	7.22 ± 0.02 *,|	7.23 ± 0.02 *,|	7.26 ± 0.01 *,|	7.26 ± 0.01 *,|	7.33 ± 0.01
$PaCO_2$	A	35.5 ± 1.0	37.5 ± 2.5	38.0 ± 3.0	37.1 ± 2.9	36.8 ± 2.0	40.3 ± 2.1	38.3 ± 2.0
mm Hg	B	43.8 ± 1.5	44.1 ± 1.6	40.5 ± 2.2	43.0 ± 1.6	31.0 ± 0.7	29.5 ± 1.1	32.4 ± 1.0
	C	57.5 ± 1.7 *,|,§	57.9 ± 1.2 *,|,§	56.5 ± 0.9 *,|,§	55.3 ± 1.5 *,|,§	57.5 ± 1.6 |	42.4 ± 1.8 |	39.4 ± 1.6 |
	D	57.9 ± 1.2 *,|,§	56.5 ± 0.9 *,|,§	55.3 ± 1.5 *,|,§	57.5 ± 1.6 *,|,§	42.4 ± 1.8 *,|	45.5 ± 1.7 |	39.4 ± 1.6 |
	E	50.0 ± 3.0 |	50.3 ± 2.1 |	49.5 ± 2.5 |	47.3 ± 2.2 |	39.9 ± 1.7 |	40.4 ± 3.0 |	42.8 ± 1.4 |

Data are expressed as mean ± standard deviation. * significantly different from group A ($p < 0.05$)

| significantly different from group B ($p < 0.05$); § significantly different from group E ($p < 0.05$).

Following the end of inhalation anaesthesia RR increased in all groups. RR was lower in sufentanil treated inhalation groups compared to group B (control sevo). This difference was significant at T_{120} for group E^{30} ($p<0.05$) , at T_{240} for groups D^{15} and E^{30} ($p<0.01$) and at T_{1440} for groups C^{0}, D^{15} and E^{30} ($p<0.05$ and $p<0.01$). There was no significant difference between the sufentanil treated inhalation groups; except at T_{120} where group E^{30} had a lower RR compared to D^{15} ($p<0.05$). Respiratory rate in group A (control suf) was higher than in the sufentanil treated inhalation groups in the post-anaesthetic period. This difference was significant at T_{120} compared to groups C^{0} and E^{30} ($p<0.05$ and $p<0.01$). The min-max values for RR were 12 (1 dog in groups A, C^{0}, D^{15} and E^{30} at T_{240}) and 160 (group B at T_{240}) breaths/minute. Following the end of inhalation anaesthesia $PaCO_2$ decreased rapidly in all groups until T_{120} and remained stable for the remainder of the post-anaesthetic period. $PaCO_2$ was significantly higher in the sufentanil treated inhalation groups compared to group B (control sevo) at all time points ($p<0.001$ and $p<0.05$). $PaCO_2$ in group A (control suf) was similar as in the sufentanil treated inhalation groups; except at T_{120} where $PaCO_2$ was significantly higher in group D^{15} compared to A ($p<0.05$). Min-max values for $PaCO_2$ were 25 (group B at T_{240}) and 54 (group D^{15} at T_{240}). Following the end of inhalation anaesthesia PaO_2 decreased rapidly to baseline values in all groups. PaO_2 was lower in the sufentanil treated inhalation groups compared to group B (control sevo). This difference was significant at all time points (at T_{120} not for group E^{30}) (from $p<0.05$ to $p<0.001$). No significant differences existed between the sufentanil treated inhalation groups (C^{0}, D^{15} and E^{30}) and group A (control suf). Min-max values for PaO_2 were 75 (group C^{0} at T_{1440}) and 122 (group B at T_{240}) mm Hg. SaO_2 was lower in the sufentanil treated inhalation groups compared to group B (control sevo). At time point T_{120} the difference

was significant for group C^0 and D^{15} ($p<0.01$ and $p<0.05$), at T_{240} for group D^{15} ($p<0.01$) and at T_{1440} for groups C^0 and E^{30} ($p<0.05$). No significant differences existed between the sufentanil treated inhalation groups (C^0, D^{15} and E^{30}) and group A (control suf). Min-max values for SaO_2 were 92 (group A and C^0 at T_{1440}) and 99 (group E^{30} at T_{120}) %. pH was significantly lower in the sufentanil treated inhalation groups compared to group B (control sevo) at all time points ($p<0.05$ to $p<0.001$); except for groups D^{15} and E^{30} at T_{1440}. pH in group A (control suf) was higher compared to the other sufentanil groups; but this was only significant for group E^{30} at T_{120} and T_{240} and for group D^{15} at T_{240}. Min-max values for pH were 7.22 (group D^{15} at T_{120} and group E^{30} at T_{120} and T_{240}) and 7.40 (group A at T_{1440} and group B at T_{240}).

Critical events

Incidence of critical events for the different parameters and groups are given in Table 5. A HR below the critical value of 45 beats/minute was observed in only one dog (group E^{30} at T_{240}). In group A (control suf) MAP (71 mm Hg) decreased below the critical value in only one dog at T_{120}. All dogs of all inhalation groups showed MAP values below the critical value of 75 mmHg at one or more time points compared to only one dog in group A ($p<0.01$). No significant differences in critical MAP values between the sufentanil treated inhalation groups compared to group B (control sevo) were observed. The majority of the dogs of each inhalation group showed critical events for RR. There were no significant differences in the number of critical values between the sufentanil treated inhalation groups compared to group B (control sevo). Significantly more RR values below the critical level of 15 breaths/min occurred in groups C^0, D^{15} and E^{30} compared to group A ($p<0.05$). Manual ventilation was applied

3 times (2 dogs in group C^0 and 1 in group E^{30}), for the dog in group E^{30} controlled ventilation was necessary during the complete anaesthetic period. Critical events (above 55 mm Hg) for $PaCO_2$ were only observed during the anaesthesia period, whereby significantly more critical $PaCO_2$ values were seen in groups C^0 and D^{15} compared to group A and B (control sevo) ($p<0.05$ and $p<0.01$). Only one critical value (below 75 mm Hg) with a PaO_2 of 63 mm Hg occurred in group C^0 immediately after anaesthesia induction (T_0). Over the entire study period (T_0 to T_{1440}) only one dog showed a SaO_2 % below the critical value of 90% (88% in group C^0 at T_0). Most of the critical pH values (below 7.25) occurred during the inhalation period. Four dogs showed critical values in group B compared to 8 dogs in groups C^0, D^{15} and E^{30}, respectively. Significantly more pH values over time (T_0 to T_{1440}) below 7.25 were observed in groups C^0, D^{15} and E^{30} compared to group A ($p<0.01$) but not compared to group B.

DISCUSSION

In the present study HR during the anaesthetic period (T_0 to T_{90}) was lower in the groups treated with sufentanil compared to group B (control sevo). This decrease in HR was expected to occur with sufentanil administration. Opioids and especially potent narcotic drugs such as sufentanil induce a dose-dependent centrally mediated bradycardia, which may be obtund by parasympathicolytic drugs (Reddy, 1980; De Hert, 1991; Nolan and Reid, 1991). Studies in dogs have shown that anaesthesia with high doses of sufentanil produced only minimal haemodynamic changes (De Castro et al., 1979; Reddy et al., 1980; Eriksen et al., 1981; Philbin et al., 1984; Abdul-Rasool and Ward, 1989). In all inhalation groups however an initial rise in HR followed by a decline after 20 minutes was observed. This initial

increase might be related to thiopental used for induction. Thiopental administration was reported to induce an initial increase in HR probably due to the baroreceptor mediated sympathetic reflex stimulation of the heart followed by a decrease in HR. This is in line with the findings in the present study (Turner and Ilkiw, 1990; De Hert, 1991; Ilkiw et al., 1991). The degree of bradycardia observed in all sufentanil treated inhalation groups could also be influenced by sevoflurane anaesthesia, since tachycardia resulting from sympathetic and baroreceptor reflex stimulation was observed in sevoflurane anaesthetized dogs (Mutoh et al., 1997; Polis et al., 2001a). In contrast to the anaesthetic period where bradycardia was probably partially compensated by thiopental (induction) and sevoflurane (maintenance), a long-lasting bradycardia persisted for 24 hours after anaesthesia. HR decreased below the critical value of 45 beats/min in only one dog (E^{30} at T_{240}) out of 40 dogs. This critical value for HR was chosen arbitrarily. The importance of a bradycardia as factor of oxygen delivery to the tissues will depend also on concomitant factors such as haemoglobin concentration, oxygen saturation and oxygen consumption.

In group A (control suf) MAP decreased moderately during the first 2 hours after administration, afterwards MAP remained slightly below baseline values for 24 hours after administration. Small decreases in MAP were reported after sufentanil administration in dogs (De Castro et al., 1979; Berthelsen et al., 1980; Reddy, 1980; Berthelsen et al., 1981) and this was confirmed in the present study. During the anaesthesia period (T_0 to T_{90}) the lower MAP in the inhalation groups and the increased incidence of mean blood pressure values below 75 mm Hg (critical value) could be attributed to the effect of sevoflurane. The latter is reported to depress systemic blood

pressure in dogs in a dose-dependent manner (Bernard et al., 1990; Frink et al., 1992; Harkin et al., 1994; Mutoh et al., 1997; Polis et al., 2001a). In this study sevoflurane administration was adjusted according to the reaction to a standardised pain stimulus. During anaesthesia all inhalation groups had a similar MAP course despite different end-tidal sevoflurane concentration were used. End-tidal sevoflurane concentrations used in the sufentanil treated inhalation groups were lower than in the sevoflurane control group. The similar MAP in the different groups can be explained by a relatively small difference in end-tidal sevoflurane concentration between the different groups (see study part II).

In group A (control suf) RR increased sharply after sufentanil LA administration up to 160 breaths/min while $PaCO_2$ showed only a slight increase. An initial transient period of panting is a common finding in dogs when high doses of opioids are administered or when neurolept-analgesic combinations are given (Lukasik, 1999; Nolan, 2000). The occurrence of panting is probably related to alteration of the thermoregulatory centre in the hypothalamus (Lascelles, 2000). To the contrary, in all inhalation groups a respiratory depression characterised by a decreased RR and pH and increased $PaCO_2$ developed accompanied by an increased incidence of critical values for these parameters. This depression was, as expected, more pronounced in the sufentanil treated inhalation groups. First, inhalation anaesthetics including sevoflurane depress spontaneous ventilation in a dose-dependent manner (Mutoh et al., 1997). Secondly, sufentanil like other opioids produces also a dose-dependent respiratory depression, which may occasionally be rapid and severe (Monk et al., 1988; Abdul-Rasool and Ward, 1989). The respiratory depression is caused by a decreased responsiveness of

the respiratory centre to carbon dioxide, while the hypoxic stimulus to breathing is unaffected (Florez et al., 1968). This is potentially one of the most serious side effects in humans, but it is rarely a clinical problem in dogs and cats unless the drugs are combined with other potent respiratory depressants as is the case during general anaesthesia (Nolan and Reid, 1991). The more pronounced respiratory depression during sevoflurane anaesthesia following sufentanil treatment can also be explained by the combined respiratory depressant effect of sufentanil and sevoflurane (Steffey et al., 1993; Steffey et al., 1994; Mutoh et al., 1997). The rather smaller increase in $PaCO_2$ in group E during anaesthesia ($PaCO_2$ significantly lower compared to C^0 and D^{15}) suggests a lower degree of respiratory depression when sufentanil LA premedication was done 30 minutes before induction of anaesthesia. In the postanaesthetic period RR was higher in group B (control sevo) compared to the sufentanil treated inhalation groups. This can be explained by the specific pharmacokinetic profile of sufentanil LA with long lasting plasma levels (Short, 1996).

PaO_2 and SaO_2 during anaesthesia were significantly higher in all inhalation groups compared to group A (control suf) due to a high inspired oxygen fraction. For the same reason PaO_2 and SaO_2 values were normal during anaesthesia and not different between the inhalation groups despite a higher $PaCO_2$ and lower RR due to enhanced respiratory depression in the sufentanil treated groups. During the postanaesthetic period however when room air was breathed the persistent respiratory depression can explain the lower PaO_2 in groups C^0, D^{15} and E^{30} compared to group B (control sevo). Since no hypoxia (no value below 75 mm Hg) occurred, this was probably clinically not relevant.

In the present study use of sufentanil LA as premedication moderately enhanced some cardiopulmonary side effects accompanying clinically adjusted sevoflurane anaesthesia. The addition of sufentanil LA as premedication caused a decrease in HR and an increase in $PaCO_2$, while MAP was well maintained. The clinical importance is probably limited during inhalation anaesthesia where a high inspired oxygen fraction was accompanied by a high PaO_2 and SaO_2 (with exception of only one dog shortly after induction). Temporary support of ventilation with IPPV however might be occasionally necessary. Therefore clinical observation and/or respiratory function monitoring with spirometry or capnography would be helpful. Thirty minutes between sufentanil LA premedication and induction of anaesthesia might be preferable, since less respiratory depression occurred in group E^{30}. In the postanaesthetic period the bradycardia persisted and was still present after 24 hours. Although RR was lower then the control group without sufentanil pretreatment, $PaCO_2$ and PaO_2 were within an acceptable range in the postanaesthetic period up to 24 hours.

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CHAPTER 8

PERIANAESTHETIC CARDIOPULMONARY, SEDATIVE AND ANTINOCICEPTIVE EFFECTS OF A LONG ACTING FORMULATION OF SUFENTANIL ADMINISTERED BEFORE SEVOFLURANE ANAESTHESIA IN DOGS.

PART II. ANTINOCICEPTIVE AND SEDATIVE EFFECTS

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SUMMARY

The purpose of the present study was to determine an optimal time interval between the administration of sufentanil long acting and the induction of sevoflurane anaesthesia induced by thiopental in dogs. The occurrence of sedation, antinociceptive and sevoflurane-sparing effects together with other potential side effects were evaluated. Forty dogs were divided over 5 parallel groups of 8 dogs each. Two control groups were used: one group of dogs (A) received sufentanil LA (50 µg/kg IM) and a second group (B) the sufentanil vehicle followed by a standard inhalation anaesthesia of 90 minutes. After premedication with sufentanil LA immediately before (C^0), 15 minutes (D^{15}) or 30 minutes (E^{30}) prior to induction with thiopental (IV) the dogs were anaesthetized for 90 minutes with sevoflurane in oxygen.

Pain and sedation scores were evaluated every 10 minutes during anaesthesia and at 2 (T_{120}), 4 (T_{240}) and 24 hours (T_{1440}) after induction. The occurrence of adverse events such as hypothermia, lateral recumbency, ataxia, noise-sensitivity, vomiting, defaecation, salivation, nystagmus, excitation… was observed at the same time points.

In the post-anaesthetic period pain scores were lower and sedation scores higher in the sufentanil treated groups. In many dogs diminished pain and elevated sedation scores persisted for 24 hours. Sufentanil LA offered a significant sevoflurane sparing effect, which was most pronounced when it was administered 15 minutes before induction of anaesthesia. Several dogs showed ataxia, lateral recumbency, arousal on auditory stimulation, defaecation, salivation and excitation at several time points after sufentanil administration.

In conclusion, sufentanil LA in addition to sevoflurane anaesthesia offered beneficial dosage reducing analgesic effects; although several clinically irrelevant opioid side effects occurred. The most advantageous dosage reducing effect occurred when premedication with sufentanil LA was done 15 minutes before induction of sevoflurane anaesthesia.

INTRODUCTION

Opioid drugs have been used for the relief of pain for over 2000 years and today they are still of enormous therapeutic importance as the drug of choice for the treatment of moderate to severe pain. Pre-emptive analgesia is used to reduce surgical nociceptive input and subsequent postoperative pain (Pascoe, 1992). A clinical advantage of pre-emptive analgesia is the dose reduction of anaesthetic drugs by integrating analgesic therapy into a balanced anaesthetic regimen, which eventually results in improved patient safety (Brunner et al., 1994; Moon et al., 1995).

The short-acting narcotic, sufentanil, is used as an anaesthetic supplement to provide analgesia in balanced anaesthesia protocols in both men and dogs. (Hellebrekers and Sap, 1991). The intermittent administration of short-acting opioids however might be associated with specific problems as too lengthy dosing intervals. This might be overcome with the intramuscular administration of a potent opioid in a long-acting formulation. In the present study a long acting formulation of sufentanil (sufentanil LA) was used as premedication to provide effective analgesia for an extended period of time. It was postulated that the pharmacokinetic properties of sufentanil LA might overcome the problems associated with the use of short acting opioids, such as peaks and troughs in drug plasma level contributing to poor postoperative analgesia (Oden, 1989; Sinatra, 1991). Several

preclinical studies pointed out that a dose of 50 µg/kg IM of sufentanil LA was effective in dogs (Engelen et al., 1996a; Engelen et al., 1996b; Engelen et al., 1996c; Short and Vlaminck, 1998; Verbeeck et al., 1998).

Sevoflurane, a halogenated hydrocarbon developed by Wallin et al. (1975), is used as a volatile anaesthetic in men and animals. Its use in veterinary anaesthesia is expected to increase in the future. Like all volatile anaesthetics it affects the cardiovascular and respiratory system (Mutoh et al., 1997; Polis et al., 2001). Thiopental, a popular induction agent, is known to induce induction apnoea, respiratory acidosis and hypoxaemia (Rawlings and Kolata, 1983; Muir, 1998a; Muir, 1998b). It also affects the cardiovascular system with hypotension, bradycardia followed by reflex tachycardia, hypertension and arrhythmias (Muir, 1998a; Muir, 1998b).

The present experiments were performed to determine an optimal time interval between sufentanil LA administration and induction of sevoflurane anaesthesia in dogs. The occurrence of sedation, antinociceptive and sevoflurane-sparing effects together with other potential side effects such as hypothermia, lateral recumbency, ataxia, noise-sensitivity, vomiting, defaecation, salivation, nystagmus and excitation were evaluated.

MATERIALS AND METHODS

The study was approved by the Ethical committee of the Faculty of Veterinary Medicine, Ghent University (filenumber: 39/2000). Forty adult female Beagles weighing 8.4 to 13.6 kg from 1 to 2 years old were used in the study. The dogs were dewormed and vaccinated before the experiment. Clinical examination one week before the experiment confirmed the good health status of the

animals. No specific medication altering anaesthetic or analgesic requirements was administered previously to the dogs.

Study Protocol

The present study was an open randomised study with 40 dogs divided over 5 parallel groups (n=8). The study was conducted in 40 phases; each phase consisted of 1 dog monitored 24 hours after the administration of the drugs. No blinding was performed.

The dogs in group A (control suf) received sufentanil LA at T_0 without inhalation anaesthesia. The dogs from group B (control sevo) received only the sufentanil-vehicle at T_0 followed by inhalation anaesthesia. In groups C^0, D^{15} and E^{30} a time interval of respectively 0, 15 and 30 minutes between sufentanil LA administration and anaesthesia induction was respected (Table 1).

Premedication and Induction of Anaesthesia

The dogs of groups A, C^0, D^{15} and E^{30} received sufentanil long acting formulation (sufentanil (0.5 mg/ml); Janssen Animal Health, Beerse, Belgium) at a dosage of 50 µg/kg of BWT administered IM in the lumbar muscles. The dogs of group B received only sufentanil-vehicle. Anaesthesia (group B, C^0, D^{15} and E^{30}) was induced with thiopental (Pentothal®, Abbott Laboratories Ltd., Queenborough, UK). Four mg/kg was injected as a bolus and further dosing was slowly done to effect. “Effect” was defined as the moment that eyeballs rotated ventrally and that intubation could be easily performed. Mean injection dose was 13.3 ± 2.5 mg/kg of BWT.

Maintenance of Anaesthesia

The dogs were positioned in lateral recumbency on a surgery table supplied with a thick isolating pad. Room temperature was kept relatively high and was stable during the experiments. Overall mean

room temperature was 23.0 ± 3.0°C. The dogs were connected to an anaesthetic machine with a circle system (Titus®, Dräger, Lübeck, Germany) and a sevoflurane out of circuit vaporiser (Vapor 19.3®, Dräger, Lübeck, Germany). The anaesthetic circuit was flushed with 100 % oxygen for 5 minutes before the experiment. During the first 5 minutes of anaesthesia, a fresh gas flow of 2 l/min O_2 was used which was subsequently reduced to 1 l/min. During anaesthesia the percentage of sevoflurane was adjusted to obtain and maintain an anaesthetic depth suitable to perform surgical interventions much like it would have been done under clinical conditions. Such a level was thought to exist when the eye-lid reflex was absent and the eyeballs were ventrally rotated. Moreover a standardised pain stimulus was administered (see further). If a reaction (a movement, or an increase in HR of more than 15%) was observed, vaporizer settings were increased by 0.5% on the dial. If no reaction occurred, vaporizer settings were decreased in the same way. Depth of anaesthesia was also controlled by observation of eye-lid reflex and position of the eyeballs and if necessary adjusted. Anaesthesia was continued for 90 minutes. No intravenous infusions were administered during the study.

Measurements and Monitoring

A calibrated multigas analyser including a pulse oximetry unit (Quick Cal TM calibration gas® and Capnomac Ultima®, Datex Engstrom Instrumentation Corp., Helsinki, Finland) was used to monitor heart rate, respiratory rate, end tidal CO_2%, inspiratory and end tidal sevoflurane concentrations and arterial oxygen haemoglobin saturation (SpO_2%). Mean arterial blood pressure (MAP) was recorded using a blood pressure transducer (Vascumed N.V., Gent, Belgium) connected to a blood pressure measuring device (Hellige Servomed SMV 104, Germany) following standard calibration procedure. The rectal temperature was measured with a digital

thermometer with an accuracy of 0.1°C (C402®, Terumo Europe N.V., Leuven, Belgium).

Pain and sedation scores were only recorded in the pre- and post-anaesthetic period. Sedation and analgesia were always scored by the same observer. Scoring system and results are listed in Tables 2 and 3. The degree of analgesia was evaluated using a standardised pain stimulus. This consisted in clamping the tail at a distance of approximately 3 cm from its top with a straight Rochester-Carmalt haemostatic forceps closed to the first ratchet lock for 5 seconds. Any reaction to this stimulus (movement, more than a 15% increase in HR) was considered as a pain response and scored according to the scoring system in Table 2. During anaesthesia the same pain stimulus was used to adjust depth of anaesthesia.

Table 2 : Sedation and pain scores in sufentanil long-acting and sevoflurane anaesthetized dogs.

Scores	Sedation	Pain
0	no sedation	no pain
1	drowsiness	minimal response #
2	mild sedation *	clear response ##
3	deep sedation **	

* responsive to environmental stimuli
** unresponsive to environmental stimuli
# minimal aversive movements
strong aversive movements

Rectal temperature was measured immediately before IM sufentanil LA or the vehicle administration, immediately before inhalation anaesthesia (T_0), each 10 minutes from T_0 till T_{90} (except for the adverse effects), at T_{120}, T_{240} and T_{1440}. All dogs were observed for sedative and analgesic effects and the occurrence of adverse events

(lateral recumbency, ataxia, noise-sensitivity, vomiting, defaecation, salivation, nystagmus, excitation, …) immediately before administration of sufentanil/vehicle, immediately before initiation of inhalation anaesthesia (T_0) and at T_{90}, T_{120}, T_{240} and T_{1440}.

At the end of inhalation anaesthesia, oxygen was supplied until extubation was possible. The dogs were transferred to the recovery box. If the rectal temperature was lower than 36°C, an infrared heating source was installed in the recovery box.

Statistical Analysis

The dogs were sorted according to decreasing body weight and divided into 8 classes of 5 dogs each. In each class, the body weights were comparable. Within each class the 5 dogs were randomly allocated to the five different study groups and the 40 phases by a computer randomisation program. The statistical tests were two-sided and used a 0.05 type I error (α=5%).

The StatXact software (StatXact 3 For Windows (1995), Users Manual, CYTEL Software, Cambridge, MA 02139 USA) was used for the Kruskal-Wallis one-way analysis of variance tests, for the Wilcoxon Mann-Whitney U tests and for the Fisher's exact tests (Siegel, 1977).

The treatment groups A (control suf) and B (control sevo) were control groups. No statistics were done for these groups, since the effects of sufentanil LA and sevoflurane were studied previously in dogs (Bernard et al., 1990; Engelen et al., 1996a; Engelen et al., 1996b; Engelen et al., 1996c; Short, 1996; Short and Vlaminck, 1998; Verbeeck et al., 1998; Hoeben et al., 1999; Sterkens et al., 1999).

The body weights recorded seven days before the first study phase were compared by means of the Kruskal-Wallis one-way analysis of variance test to check the randomisation procedure. To evaluate the homogeneity of the several treatment groups, baseline comparisons (T_0) were also performed on rectal temperature, sedation scores and analgesia scores of each treatment group by means of the Kruskal-Wallis one-way analysis of variance test.

For each parameter (rectal temperature, overall analysis of critical events, adverse events) the following tests were performed: statistical comparisons on the mean over time (T_0 to T_{90}) was performed between the treatment groups C^0, D^{15} and E^{30} by means of the Kruskal-Wallis one-way analysis of variance test followed by two-by-two Wilcoxon Mann-Whitney U tests. Each of the treatment groups C^0, D^{15} and E^{30} was compared with the control groups A and B by Wilcoxon Mann-Whitney U tests.

The individual time points after inhalation anaesthesia (T_{120}, T_{240} and T_{1140}) were analysed in the same way as the variable mean over time. For sedation and analgesia scores statistics were performed on the individual values of each time point (T_{120}, T_{240} and T_{1140}). Statistical comparisons were performed between the treatment groups C^0, D^{15} and E^{30} by means of the Kruskal-Wallis one-way analysis of variance test followed by two-by-two Wilcoxon Mann-Whitney U tests. Each of the treatment groups C^0, D^{15} and E^{30} were compared with the treatment groups A and B by Wilcoxon Mann-Whitney U tests.

RESULTS

Results for different measured variables are given in Table 3 and 4. No significant differences in baseline values per study group and per parameter were observed. At T_0 sedation scores were significantly higher in groups D^{15} and E^{30} (injected 15 and 30 minutes before T_0 respectively) compared to groups A, B and C^0 ($p<0.01$ and $p<0.001$). In the post-anaesthetic period, compared to group B (control sevo) sedation scores in sufentanil treated inhalation groups were significantly higher at T_{120} in group E^{30} ($p<0.01$), at T_{240} in group C^0, D^{15} and E^{30} ($p<0.001$) and at T_{1440} in group E^{30} ($p<0.05$). At T_{120} sedation scores in group E^{30} were significantly higher compared to group A (control suf) ($p<0.05$).

Antinociceptive effects of sufentanil LA were suggested by differences in pain scores in the pre- and post-anaesthetic period. Pain score at T_0 was significantly lower in group E^{30} compared to group B and C^0 ($p<0.05$). Compared to group B (control sevo) pain scores in sufentanil treated inhalation groups were significantly lower at T_{120} in group C^0 and E^{30} ($p<0.01$ and $p<0.05$), at T_{240} in group C^0, D^{15} and E^{30} ($p<0.01$; $p<0.05$ and $p<0.01$) and at T_{1440} in group C^0 and E^{30} ($p<0.05$). At T_{120} pain scores in group C^0 were significantly lower compared to group A (control suf) ($p<0.05$).

Table 3: Sedation and pain scores in sufentanil LA and sevoflurane anaesthetized dogs (n = 40).

		Amount of dogs per study group					
Dog groups	Sedation Score	Tpresuf	T0	T90	T120	T240	T1440
Group A	0		8	0	1	0	5
	1		0	2	5	6	3
	2		0	6	2	2	0
	3		0	0	0	0	0
Group B	0		8	0	1	8	8
	1		0	0	7	0	0
	2		0	0	0	0	0
	3		0	8	0	0	0
Group C	0		8	0	0	0	4
	1		0	0	5	6	4
	2		0	0	1	2	0
	3		0	8	2	0	0
Group D	0	8	2	0	0	0	5
	1	0	6	0	5	3	3
	2	0	0	0	2	5	0
	3	0	0	8	1	0	0
Group E	0	8	0	0	0	0	3
	1	0	7	0	2	3	5
	2	0	1	0	3	5	0
	3	0	0	8	3	0	0
Dog groups	Pain Score	Tpresuf	T0	T90	T120	T240	T1440
Group A	0		1	4	3	5	4
	1		2	2	3	1	0
	2		5	2	2	2	4
Group B	0		1	8	1	1	1
	1		0	0	0	0	0
	2		7	0	7	7	7
Group C	0		0	8	8	8	7
	1		2	0	0	0	0
	2		6	0	0	0	1
Group D	0	1	3	8	5	7	4
	1	1	0	0	0	0	1
	2	6	5	0	3	1	3
Group E	0	1	5	8	7	7	6
	1	1	1	0	0	1	0
	2	6	2	0	1	0	2

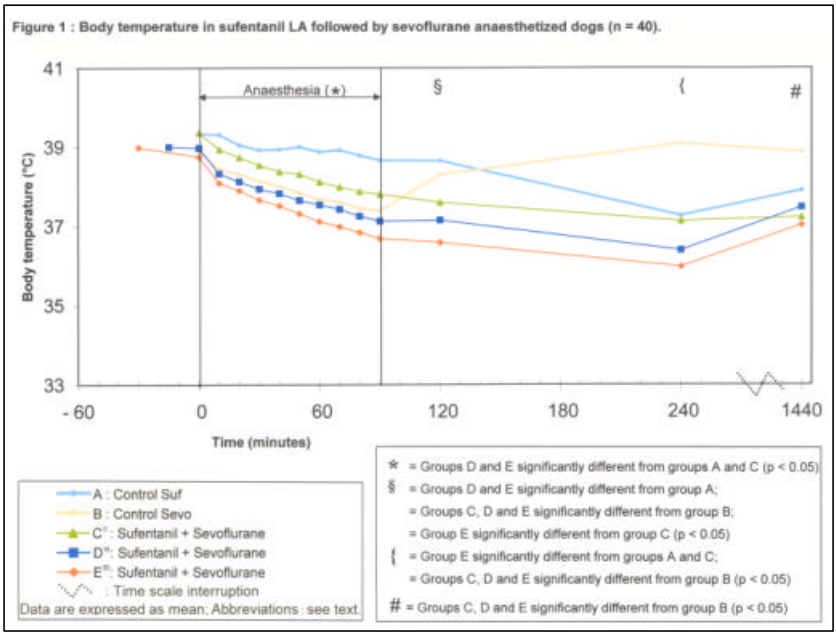
Sedation score: 0 = no sedation present; 1 = drowsiness; 2 = mild sedation; 3 = deep sedation

Pain score: 0 = no evidence of pain; 1 = minimum response; 2 = clear response

The mean end-tidal sevoflurane concentration (Sevo ET%) in group B (control sevo) over the time T_0 to T_{90} was 2.4 ± 0.2% and considered to be 100%. There was a significant reduction in Sevo ET% in all sufentanil treated groups (C^0, D^{15}, E^{30}) compared to group B ($p<0.05$; $p<0.01$ and $p<0.001$). Differences between these groups were not significant. Sevo ET% was reduced by 29.2% in group D^{15} (mean Sevo ET%: 1.7 ± 0.4%), by 19.8% in group C^0 (mean Sevo ET%: 1.9 ± 0.5%) and by 16.2% in group E^{30} (mean Sevo ET%: 2.0 ± 0.1%). The amount of thiopental administered in group B was considered to be 100% (mean: 15.9 mg/kg ± 2.7). The amount of thiopental needed for induction in sufentanil treated groups was significantly reduced. This reduction was 6.8% (mean: 14.8 ± 1.4 mg/kg) in group C^0 (non-significant), 30.2% (mean: 11.1 ± 1.6 mg/kg) in group D^{15} ($p<0.01$) and 29.4% (mean: 11.2 ± 2.5 mg/kg) in group E^{30} ($p<0.01$), all compared to group B. The reduction in administered thiopental was significantly lower in groups D^{15} and E^{30} compared to group C^0 ($p<0.01$).

Body temperature decreased in all groups during the anaesthesia period (T_0 to T_{90}). Body temperature in group D^{15} and E^{30} was significantly lower compared to group A and C^0 ($p<0.01$ and $p<0,05$). There was no significant differences between group B (control sevo) and the sufentanil treated inhalation groups. In group A (control suf) the initial decrease in temperature was more gradually than in the inhalation groups. In the post-anaesthetic period body temperature returned quickly to baseline values in group B (control sevo). In the sufentanil treated groups C^0, D^{15} and E^{30} body temperature remained low and compared to group B the difference was significant at every time point (T_{120}, T_{240} and T_{1440}). In the post-anaesthetic period body temperature remained rather constant in all

sufentanil groups and hypothermia was observed even after 24 hours. Body temperature was significantly lower in group E^{30} compared to C^0 at T_{120} and T_{240} ($p<0.05$). Body temperature was significantly lower compared to group A at T_{120} in groups D^{15} and E^{30} ($p<0.05$ and $p<0.01$) and at T_{240} in group E^{30} ($p<0.05$). Minimum body temperature observed were in group A 36.3°C (T_{240}), in group B 36.7°C (T_{80}, T_{90}), in group C^0 35.9°C (T_{240}), in group D^{15} 35.7°C (T_{90}, T_{120}) and in group E^{30} 35.3°C (T_{70}, T_{240}). When body temperature in the post-anaesthetic period descended below 36.0°C an infrared heating source was installed at ± 70 cm above the dogs.



In the post-anaesthetic period lateral recumbency was not observed in group B (control sevo). The incidence of lateral recumbency in group C^0 decreased from 62.5% (T_{120}) to 12.5% (T_{240}) and 0% (T_{1440}). In group D^{15} incidence of lateral recumbency decreased from 25% (T_{120}) to12.5% (T_{240}) and 0% (T_{1440}). In group E^{30}

this decrease was from 75% to 62.5% and 12.5% respectively. In group A (control suf) lateral recumbency was observed in maximally 50% of the dogs (T_{90}), this decreased to 12.5% (T_{120}), 25.0% (T_{240}) and 0% (T_{1440}).

At T_0 12.5% of the dogs in group E^{30} were ataxic and none in the other groups. In the control group B (control sevo) ataxia was only observed in 50% of the dogs at T_{120} . The incidence of ataxia in group C^0 was 37.5% (T_{120}), this increased to 87.5% (T_{240}) and decreased to 0% (T_{1440}). In group D^{15} ataxia was 50% (T_{120}), this decreased to 37.5% (T_{240}) and 12.5% (T_{1440}). In group E^{30} the incidence of ataxia was 50% (T_{120}), this decreased to 37.5% (T_{240} and T_{1440}). In group A (control suf) ataxia was observed in 37.5% of the dogs (T_{90}), this changed to 12.5% (T_{120}), 75.0 % (T_{240}) and 12.5% (T_{1440}).

Incidence of increased noise sensitivity at T_{120} was 25% (group B), 62.5% (group C^0), 25% (group D^{15} and E^{30}). At T_{240} the incidence was 25% (group B), 50% (group C^0 and E^{30}), 62.5% (group D^{15}). Incidence of increased noise sensitivity was observed in group A in 87.5% (T_{120}), 100% (T_{240}) and 75.0% (T_{1440}).

In group B (control sevo) 12.5% of the dogs defaecated in the period T_{240}-T_{1440}. Defaecation was observed in group C^0 in the period T_{120}- T_{240} (12.5%). Defaecation was seen in group D^{15} in the period T_{90}-T_{120} (62.5%) and T_{120}-T_{240} (12.5%). Defaecation was seen in group E^{30} in the period T_{120}-T_{240} (50.0%) and T_{240}-T_{1440} (12.5%). In group A (control suf) 12,5% of the dogs defaecated in de period T_{90}- T_{120} and T_{120}-T_{240}. Vomiting nor the presence of nystagmus was observed in any dog at any time point. Salivation was seen in group A (control suf) in 25.0% and 12.5% of the dogs at T_{90} and at T_{120} respectively. 25.0% of the dogs in groups B, C^0 and D^{15} showed excitation at T_{120}. No other adverse events were observed at any time point.

Table 4: The presence of adverse events (%) in sufentanil long-acting and sevoflurane anaesthetized dogs (n= 40).

Adverse Effects	Dog groups	T90	T120	T240	T1440
Lateral recumbency	A	50	12,5	25	0
	B	100	0	0	0
	C	100	62,5	12,5	0
	D	100	25	12,5	0
	E	100	75	62,5	12,5
Ataxia	A	37,5	12,5	75	12,5
	B	0	50	0	0
	C	0	37,5	87,5	0
	D	0	50	37,5	12,5
	E	0	50	37,5	37,5
Noise-sensitivity	A	100	87,5	100	75
	B	0	25	25	25
	C	0	62,5	50	25
	D	0	25	62,5	0
	E	0	25	50	12,5
Defaecation	A	25	12,5	12,5	0
	B	0	0	0	12,5
	C	0	0	12,5	0
	D	12,5	62,5	12,5	0
	E	0	0	50	12,5
Salivation	A	25,0	12,5	0	0
	B	0	0	0	0
	C	0	0	0	0
	D	0	0	0	0
	E	0	0	0	0
Excitation	A	0	0	0	0
	B	0	25	0	0
	C	0	25	0	0
	D	0	25	0	0
	E	0	0	0	0

Presence of adverse events is expressed as percentage per study group.

DISCUSSION

Haemodynamic observations during this study were discussed in the first part (Chapter 7). Additional observations were the degree of sedation, antinociceptive and sevoflurane-sparing effects and the occurrence of side effects.

Early signs of sedation and analgesia occurred 15 minutes after sufentanil LA administration and were long lasting (24 hours). The fast decrease in pain scores in groups D^{15} and E^{30} with respectively 3 and 5 dogs/8 with minimal pain scores at T_0 indicated a rapid systemic resorption from the IM injection site. In previous studies sufentanil LA plasma levels very rapidly increased (0.55 ± 0.12 ng/ml and 0.59 ± 0.34 ng/ml (mean ± SD) 15 and 30 minutes after intramuscular administration respectively) and peak levels around 1.53 ± 0.45 ng/ml were observed around 6 hours after IM injection. Sufentanil LA plasma levels of 0.85 ng/ml were necessary to provide good analgesia during major surgery (Short, 1996; Short and Vlaminck, 1998; Verbeeck et al., 1998; Hoeben et al., 1999; Sterkens et al., 1999). Only one dog showed mild sedation at T_0. The analgesic effect was pronounced with 20/24 dogs at T_{120} and 22/24 dogs at T_{240} with minimal pain scores.

Analgesic effects and to a lesser extent, the sedative effects, were long lasting (24 hours). At T_{1440} still 17/24 dogs showed minimal pain scores compared to only one dog in group B (control sevo). In group B (control sevo) no recumbency was observed in the recovery period. In groups C^0, D^{15} and E^{30} 25% to 75% dogs were still recumbent at T_{120} and 12.5%- 62.5% at T_{240}. This illustrates the strong sedative effects of sufentanil LA. A specific problem rose when the

presence of ataxia in the dogs had to be evaluated, because many dogs couldn't walk, adequate scoring was not always possible. Probably the dogs were ataxic at those time points. Nevertheless, at T_{240} when no dogs were ataxic in group B ataxia was still observed in several dogs in all sufentanil groups at T_{240} (37.5%-87.5%) and T_{1440} (12.5%-37.5%). This was indicative for the long residual sedative effect of sufentanil LA in these dogs. Sedative effects at T_{1440} were limited to drowsiness in 12/24 dogs compared to none in group B (control sevo). The long lasting analgesic and sedative effects in all sufentanil groups could be related to a slow decrease in plasma sufentanil concentration. $T_{1/2}$ of sufentanil was reported to be 15.8 ± 5.1 hours (Verbeeck et al., 1998; Hoeben et al., 1999; Sterkens, 1999).

Significantly more sevoflurane (100%) had to be administered in group B (control sevo) compared to the sufentanil-sevoflurane groups. The sparing effect of sufentanil LA after IM administration on sevoflurane anaesthesia found (29.2%) was very similar as the sparing effect accompanying IV administration of fentanyl and sufentanil during enflurane and isoflurane anaesthesia in dogs (Hall et al., 1987a; Schwieger et al., 1991; Hellyer et al., 2001). To our knowledge sevoflurane sparing effects of opioids in dogs are not yet described. The anesthetic sparing effect is likely caused by a "reduction" of the MAC value of the inhalation anesthetic. The MAC-value of potent volatile anaesthetics is reduced by increasing plasma concentrations of opioids (Valverde et al., 1989; Sebel et al., 1992; Brunner et al., 1994; Ilkiw et al., 1997). The degree by which MAC is reduced may be used as a measure of opioids potency (McEwan et al., 1993). Following intravenous application of opioids (alfentanil, butorphanol, fentanyl, morphine, nalbuphine, remifentanil, sufentanil)

during inhalation anaesthesia MAC reductions up to 73% have been reported (Murphy and Hug, 1982a; Murphy and Hug, 1982b; Hall et al., 1987a; Hall et al., 1987b; Schwieger et al., 1991; Michelsen et al., 1996; Hellyer et al., 2001).

The barbiturate-sparing effect was very similar in groups D^{15} (30.2%) and E^{30} (29.4%), but, as expected, much less (6.8%) in group C^{0}. The barbiturate induction dosage amount is markedly less reduced (10-20%) when tranquilizers are used as premedication. Premedication with midazolam and diazepam, two benzodiazepines, reduced the thiamylal (ultra-short acting barbiturate) dose required to accomplish endotracheal intubation in dogs (Muir et al., 1991; Tranquilli et al., 1991; Greene et al., 1993). The amount of thiopental required to produce loss of the eyelid reflex is reduced with the concomitant use of opiates and benzodiazepines (butorphanol and diazepam) for premedication in humans (Sklar et al., 1989). To our knowledge, barbiturate sparing effects of opioids were not reported in dogs.

An important side effect was the development of hypothermia in all sufentanil treated groups that persisted for 24 hours even in the presence of an external heating source. Body temperature is controlled by a complex, highly integrated system that carefully balances heat production and heat loss. Heat is produced as a byproduct of metabolism, and as a result of muscular work, shivering, and chemical thermogenesis, whereas heat is lost from the body through the channels of heat exchange: radiation, conduction, convection and evaporation (Machon et al., 1999). In the present study the decreased body temperature during inhalation anaesthesia was expected since hypothermia is a common and potentially serious complication of general anaesthesia on one hand and opioid

administration on the other hand (Bissonnette, 1991). Opioids as alfentanil, pethidine, fentanyl and sufentanil impair thermoregulatory control by increasing the thresholds for sweating and decreasing the thresholds for vasoconstriction and shivering (Ikeda et al., 1997; Alfonsi, 1998). As expected, the body temperature of the dogs from group B (control sevo) returned very fast to base line values. Hypothermia was probably partially induced by stimulation of the serotonine receptors and by cessation of shivering in the dogs. Shivering is a source of metabolic heat production (Okada et al., 1998). Body temperature deregulating effects by inhibition of shivering are also described in humans after parenteral administration of pethidine, sufentanil and alfentanil (Ikeda et al., 1997; Alfonsi et al., 1998).

Noise sensitivity was evaluated with hand clapping; a clear response of the dog was scored as present noise sensitivity. In the post-anaesthetic period the treated sufentanil dogs could be easily aroused from their sedation by auditory stimulation. Their reaction to hand clapping was exaggerated, but they were sedated again soon after cessation of hand clapping. This exaggerated response to loud noises is also seen after fentanyl administration (Thurmon et al., 1996; Lukasik, 1999).

None of the dogs of any study group vomited over the entire study protocol. Initially, morphine induces vomiting by activating the chemoreceptor trigger zone, probably through a partial dopamine agonist effect, but appears to be the only opioid, which induces vomiting in dogs and cats (Kromer, 1988; Zuckerman and Ferrante, 1998). Defaecation in sufentanil treated dogs tended to be more frequent than in the control group B with up to 60% at certain time points compared to 12%. Defaecation is also frequently seen after

fentanyl injection due to the occurring anal sphincter relaxation (Thurmon et al., 1996; Lukasik, 1999). In contrast, in human studies opioids are associated with a generalized depressant effect on gastrointestinal motility with reduced propulsive peristaltic activity during prolonged opioid administration (reflex inhibition) (Zuckerman and Ferrante, 1998). Salivation was noticed in group A at T_{90} and T_{120}, but not in other groups. Salivation was also described after morphine administration in cats and after methadone administration in dogs (Burroughs, 1953; Davis and Donnely, 1968).

Excitation was only seen at T_{120} in groups B, C^0 and D^{15} in two dogs per group. Morphine in clinical doses can induce excitement on rare occasions in dogs and cats (Lukasik, 1999; Nolan, 2000). Excitation after sufentanil administration is not mentioned in literature, probably because the registered short acting formulation of sufentanil is mostly used for intra-operative analgesia and not for postoperative pain relief.

In conclusion, the present study showed that the combination of sufentanil LA and sevoflurane anaesthesia was associated with a significant reduction in end-tidal sevoflurane concentrations necessary to avoid reaction to a standardized pain stimulus. This effect was most pronounced when sufentanil LA was administered 15 minutes before induction of anaesthesia. In the post-anaesthetic period pain scores were lower and sedation scores higher in the sufentanil-treated groups. In many dogs diminished pain and elevated sedation scores persisted during 24 hours. Hypothermia was observed in all sufentanil groups and persisted during 24 hours in spite of external heating source. Other side effects such as lateral recumbency, ataxia, arousal on auditory stimulation, defaecation, salivation and excitation in some dogs were not clinically relevant.

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GENERAL DISCUSSION

Major progress in human and veterinary anaesthesia has been established the last few decades. Sevoflurane was introduced into the anaesthetic theatre in the early seventies (Wallin et al., 1975). Sevoflurane meets entirely the new trend in volatile anaesthetic drugs permitting more precise control of anaesthesia and perhaps most importantly, more rapid recovery from the effects of anaesthesia (Eger, 1994). Up to now, a lot of research has been done on sevoflurane anaesthesia in human medicine (Katoh and Ikeda, 1987; Lerman, 1993). However, research on sevoflurane in veterinary anaesthesia is rather limited. Especially its clinical use in dogs and the potential clinical applications of sevoflurane in small animal anaesthesia are not studied widely yet. A review on the physico-chemical and anaesthetic properties of sevoflurane in human and small animal medicine was described in chapters 1 and 2.

In chapter 3 the influences of sevoflurane on recovery times and haemodynamic parameters in dogs after 1 hour of anaesthesia were evaluated in a clinical study. The emphasis was put on the clinical aspect of the study. Was the low blood-gas solubility of sevoflurane also accompanied by rapid recoveries in premedicated dogs? Moreover, emergency times were compared with those after halothane and isoflurane anaesthesia at 2 anaesthetic concentrations (1.5 and 2 MAC). A neurolept-analgesic mixture, fentanyl and droperidol, was chosen as premedication to simulate clinical anaesthesia. Droperidol has a long duration of action and can influence the recovery profile (Thurmon et al., 1996; Bissonnette et al., 1999). Anaesthesia was induced with propofol, a short acting induction agent, with rapid metabolisation (Shafer et al., 1988). Its low biological half life was probably minimally influencing recovery after 1 hour of anaesthesia (Shafer, 1993; Smith et al., 1994).

However, anaesthetic recovery is influenced by many other factors. The most important factor is the blood/gas partition coefficient of the anaesthetic agent. A low blood/gas partition coefficient allows more rapid drug elimination and results in a shorter emergence time. The blood/gas solubilities of sevoflurane, isoflurane and halothane in man are respectively 0.68, 1.46 and 2.54 (Strum and Eger, 1987; Steffey, 1996). Of minor importance for anaesthetic recovery are the oil/gas partition coefficient, metabolisation percentage, alveolar ventilation, cardiac output, duration of anaesthesia, percutaneous losses, etc. (Stoelting and Eger, 1969; Carpenter et al., 1987; Lockhart et al., 1991; Steffey, 1996).

In the present work no significant emergence times between the 3 anaesthetic agents occurred, although the emergence time was the longest for halothane at both anaesthetic concentrations. It could be concluded that it was more difficult to show the kinetic advantages of less soluble anaesthetics, as sevoflurane after short duration anaesthetic exposures of 1 hour (Eger and Johnson, 1987). In addition, residual effects of premedication in clinical anaesthesia exerted a depressant effect on cognitive function nullifying any kinetic advantage of sevoflurane over isoflurane and halothane. In conclusion, clinically there was little difference in emergence times between halothane, isoflurane, and sevoflurane in premedicated dogs after 1 hour of inhalation anaesthesia.

The influence of ventilation mode on cardiopulmonary parameters in sevoflurane anaesthetized dogs was also evaluated during clinical anaesthesia (chapter 4). Three types of ventilation namely spontaneous ventilation, intermittent positive pressure ventilation and positive end expiratory pressure (5 cm H_2O) were

compared at 2 anaesthetic concentrations (1.5 and 2 MAC) of sevoflurane in a clinical protocol including standard premedication and induction. This study shows that in anaesthetized spontaneously ventilating dogs increasing MAC values of sevoflurane from 1.5 to 2 induced a pronounced cardiopulmonary depression together with a significant increase in HR. However, this increase was clinically not very relevant. The increased HR could be explained by the baroreceptor-reflex and/or by sympathetic stimulation. The cardiopulmonary depression was characterized by decreases in SI, CI, LVSWI and increases in PCWP and PAP. This cardiac depression was probably related to the presence of a decreased myocardial contractility caused by increasing the MAC value (Suga et al., 1985; Mutoh et al., 1997). A reduced myocardial contractility is often compensated by an increase in end diastolic pressure (Kittleson, 1988). Hence, PCWP and PAP which are good reflections of the end diastolic pressure, increased in the present study (Brutsaert et al., 1985). However, it should be underlined that it remains difficult to explain the pharmacologic effects in this setting because several drugs were used concomitantly.

Changing from SpV to IPPV or PEEP using 1.5 MAC induced a small increase of arterial blood pressures, right cardiac pressures and HR. Little to no influences on other cardiac parameters were observed. On the other hand, the situation changed completely with increasing to 2 MAC. Artificial ventilation with 2 MAC sevoflurane induced a sever impact on the arterial pressures and cardiac related parameters. CO, CI, SV, SI, LVSWI and RVSWI decreased significantly. The impact was more pronounced with PEEP, but the difference between PEEP and IPPV was not significant. Right cardiac pressures increased, while arterial pressures decreased. The main

patho-physiologic mechanism for these cardiovascular side effects of PEEP was a decreased venous return due to the increased intrathoracic pressure and a decreased coronary blood flow inversely related with the PEEP level (Jacobs and Venus, 1983; Versprille, 1990).

In conclusion, sevoflurane anaesthesia at 1.5 MAC in premedicated healthy dogs induced a relatively moderate cardiopulmonary depression during spontaneous and controlled ventilation (IPPV and PEEP of 5 cm H_2O) and could therefore be used safely for clinical anaesthesia. On the contrary, increasing the MAC from 1.5 to 2 caused a marked cardiopulmonary depression. Consequently, higher concentrations of sevoflurane must be avoided during all ventilation modes in dogs.

The following chapters discussed some practical applications of sevoflurane in specific anaesthesia protocols (TLV with CO_2-insufflation, the use of pre-emptive analgesia: sevoflurane in combination with sufentanil LA). In chapter 5 the effects of intrathoracic pressure elevation during continuous two-lung ventilation for thoracoscopy on the cardio-respiratory parameters in sevoflurane anaesthetized dogs were studied. An anaesthesia protocol using standard endotracheal intubation was studied to evaluate its potential use in veterinary practice, since alternative techniques using OLV with bronchial blockers or double lumen tubes are technically difficult or expensive for veterinary practice. Moreover, these techniques require bronchoscopic confirmation of adequate tube placement (Smith et al., 1986; Benumof, 1993). Therefore, TLV with active lung collapse was chosen in the protocol. This technique was accompanied by a severe hypoxemia induced by the collapse of one lung. Regions of atelectasis

were clearly observed during thoracoscopy confirming the occurrence of ventilation-perfusion mismatches due to intra-pulmonary shunting (Cohen et al., 1988). Nevertheless, active vasoconstrictive mechanisms in the non-ventilated lung might reduce the blood flow and minimize the shunt. This is known as the so-called hypoxic pulmonary vasoconstriction reflex. Recently it has been shown in dogs and piglets that sevoflurane (up to 2 MAC) had no significant effect on HPV (Domino et al., 1986; Okutomi and Ikeda, 1990; Lesitsky et al., 1998; Kerbaul et al., 2000).

Three different levels of intrathoracic pressure elevation in the left hemi-thorax (CO_2-insufflation 3, 5 and 2 mm Hg) were evaluated during IPPV in the present study. All direct cardiac parameters (blood pressures, CO, SV, SI, LVSWI) initially decreased significantly during ITP increase to 3, 5 and 2 mm Hg. Afterwards there was a gradual correction of these parameters probably induced by the occurring hypercapnia (Walley et al., 1990). Hypercapnia was observed during CO_2-insufflation most likely because of the induced capnothorax (Peden and Prys-Roberts, 1993). The decrease in direct cardiac parameters was probably due to decreased venous return caused by ITP elevation and/or to a decreased myocardial contractility induced by sevoflurane (Mutoh et al., 1997; Brock et al., 2000; Polis et al., 2001). On the other hand, right cardiac parameters (RAP, PAP, PCWP) increased significantly during ITP elevation at every level compared to values before CO_2-insufflation. Possible explanations were the pulmonary tissue pressure rise and the potential hypoxic pulmonary vasoconstriction in the collapsed pulmonary parenchyma (Ohtsuka et al., 1999). ITP increase resulted in decreased venous return and increased pulmonary vascular pressure compromising SI and CO and resulting in hypotension and hypoperfusion (Lenaghan et

al., 1969; Connolly, 1993). As expected, SpO_2 and PaO_2 decreased significantly after CO_2-insufflation, whereby the decrease was more rapid and pronounced after consecutive ITP elevations compared to the first pressure rise. In contrast with SpO_2, PaO_2 remained low at the end of anaesthesia probably by an increased amount of blood flow in the underlying lung, while its lung volume was compressed by the mediastinal weight. This resulted in hypoxemia caused by existing ventilation/perfusion mismatch and blood shunting.

In conclusion, thoracoscopic procedures in sevoflurane (1.5 MAC) anaesthetized dogs at low pressure (2 mm Hg CO_2-insufflation) into one hemithorax allowed an optimal visualisation of the intrathoracic structures for short periods. The TLV technique with standard intubation and CO_2-insufflation using sevoflurane can be applied in veterinary practice, although the thoracoscopy should be accomplished in one short period of CO_2-insufflation since additional insufflation periods could lead to more rapidly occurring and more pronounced cardiopulmonary depression. Therefore, it might be interesting to compare this technique with OLV using bronchial blockers in a following study, however OLV is technically more difficult to perform and requires more equipment (bronchial blockers, double lumen tubes, bronchoscope).

In the following chapters the combination of sufentanil LA with sevoflurane was studied. Repetitive blood sampling and blood pressure monitoring in unrestrained animals over a relatively long period of time were required. The repetitive puncture of arteries and veins or multiple consecutive peripheral catheter placement is certainly accompanied by technical problems and stress responses, but also by iatrogenically induced damage of the blood vessels

including thrombosis and sclerosis (Mesfin et al., 1988; Bagley and Flanders, 1990; Endres et al., 1990; Grosse-Siestrup and Lajous-Petter, 1990). Hence, a totally implantable catheter technique with titanium vascular access port was used in the haemodynamic study on sufentanil LA and sevoflurane combination (Chapter 6). The catheters were implanted in the femoral artery of the dogs, while the vascular access ports were secured on the lumbar region. This location was chosen to facilitate repeated port punctures. All catheters remained patent during the study. No problems concerning wound healing occurred. Blood sampling and blood pressure measurement were easy to perform requiring only minimal animal restraint. Four dogs showed an increased body temperature without signs of lameness or local infection at the incision sites. A contamination of the flush solution with *Pseudomonas aeruginosa* was the aetiology of this finding. The problem was solved after a few days of antibiotic treatment. Nevertheless, this problem showed the importance of aseptic preparation and storage of the flush solution. Furthermore, only some minor problems of little clinical importance occurred. In conclusion the described arterial catheterisation technique with vascular access ports was suitable and technically feasible for experimental haemodynamic protocols.

The cardiopulmonary effects during and following clinically conducted sevoflurane anaesthesia in sufentanil LA premedicated dogs were evaluated (Chapter 7). Opioids are often included into the premedication protocol because of their analgesic properties. In order to overcome the problems associated with intermittent administration of short acting opioids, it was postulated that a single intramuscular administration of a potent opioid (sufentanil) in a long acting formulation could be used as premedication, providing effective pre-

emptive analgesia over an extended period of time. The goal of this study was to evaluate potential deterioration of cardiopulmonary influences of sufentanil LA administered at different time points in combination with sevoflurane anaesthesia in dogs. During anaesthesia the expected bradycardia was masked by thiopental and sevoflurane (sympathetic and baroreceptor-reflex stimulation), while a long lasting, but clinically not relevant bradycardia persisted for 24 hours after anaesthesia (Mutoh et al., 1997; Polis et al., 2001). In all anaesthesia groups MAP showed a similar pattern while MAP values were lower compared to the sufentanil group. An initial transient period of panting occurred after sufentanil LA administration. This panting was probably related to alterations in the thermoregulatory centre induced by the opioid (Lukasik, 1999; Lascelles, 2000; Nolan, 2000). Respiratory depression was observed in the sufentanil-sevoflurane groups during anaesthesia. This was probably clinically irrelevant since high PaO_2 and SaO_2 values occurred during anaesthesia. However, temporary support of ventilation with IPPV however might be occasionally indicated. Therefore, clinical observation and/or respiratory function monitoring with spirometry or capnography would be helpful. Thirty minutes between sufentanil LA premedication and induction of anaesthesia might be preferable, since less respiratory depression occurred in this group. Obviously, in clinically adjusted sevoflurane anaesthesia the addition of sufentanil LA as premedication moderately enhanced the occurring cardiopulmonary side effects during anaesthesia. No marked differences were observed between the different sufentanil LA-sevoflurane groups.

In the second part of this study, the antinociceptive and sedative effects of sufentanil LA were emphasised together with other

potential side effects (hypothermia, lateral recumbency, ataxia, noise-sensitivity, defaecation, salivation, excitation,…) (Chapter 8). In addition, the potential dosage reducing effect of sufentanil LA on thiopental induction dosage and sevoflurane end-tidal concentration were evaluated and an optimal time interval between the IM administration of sufentanil LA and the beginning of sevoflurane anaesthesia induced by thiopental was determined.

A similar sedation and analgesia pattern was observed in all sufentanil groups. Signs of sedation and analgesia occurred 15 minutes after sufentanil LA administration and were long lasting. This was indicative for a fast systemic resorption from sufentanil LA and a slow decrease in plasma concentration afterwards (Verbeeck et al., 1998; Hoeben et al., 1999). In the postanaesthetic period pain scores were lower and sedation scores higher in the sufentanil-treated groups. In many dogs diminished pain and elevated sedation scores persisted during 24 hours. The present study showed that the combination of sufentanil LA and clinically directed sevoflurane anaesthesia was associated with a significant reduction in end-tidal sevoflurane concentrations necessary to avoid reaction to a standardized pain stimulus. This effect was most pronounced when sufentanil LA was administered 15 minutes before induction of anaesthesia. This dose dependent MAC reducing effect was previously reported for other opioids (Valverde et al., 1989; Sebel et al., 1992; McEwan et al., 1993; Brunner et al., 1994; Michelsen et al., 1996; Ilkiw et al., 1997). Severe hypothermia was observed in all sufentanil groups even after 24 hours. Hypothermia could be expected because it is a common and potentially serious complication of general anaesthesia and opioid administration in particular (Bissonnette, 1991). The persistence of hypothermia was probably due to the long acting effect of sufentanil LA causing cessation of

shivering and of metabolic heat production (Okada et al., 1998). Furthermore, some minor side effects as lateral recumbency and ataxia were observed illustrating the sedative effects of sufentanil LA. The presence of defaecation, excitation, salivation, and arousal on auditory stimulation in some dogs was of little clinical importance. It could be concluded that sufentanil LA in addition to sevoflurane anaesthesia offered beneficial dosage reducing analgesic effects. Because cardiopulmonary depression induced by sevoflurane was marked at higher concentrations, its combination with an opioid is advisable to lower anaesthetic concentration needed for surgical interventions.

CONCLUSIONS

1/ Little difference in emergence times between halothane, isoflurane and sevoflurane in premedicated dogs after 1 hour of inhalation anaesthesia occurred (chapter 3).

2/ Sevoflurane anaesthesia at 1.5 MAC in premedicated healthy dogs induced a relatively moderate cardiopulmonary depression during spontaneous and controlled ventilation and can be used safely. Increasing the anaesthetic concentration from 1.5 to 2 MAC caused a marked cardiopulmonary depression. Higher concentrations of sevoflurane are better avoided during all ventilation modes in dogs.

3/ Thoracoscopic procedures in sevoflurane (1.5 MAC) anaesthetized dogs with low pressure (2 mm Hg) CO_2-insufflation into one hemithorax allowed an optimal visualization of the intrathoracic structures for short periods. However, the thoracoscopic procedure should be accomplished in one short episode since additional

insufflation periods could lead to more rapidly occurring and more pronounced cardiopulmonary depression.

4/ Femoral artery catheterisation with vascular access ports was considered suitable and technically feasible for experimental haemodynamic protocols in dogs.

5/ The addition of sufentanil LA as premedication before clinically adjusted sevoflurane anaesthesia moderately enhanced the occurring cardiopulmonary depression.

6/ Sufentanil LA in addition to sevoflurane anaesthesia offered beneficial dosage reducing effects. Long lasting hypothermia was a major side effect. An optimal time period of 15 minutes should be respected between sufentanil LA administration and induction of sevoflurane anaesthesia to benefit from the reduction in sevoflurane.

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SUMMARY

The use of inhalation anaesthesia in veterinary small animal practice is quickly gaining ground under the impulse of recent developments in human anaesthesia. Until now, halothane and to a lesser extent isoflurane are commonly used as inhalant anaesthetic agents for veterinary anaesthesia. Recently, sevoflurane has been developed and is nowadays routinely used in human anaesthesia. Physico-chemical characteristics of sevoflurane, its influences on body systems and economic considerations of sevoflurane in clinical anaesthesia practice are described and summarised in chapters 1 and 2 of this work. The major objectives of this thesis were to examine the clinical use of sevoflurane in veterinary anaesthesia and the potential application of sevoflurane in some specific anaesthesia protocols.

In the first part of this work the influences of sevoflurane on recovery times and on cardiopulmonary parameters with different ventilation patterns and at 2 MAC multiples (1.5 and 2 MAC) were determined (chapter 3 and 4). The influence of 3 volatile agents (Halo, Iso and Sevo) at 2 concentrations (1.5 and 2 MAC) on non-invasive cardio-respiratory parameters and recovery times (first eyelid reflex, emergence time) following clinical anaesthesia was studied. After premedication with fentanyl-droperidol (5 µg/kg and 0.25 mg/kg IM) and induction with propofol (5 mg/kg IV) six dogs were randomly anaesthetised for one hour for a standard neurologic stimulation test. A wide individual variation in respiration rate (induced by an initial hyperpnea) was observed in the 1.5 MAC protocols. Heart rate was significantly lower during 1.5 and 2 MAC halothane when compared to isoflurane and sevoflurane. An increase from 1.5 to 2 MAC induced significant decreases in diastolic and mean arterial blood pressure in all groups without significant changes in the systolic arterial pressures. Time for a first eyelid reflex was significantly longer after 2 MAC

compared to the 1.5 MAC protocol. There was no significant difference between the 3 anaesthetic agents. Although emergence time was longest for halothane at both anaesthetic concentrations, no significant difference in emergence time was observed for the 3 volatile agents. Clinically there was little difference in emergence times between halothane, isoflurane, and sevoflurane in premedicated dogs after 1 hour of inhalation anaesthesia.

Furthermore, the effects of sevoflurane on cardiopulmonary parameters were emphasized. Three types of ventilation (SpV, IPPV and PEEP) were compared at 2 anaesthetic concentrations (1.5 and 2 MAC). Increasing the MAC value during sevoflurane anaesthesia with spontaneous ventilation induced a marked cardiopulmonary depression; on the other hand, HR increased significantly, but this was clinically not relevant. The influences of artificial respiration on cardiopulmonary parameters during 1.5 MAC sevoflurane anaesthesia were moderate and clinically acceptable. In contrast, PEEP ventilation during 2 MAC concentration had very pronounced depressant influences, especially on right cardiac parameters. In conclusion, at 1.5 MAC, a surgical anaesthesia level, sevoflurane could be used safely in healthy dogs during spontaneous and controlled ventilation (IPPV and PEEP of 5 cm H_2O). Higher concentrations of sevoflurane should better be avoided during all ventilation modes in dogs, because of marked cardiopulmonary depression.

In the second part of the thesis, the application of sevoflurane in different anaesthesia protocols was studied. First, the cardiopulmonary influences of different levels of carbon dioxide insufflation (3, 5 and 2 mm Hg) during two-lung ventilation were studied in 6 sevoflurane (1.5 MAC) anaesthetized dogs for left sided

thoracoscopy (chapter 5). Although carbon dioxide insufflation into the left hemithorax with an intrapleural pressure of 2 to 5 mm Hg compromised cardiac functioning in 1.5 MAC sevoflurane anaesthetized dogs, it could be an efficacious adjunct for thoracoscopic procedures. Intrathoracic view was satisfactory with an intrapleural pressure of 2 mm Hg. Therefore, the intrathoracic pressure rise during thoracoscopy with two-lung ventilation should be kept as low as possible. Additional insufflation periods should be avoided, since a more rapid and more severe cardiopulmonary depression would occur.

Secondly, the cardiopulmonary effects of sufentanil LA in sevoflurane anaesthetized dogs was evaluated together with the occurrence of antinociceptive and sedative effects and other opioid side effects. An optimal time interval between the administration of sufentanil LA and the induction of sevoflurane anaesthesia was examined in addition to the possible dosage reducing effects of sufentanil LA on thiopental and sevoflurane (chapter 7 and 8). The combination of sufentanil LA followed by clinically adjusted sevoflurane anaesthesia induced a moderate cardiopulmonary depression. The combination of sufentanil LA and clinically directed sevoflurane anaesthesia was associated with a significant reduction in the sevoflurane end-tidal concentration necessary to avoid reaction to a standardized pain stimulus. This effect was most pronounced when sufentanil LA was administered 15 minutes before induction of anaesthesia. In the post-anaesthetic period pain scores were lower and sedation scores higher in the sufentanil-treated groups. In many dogs diminished pain and elevated sedation scores persisted during 24 hours. In conclusion, sufentanil LA in addition to sevoflurane anaesthesia offered beneficial dosage reducing analgesic effects;

although some minor side effects (hypothermia, lateral recumbency, ataxia, arousal on auditory stimulation, defaecation, salivation and excitation occurred. To achieve this advantageous dosage reducing effect 15 minutes should be respected between sufentanil LA administration and induction of sevoflurane anaesthesia.

For this hemodynamic study repetitive arterial blood samples and blood pressure measurement were required. Therefore, a method using coated polyurethane catheters and titanium vascular access ports (VAP) with a silicone membrane providing arterial access for a longer period was described in forty dogs (chapter 6). This technique allowed repeated arterial blood pressure measurement and blood sampling in unrestrained conscious and anaesthetised dogs. Catheter extraction caused by the dogs did not occur. On the other hand, infection with *Pseudomonas aeruginosa* due to a contaminated heparinised flush solution was diagnosed in 4 dogs. The dogs healed rapidly after an appropriate antibiotic therapy. It could be concluded that the described arterial catheterisation technique with vascular access port over a two weeks period was suitable and technically feasible for experimental protocols in dogs.

SAMENVATTING

Onder invloed van recente ontwikkelingen in de humane anesthesie neemt het gebruik van inhalatie anesthesie in de kleine huisdierenpraktijk snel toe. Tot op heden werd als inhalatie anestheticum meestal gebruik gemaakt van halothaan of in iets mindere mate van isofluraan. Sevofluraan dat recent op de markt kwam, wordt tegenwoordig al veel aangewend in de humane anesthesie. In hoofdstuk 1 en 2 van dit proefschrift wordt als inleiding eerst ingegaan op de fysisch-chemische eigenschappen, de invloed op de verschillende orgaansystemen en enkele economische aspecten van sevofluraan gebruik tijdens de klinische anesthesie voornamelijk bij de mens. Hoofdstukken 3 - 5 en 7 – 8 zijn gewijd aan onderzoek over het gebruik van sevofluraan bij de hond. Evaluatie van de klinische aanwending van sevofluraan in de kleine huisdierenpraktijk enerzijds en evaluatie van enkele mogelijke toepassingen in specifieke anesthesie protocols vormden de belangrijkste doelstellingen van dit proefschrift.

In het eerste deel van het proefschrift werd de invloed van een eind-expiratorische concentratie van 1.5 en 2 MAC sevofluraan, isofluraan en halothaan op de ontwaaktijd (ooglid reflex en extubatietijd) en op enkele hemodynamische parameters tijdens een klinische anesthesie bij de hond onderzocht (hoofdstuk 3). De honden werden gepremediceerd met fentanyl-droperidol (5 µg/kg en 0.25 mg/kg IM) en vervolgens werd de anesthesie geïnduceerd met propofol (5 mg/kg IV). Tijdens de één uur durende anesthesie werd

een standaard neurologische stimulatietest uitgevoerd. De hartfrequentie was significant lager gedurende halothaan anesthesie dan tijdens isofluraan en sevofluraan anesthesie en dit bij beide MAC waarden. Bij concentratie toename van 1.5 naar 2 MAC ontstond een significante daling van de diastolische en gemiddelde arteriële bloeddruk in alle anesthesiegroepen. Dit ging echter niet gepaard met significante veranderingen in de systolische arteriële bloeddruk. Een positieve ooglid reflex was significant vlugger aanwezig na toepassen van het 1.5 MAC protocol in vergelijking met het 2 MAC protocol. Er was echter geen significant verschil in terugkeren van de ooglidreflex tussen de 3 inhalatie anesthetica onderling. De extubatietijd was het langst na halothaan anesthesie voor beide anesthesie concentraties, maar toch waren er geen significante verschillen merkbaar tussen de 3 anesthetica. Er werd besloten dat er na een klinische anesthesie van 1 uur bij gepremediceerde honden geen verschil was in ontwaak tijden tussen halothaan, isofluraan en sevofluraan.

Vervolgens werd de mogelijke invloed van sevofluraan op verschillende cardiopulmonaire parameters bij de hond onderzocht. Drie ventilatie technieken (spontane ventilatie, intermittent positive pressure ventilation (IPPV) en positive end expiratory pressure ventilation (PEEP)) werden vergeleken bij gebruik van 2 anesthetische concentraties (1.5 en 2 MAC). Verhogen van de eind expiratorische concentratie tot 2 MAC tijdens spontane ventilatie veroorzaakte een duidelijke cardiopulmonaire depressie, en anderzijds een significante, maar klinisch irrelevante stijging van de hartfrequentie. Tijdens IPPV waren de cardiorespiratoire invloeden met gebruik van 1.5 MAC eerder gematigd en zeker klinisch aanvaardbaar. Bij 2 MAC daarentegen waren de cardiopulmonaire invloeden van PEEP uitgesproken nefast voornamelijk op rechter hart

parameters. Er werd besloten dat een concentratie van 1.5 MAC sevofluraan (meestal gepaard gaande met een chirurgisch anesthesie niveau), veilig kon gebruikt worden bij de gezonde hond en dit zowel bij spontane als artificiële respiratie (IPPV en PEEP van 5 cm H_2O). Hogere sevofluraan concentraties daarentegen zouden beter vermeden worden voor anesthesie van de hond ongeacht de ventilatie methode.

In het tweede deel van het proefschrift werd de mogelijke toepassing van sevofluraan bij verschillende anesthesie protocols bij de hond onderzocht. Een eerste toepassing was de anesthesie voor thoracoscopie waar Two Lung Ventilation, TLV, met CO_2-insufflatie gebruikt wordt. Een tweede toepassing was de combinatie van een sevofluraan anesthesie met een premedicatie met een langwerkend opiaat, sufentanil LA.

Bij de thoracoscopie werden in eerste instantie cardiopulmonaire invloeden van CO_2-insufflatie (3, 5 en 2 mm Hg) gedurende TLV tijdens sevofluraan anesthesie bestudeerd (hoofdstuk 5). CO_2-insufflatie in de linker thorax helft met een intrapleurale druk van 2 tot 5 mm Hg onderdrukte de hartwerking tijdens 1.5 MAC sevofluraan anesthesie. Desondanks werd deze techniek als een efficiënte hulpmiddel beschouwd voor thoracoscopische ingrepen. Gezien de cardiopulmonaire onderdrukking wordt de intrathoracale druktoename tijdens thoracoscopie met TLV best zo laag mogelijk gehouden. Een intrapleurale druk van slechts 2 mm Hg gaf reeds een goede zichtbaarheid in de thorax. Hierbij is het wel aan te bevelen dat het thoracoscopisch onderzoek tijdens één enkele insufflatieperiode kan uitgevoerd worden, daar een sneller optredende en meer uitgesproken cardiopulmonaire depressie optreedt bij herinsufflatie.

Om de kombinatie van een sevofluraan anesthesie met sufentanil LA te evalueren werden de hemodynamische invloeden van een premedicatie met sufentanil LA tijdens en na sevofluraan anesthesie bij de hond onderzocht. Daarnaast werden eveneens de sedatieve, antinociceptieve en eventuele andere opiaat effecten onder de loep genomen. Het dosis reducerend effect van sufentanil LA op thiopental inductie en sevofluraan anesthesie werd bestudeerd. Er werd een optimaal tijdsinterval tussen de toediening van sufentanil LA en de inductie van sevofluraan anesthesie bepaald (hoofdstuk 7 en 8). De combinatie van sufentanil LA premedicatie en sevofluraan anesthesie induceerde een matige cardiopulmonaire onderdrukking. Door sufentanil LA premedicatie was er een lagere eind expiratoire concentratie van sevofluraan nodig om een vergelijkbare analgesie/ anesthesie te bekomen. Dit effect was meest uitgesproken wanneer sufentanil LA 15 minuten voor de inductie werd toegediend. Na de anesthesie bleven de pijnscores lager en de sedatiescores hoger in de sufentanil LA groepen. Dit analgetisch en sedatief effect van sufentanil LA bleef bij vele honden aanwezig gedurende 24 uur. Een gedurende 24 uur persisterende hypothermie was een klinisch belangrijke nevenwerking opgemerkt na sufentanil LA premedicatie.

Voor de beoordeling van de gasuitwisseling en het meten van de bloeddruk tijdens en na de sufentanil LA/ sevofluraan anesthesie was herhaalde arteriële bloedmonstername voor bloed-gas analyse en een arteriële toegang voor bloeddrukmeting noodzakelijk. De arteriële katheterisatie techniek die bij deze honden (n=40) gebruikt werd wordt beschreven (hoofdstuk 6). Deze techniek maakt gebruik van polyurethaan katheders en een titanium “vascular access port”. Herhaalde arteriële bloeddrukmetingen en bloedafnames waren

hierdoor mogelijk bij geänesthesieerde en niet geänesthesieerde honden. De honden ondervonden weinig hinder van deze techniek en deden geen pogingen om de katheter te verwijderen. Bij 4 honden werd er wel een infectie (koorts en arthritis) vastgesteld. Dit bleek te wijten aan het gebruik van gecontamineerde heparine spoelvloeistof (*Pseudomonas aeruginosa*). Verwijderen van het implantatiemateriaal en een aangepaste antibioticatherapie brachten volledige en snelle genezing.

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Ingeborgh

CURRICULUM VITAE

Ingeborgh Polis werd geboren op 21 mei 1969 te Fraipont. Na het beëindigen van het secundair onderwijs, afdeling Latijn-Grieks, aan het Onbevlekte Ontvangenis Instituut te Tongeren, is zij in 1987 gestart met de studies Diergeneeskunde aan de Universiteit Gent. Zij behaalde in 1994 het diploma van dierenarts met grote onderscheiding. Zij is in 1996 getrouwd met Geert Hoflack en in 1998 moeder geworden van Bram.

In juli 1994 trad zij in dienst bij de vakgroep Geneeskunde en Klinische Biologie van de Kleine Huisdieren, eerst als deeltijds vrij assistent. De overige 50 % was ze werkzaam in Dierenkliniek Kerberos te Leuven in samenwerking met Dr. L. Brants en Dr. P. Van Aerschot. In oktober 1995 werd ze aangesteld als voltijds assistent onder leiding van professoren De Schepper, De Rick, Van Ham, Moens en Gasthuys bij de vakgroep Geneeskunde en Klinische Biologie van de Kleine Huisdieren. Zij genoot een algemene opleiding in de geneeskunde van kleine huisdieren, maar heeft zich vooral toegelegd op de anesthesie bij kleine huisdieren in al zijn aspecten. Zij heeft het vakgebied van de anesthesie volledig uitgebouwd in de vakgroep Geneeskunde en Klinische Biologie van de Kleine Huisdieren in opdracht van Prof. Dr. Gasthuys en Prof. Dr. Moens. Zij staat in voor de praktische organisatie en coördinatie van de anesthesie in de Cel Chirurgie van de Kleine Huisdieren. Verschillende onderzoeken op het vlak van de anesthesie en de analgesie bij de kleine huisdieren in opdracht van de farmaceutische industrie werden door haar mede opgesteld en volledig uitgevoerd.

Daarnaast is zij verantwoordelijk voor het klinisch onderricht in de anesthesie van de kleine huisdieren aan de studenten van het laatste jaar. Zij heeft verschillende lessen over anesthesie en intensieve zorgen voor het Post Universitair Onderwijs en voor de cursus Vakdierenarts Kleine Huisdieren gegeven. Sinds januari 2000 volgt ze een alternatief programma van het “European College of Veterinary Anaesthesia” en zal zij na voltooiing van het programma deelnemen aan het Europees examen voor “Diplomate”.

Haar interesse voor het gebruik van sevoflurane bij de hond ontstond vanuit de dagelijkse ervaring met inhalatie anesthesie bij de hond. Het eigenlijke onderzoek werd gestart in 1999. In september 2001 behaalde zij het getuigschrift van de doctoraatsopleiding in de diergeneeskundige wetenschappen.

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