Influence of ketamine or xylazine constant rate infusion on quality of anaesthesia, cardiopulmonary function and recovery in isoflurane anaesthetised horses- a clinical trial

Thesis
Submitted in partial fulfilment of the requirements for the degree
-Doctor of Veterinary Medicine-
Doctor medicinae veterinariae
(Dr. med. vet.)

by
Nina Franziska Pöppel
Rheda

Hannover 2012
Academic supervision: Prof. Dr. S. Kästner
Clinic for small animals

1. Referee: Prof. Dr. S. Kästner
2. Referee: Prof. Dr. M. Kietzmann

Day of oral examination: 15th November 2012
For my beloved and patient parents
This study has been published in part previously:

Pöppel NF, Hopster K, Kästner SBR (2012):
Influence of ketamine or xylazine constant rate infusion on quality of anaesthesia, cardiopulmonary function and recovery in isoflurane anaesthetised horses- a clinical trial

AVA Spring Meeting
21st March – 23rd March 2012, Davos, Switzerland
Congress Proceedings, page 35.
## Contents

1. **Introduction** ................................................................................................................. 11

2. **Review of literature** .................................................................................................... 13
   2.1 **General anaesthesia in horses** .............................................................................. 13
      2.1.1 **Balanced anaesthesia in horses** ................................................................ 14
   2.2 **Influence of general anaesthesia on cardiopulmonary function and recovery in horses** ......................................................................................................................... 15
      2.2.1 **Isoflurane** ..................................................................................................... 16
      2.2.2 **Xylazine** ..................................................................................................... 18
      2.2.3 **Ketamine** ................................................................................................... 20
      2.2.4 **Midazolam** ................................................................................................ 23
      2.2.5 **Acepromazine** ............................................................................................ 24
      2.2.6 **Butorphanol** ................................................................................................ 25
      2.2.7 **Dobutamine** ................................................................................................ 27
      2.2.8 **Thiopental** .................................................................................................. 28
   2.3 **Monitoring anaesthesia** ............................................................................................ 30
      2.3.1 **Respiratory function** .................................................................................... 30
      2.3.2 **Circulation** .................................................................................................. 31
         2.3.2.1 **Cardiac output measurement** ................................................................ 31
            2.3.2.1.1 **The Fick principle** ............................................................................ 33
            2.3.2.1.2 **Indicator Dilution Methods** ............................................................... 34
               2.3.2.1.2.1 **Dye dilution** ............................................................................... 34
               2.3.2.1.2.2 **Thermodilution** ........................................................................... 35
               2.3.2.1.2.3 **Lithium dilution** ......................................................................... 35
            2.3.2.1.3 **Pulse contour analysis (PulseCO)** .................................................... 37
            2.3.2.1.4 **Other cardiac output measurement methods** ................................... 39
      2.3.3 **Determination of anaesthetic depths** ................................................................. 40
   3. **Material and Methods** ............................................................................................... 41
      3.1 **Animals** ............................................................................................................... 41
      3.2 **Assignment of animals to groups** ....................................................................... 41
      3.3 **Experimental setup** ............................................................................................ 45
         3.3.1 **Preoperative examination and preparations** ............................................... 45
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>bwt</td>
<td>body weight</td>
</tr>
<tr>
<td>CaO₂</td>
<td>arterial oxygen content</td>
</tr>
<tr>
<td>CB</td>
<td>crossbred horse</td>
</tr>
<tr>
<td>CI</td>
<td>cardiac index</td>
</tr>
<tr>
<td>CO</td>
<td>cardiac output</td>
</tr>
<tr>
<td>CRI</td>
<td>constant rate infusion</td>
</tr>
<tr>
<td>CRT</td>
<td>capillary refill time</td>
</tr>
<tr>
<td>CVP</td>
<td>central venous pressure</td>
</tr>
<tr>
<td>DO₂</td>
<td>oxygen delivery</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>ETCO₂</td>
<td>end-expiratory concentration of carbon dioxide</td>
</tr>
<tr>
<td>ETISO</td>
<td>end-expiratory concentration of isoflurane</td>
</tr>
<tr>
<td>F</td>
<td>Frisian</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
</tr>
<tr>
<td>GP</td>
<td>German riding pony</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>hb</td>
<td>haemoglobin</td>
</tr>
<tr>
<td>HES</td>
<td>hydroxyethyl starch</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>HTC</td>
<td>haematocrit</td>
</tr>
<tr>
<td>IK</td>
<td>group isoflurane-ketamine</td>
</tr>
<tr>
<td>IM</td>
<td>intramuscularly</td>
</tr>
<tr>
<td>IPPV</td>
<td>intermittent positive pressure ventilation</td>
</tr>
<tr>
<td>I</td>
<td>group isoflurane</td>
</tr>
<tr>
<td>IU</td>
<td>international unit</td>
</tr>
<tr>
<td>IV</td>
<td>intravenously</td>
</tr>
<tr>
<td>IX</td>
<td>group isoflurane-xylazine</td>
</tr>
</tbody>
</table>
List of abbreviations

kg  kilogram
kPa kilopascal
l  litre
MAC minimal alveolar concentration
MAP mean arterial pressure
ml millilitre
mmHg millimetre of mercury
mmol millimol
NFP Nina Franziska Pöppel
NICO non-invasive cardiac output monitoring system
NMDE N-methyl-D-aspartate
PaCO$_2$ arterial pressure of carbon dioxide
PAM post-anaesthetic myopathy
PaO$_2$ arterial pressure of oxygen
PIP peak inspiratory pressure
PIVA partial intravenous anaesthesia
PP plasma protein
PulseCO pulse contour analysis
RR respiratory rate
SaO$_2$ saturation of arterial blood with oxygen
SAS® statistical analysis system
SD standard deviation
SV stroke volume
SVR systemic vascular resistance
SWG standard wire gauge
TIVA total intravenous anaesthesia
vol volume
WBC white blood cell
1 Introduction

Anaesthesia in horses carries a much higher risk of mortality than in other species like humans or small animals. A mortality rate in horses undergoing elective surgery of approximately 1.0 % has been reported (JOHNSTON et al. 2002). Main cause of death is cardiac arrest in 33 %, whereas myopathy along with fractures have been figured out to be the reason for mortality in 30.4 % of cases (JOHNSTON et al. 2002). To reduce risk for morbidity and mortality peri-operatively an anaesthetic technique with minimal cardiovascular depression in conjunction with a safe and fast recovery is desired. Post-anaesthetic myopathy (PAM) is associated with different predisposing factors, among these, adequate muscle perfusion seems to be a determining factor (WEAVER et al. 1984; LINDSAY et al. 1989). Muscle perfusion is closely related to mean arterial blood pressure (MAP) and cardiac output (CO), therefore, maintaining a good cardiovascular function is the basic requirement of avoiding PAM (RICHEY et al. 1990; LEE et al. 1998; EDNER et al. 2002). Other co-factors are hypotension, bodyweight of the horse, poor padding and duration of anaesthesia (HALL 1981; GRANDY et al. 1987; LINDSAY et al. 1989; RICHEY et al. 1990; YOUNG and TAYLOR 1993; EDNER et al. 2002).

In the past, methods to measure CO like thermodilution or dye dilution have been expensive, inaccurate and invasive with various complications, therefore their use in clinical cases was contraindicated (CORLEY et al. 2003). With the development of the lithium dilution technique a non-invasive, safe and simple method is available which has been validated in horses and foals (CORLEY et al. 2002; HALLOWELL and CORLEY 2005). Unfortunately with this technique an online beat-to-beat measurement is still not possible.

Common practice for long surgical procedures in equine anaesthesia is the use of inhalation agents like isoflurane, which allow fast changes of anaesthetic depth and a fast recovery due to rapid elimination (STEFFEY et al. 1977), but unfortunately they are also characterized by dose-related cardiovascular depression affecting CO in different ways (STEFFEY and HOWLAND 1978, 1980). Therefore, the primary goal of equine anaesthesia is to reduce required volatile agents to improve cardiovascular function. This can be achieved by administering intravenous, short-acting, central
depressive drugs such as sedatives and/or analgesics during general anaesthesia maintained with volatile anaesthetics (BETTSCHART-WOLFENSBERGER and LARENZA 2007). Such “balanced anaesthesia” protocols, or “partial intravenous anaesthesia” has become more common in equine anaesthesia in the last few years. The power of reducing the amount of inhalation agents with a constant rate infusion (CRI) of different intravenous drugs (e.g. xylazine, ketamine) has been shown under experimental conditions in previous studies (MUIR and SAMS 1992; STEFFEY et al. 2000; SOLANO et al. 2006).

The aim of this study was to investigate the influence of ketamine or xylazine constant rate infusion on quality of anaesthesia, anaesthetic requirement, cardiopulmonary function and recovery in isoflurane anaesthetised horses under clinical conditions.
2 Review of literature

2.1 General anaesthesia in horses

Equine general anaesthesia poses a challenge to the anaesthesiologist due to size, temperament and body weight of these animals as those properties predispose them to nerve and muscle compression resulting in muscle ischaemia as vessels are externally compressed (THURMON 1990). Risk of muscle and nerve damage is even more amplified during general anaesthesia as both MAP and CO are decreased by anaesthetic drugs (TRIM and MASON 1973). This instance is reflected by actually high death rates (approximately 1 %) reported in clinically healthy horses undergoing elective surgery using inhalation anaesthesia (JOHNSTON et al. 2002), in contrast to published perioperative mortality rate of less than 1:10000 in man (LUNN and MUSHIN 1982) and 1:680 in small animals (CLARKE and HALL 1990). This incidence in horses may increase further if cardio-depressive horses such as those suffering from colic have to be anaesthetised.

General anaesthesia is characterized by following mainstays (WOODBRIDGE 1957): sensory blockade (analgesia), motor blockade (muscle relaxation), loss of consciousness or mental block (unconsciousness) and blockade of undesirable autonomic reflexes of the respiratory, cardiovascular, and gastrointestinal system in response to noxious stimuli. MUIR (1994) adds one further aspect in the attempt to provide an “ideal” anaesthetic state: Combination of drugs should also include a “stress” reducer, as stress related substances (e.g. catecholamines) are involved in various pathomechanisms like pain, central sensitization, inflammation and alteration of cardiac and pulmonary function. To achieve the “ideal” anaesthetic state different drugs are available influencing cardiopulmonary function and recovery in different ways. The “perfect” drug, or rather drug combination must be able to maintain both cardiovascular function and a sufficient blood flow to muscles and vital organs as well as a smooth and fast recovery from anaesthesia as many injuries and mortalities are associated with that anaesthetic period in horses (YOUNG and TAYLOR 1993; JOHNSTON et al. 2002). However, until now the perfect anaesthetic drug has not been detected.
Total intravenous anaesthesia (TIVA), provides better cardiovascular function resulting in lower morbidity and mortality rates (0.31 %) compared to inhalation anaesthesia (JOHNSTON et al. 2002), but unfortunately the use of TIVA is time-limited because of cumulative effects of most intravenous agents, associated with increased incidence of side effects and uncoordinated recoveries. This applies to ketamine in particular, one of the most common used drug in TIVA.

In conclusion, there is actually no alternative to volatile agents for prolonged (> 90 minutes) equine general anaesthesia. Unfortunately inhalation agents at clinically tolerated doses provide only two of the four mentioned main attributes of general anaesthesia- unconsciousness and immobilisation (MARCH and MUIR 2003). Therefore the technique of “balanced” anaesthesia is getting more and more common (BETTSCHART-WOLFENSBERGER and LARENZA 2007).

### 2.1.1 Balanced anaesthesia in horses

Balanced anaesthesia or partial intravenous anaesthesia (PIVA) commonly uses a combination of a volatile agent with an intravenous central depressant agent to optimise hypnosis, to provide analgesia, to improve muscle relaxation and to reduce the amount of the inhalation agent and thus improve cardiopulmonary function (BETTSCHART-WOLFENSBERGER and LARENZA 2007). CRILE (1910) firstly described a concept of combing several compounds with different types of actions (e.g. hypnosis, analgesia or reduction of autonomic reflexes). The term balanced anaesthesia was introduced 1926 in human medicine (LUNDY). Lundy combined different drugs and techniques like premedication, local anaesthesia and general anaesthesia. WOODBRIDGE (1957) mooted the idea that an “ideal” anaesthetic state can only be achieved by combining different drugs due to their pharmacodynamic properties because no anaesthetic drug is available which fulfils all four key points of general anaesthesia.

Today the term balanced anaesthesia is mostly used for a combination of different anaesthetics- mainly volatile agents- with short-acting intravenous anaesthetic adjuvants (TONNER 2005). The theory is that a combination of different drugs may
act synergistically by improving desired effects with contemporaneous less side-effects due to reduced doses of the single drugs (TONNER 2005).

Prolonged anaesthesia is often maintained with volatile agents. In addition to cardiovascular depression inhalation agents induce mainly immobilisation and unconsciousness, with very little analgesic properties at clinical doses. Moreover a deep level of anaesthesia may not avoid reflex responses to noxious stimuli during surgery (ILKIW 1999; MARCH and MUIR 2003). Animals appear sleeping because somatic motor responses are blocked at quite low doses of the used anaesthetic drug. However, even deep levels of anaesthesia may not inhibit autonomic responses to noxious stimuli by activating the sympathetic nervous system (ZBINDEN et al. 1994; ILKIW 1999). Those responses are classified as sudomotor, haemodynamic and hormonal (ILKIW 1999).

To achieve multimodal anaesthesia and to block autonomic responses, sedatives, analgesics and/or muscle relaxants can be administered providing all described aspects of general anaesthesia (ENDERLE et al. 2008). The need of volatile drugs can be decreased and thus the cardiovascular condition may be improved, which is of importance in horses with pre-existing diseases or during colic episodes.

Finally it should be considered that reduction of inhalation agents contributes to reduction of human exposure and environmental pollution (LOGAN and FARMER 1989; BERTHOUD and REILLY 1992; MUIR 1994; KENNA and JONES 1995; ANDERS 2005).

2.2 Influence of general anaesthesia on cardiopulmonary function and recovery in horses

Drugs for premedication, analgesics and anaesthetics used to prohibit pain, to calm patients and to induce and maintain general anaesthesia, may influence cardiopulmonary functions and recovery in several ways.
2.2.1 Isoflurane

Isoflurane is the only licensed volatile agent for horses in Germany and is commonly used to maintain prolonged anaesthetic procedures in horses (BRUNSON 1990; LÖSCHER 2010). Pharmacologic and chemical properties of isoflurane make it a perfect anaesthetic agent for long procedures as elimination of the drug occurs via the lung by breathing independent of liver metabolism (STEFFEY et al. 1977), whereby accumulation and therefore any type of tissue toxicity can be reduced. As a halogenated ether, isoflurane provides rapid onset of action due to its low solubility in blood (BRUNSON 1990). Among volatile agents the blood-gas coefficient of isoflurane (1.4) lies between halothane (2.4) with higher values and sevoflurane (0.7) with a quiet low coefficient (STEFFEY 2009) explaining the rapid and good regulation of anaesthetic depth by adapting the delivered concentrations by a vaporizer (BRUNSON 1990).

For all volatile agents the minimum alveolar concentration (MAC) describes the anaesthetic potency. The MAC is defined as that dose of anaesthetic drug in the alveolus required that prevents purposeful movement in response to a noxious stimulus in 50 % of the subjects (QUASHA et al. 1980; STEFFEY et al. 2000). The published MAC for isoflurane in horses ranges between 1.3 and 1.6 vol % (STEFFEY et al. 1977; STEFFEY et al. 2000).

Unfortunately volatile anaesthetics induce dose-related cardiovascular depression by various mechanisms (STEFFEY and HOWLAND 1978, 1980), which are associated with peri- and postoperative morbidity (GRANDY et al. 1987; LINDSAY et al. 1989) contributing to the high mortality rate in horses (JOHNSTON et al. 1995). In detail, isoflurane depresses the cardiovascular system by reducing both cardiac output and in particular the stroke volume. Isoflurane causes vasodilatation and reduces systemic vascular resistance leading to reduced MAP (STEFFEY and HOWLAND 1980). In comparison to halothane, isoflurane and sevoflurane were able to provide higher cardiac output values by less reduction in myocardial contractility and preload, while MAP and HR were not affected differently by the diverse volatile agents (GROSENBAUGH and MUIR 1998; RAISIS et al. 2000a).
Depression of the respiratory system, in isoflurane and sevoflurane anaesthetised horses, is characterized by a reduced respiratory rate (5-10 breaths per minute in conjunction with minimally altered tidal volume) (STEFFEY et al. 1977) consequentially leading to increased PaCO$_2$ because of decreased minute ventilation (BRUNSON 1990; GROSENBAUGH and MUIR 1998). To prevent hypercapnia and respiratory acidosis, mechanical ventilation could be required in prolonged anaesthesia (BRUNSON 1990; BLISSITT et al. 2008). In contrast to isoflurane, spontaneously breathing horses anaesthetised with halothane are less depressed in breathing and respiratory rate is maintained at around 15 breaths per minute (STEFFEY and HOWLAND 1980).

Recovery from general anaesthesia is generally contributed to redistribution of the agent from the side of action or metabolism and elimination of the anaesthetic drug of the body. Elimination of volatile agents, mainly via the lung, depends therefore on blood solubility of the drug, minute ventilation and duration of anaesthesia (WHITEHAIR et al. 1993). The lower the blood-gas distribution coefficient, the shorter the recovery period (AUER et al. 1978). Accordingly isoflurane and sevoflurane anaesthetised horses recover faster in contrast to recovery after general anaesthesia maintained with halothane (MATTHEWS et al. 1992; WHITEHAIR et al. 1993; GROSENBAUGH and MUIR 1998). However, studies investigating quality of recovery from inhalation anaesthesia have conflicting results about the quality of recovery with isoflurane. In an early study in ponies (AUER et al. 1978), recovery after isoflurane anaesthesia was characterized as being smoother with a quiet and prolonged sternal recumbency with excellent coordination compared to halothane. In horses MATTHEWS et al. (1992) did not observe any difference in recovery quality between halothane and isoflurane, whereas WHITEHAIR et al. (1993) saw a less controlled recovery with isoflurane than with halothane because horses tried to arise before their muscles were strong enough to carry the whole bodyweight. It seems that isoflurane might induce a worse recovery quality directly because sevoflurane (providing even a lower blood-gas coefficient than isoflurane) creates improved recovery quality compared to isoflurane (GROSENBAUGH and MUIR 1998; MATTHEWS et al. 1998). Because of those findings sedation with a low dose of
xylazine (e.g. 0.1 mg kg\(^{-1}\) IV) before recovery has become general practice after isoflurane anaesthesia (CLARK-PRICE et al. 2008). The sedative property of xylazine calms horses and keeps them on the ground while they eliminate isoflurane, thus recovery time is prolonged, but improved. Those recoveries are described as being smoother, free of both excitation and ataxia and with minimal cardiopulmonary effects (SANTOS et al. 2003). Nevertheless, isoflurane produces still a worse recovery period compared to halothane if horses have received xylazine before recovery (DONALDSON et al. 2000).

2.2.2 Xylazine

Xylazine is a popular and commonly used drug for sedation, analgesia, premedication and sedation before or during recovery in horses, belonging to the pharmacological group of alpha\(_2\)-agonists (ENGLAND and CLARKE 1996). It was the first described and approved alpha\(_2\)-agonists for use in horses (CLARKE and HALL 1969). Effects are based on binding and stimulation of alpha\(_2\)-adrenoreceptors in the central and peripheral nervous system (MAZE and TRANQUILLI 1991). Furthermore, xylazine has potent analgesic properties and reduces the need of inhalation agents dose- and time-dependently in horses (STEFFEY et al. 2000; BENNETT et al. 2004) and dogs (TRANQUILLI et al. 1984). Unfortunately all drugs belonging to the group of alpha\(_2\)-agonists produce similar cardiopulmonary changes in horses (ENGLAND and CLARKE 1996) in terms of a decreased HR, an increased incidence of second-degree atrioventricular block, reduced CO up to 40 % (KERR et al. 1972) and transient hypertension, followed by hypotension, despite increased systemic vascular resistance (WAGNER et al. 1991). Vasoconstriction by stimulation of vascular peripheral alpha\(_2\)-adrenoreceptors is followed by a baroreceptor response leading to a decreased HR, which is later on succeeded by central sympatholysis with hypotension and bradycardia (KERR et al. 1972; ENOURI et al. 2008). Cardiovascular function is much more compromised after bolus injection compared to CRIs, which avoid sudden peripheral vasoconstriction (BETTSCHART-WOLFENSBERGER et al. 1999).
There are conflicting reports about the influence of xylazine on respiratory function. KERR et al. (1972) observed no significant effects on respiratory rate (RR) or minute ventilation, but with wide variations of RR in the control group. Several other studies reported a significant reduction in RR after xylazine (MCCASHIN and GABEL 1975; REITEMEYER et al. 1986; WAGNER et al. 1991). Despite a reduction in respiratory rate, hypoventilation, defined by an increased PaCO₂, could not be seen by WAGNER et al. (1991) and MCCASHIN and GABEL (1975). Moreover a mild, but significant decrease in PaO₂ five minutes after injection of xylazine or detomidine was demonstrated in several studies (SHORT et al. 1986; WAGNER et al. 1991), which might have been associated with haemodynamic changes such as vasoconstriction, reduced CO and an increase in pulmonary vascular resistance, leading to a decreased pulmonary blood flow. Another side effect of xylazine is the development of a dose-dependent hyperglycaemia because of transient hypoinsulinaemia and development of osmotic diuresis (THURMON et al. 1982; STEFFEY et al. 2000). Alpha₂-agonists provide muscle relaxation resulting in ataxia. The degree of ataxia differs among drugs. Ataxia with xylazine and detomidine seems to be more severe than with romifidine at equipotent dose (ENGLAND et al. 1992). Reported doses of xylazine, as a sedative and premedication drug, range from 0.5 to 1.1 mg kg⁻¹ IV (KERR et al. 1972). At these doses duration of action lasts between 30 and 60 minutes (CLARKE and HALL 1969; HOFFMAN 1974). Higher doses demonstrate no more sedative effects, but are associated with more side effects such as ataxia due to a greater extent of muscle relaxation (KERR et al. 1972). A benefit of xylazine administration in addition to general anaesthesia might be seen in improved cardiovascular function due to a reduction of the amount of volatile agents (STEFFEY et al. 2000; BENNETT et al. 2004). On the other hand, respiratory and circulatory effects could be enhanced when administering alpha₂-agonists during general anaesthesia maintained by volatile anaesthetics and may lead to undesired side effects such as bradycardia and decreased CO (BETTSCHART-WOLFENSBERGER and LARENZA 2007). In halothane anaesthetised horses it has to be considered, that alpha₂-agonists in the presence of halothane, which is known
to sensitize the myocardium against catecholamines, can lead to life-threatening arrhythmias (STEFFEY et al. 1985). However, as halothane has become obsolete, and the newer volatile agents do not sensitize the myocardium, more and more studies investigated cardiopulmonary effects of alpha₂ agonists during anaesthesia. A quite early pilot study was published by WAGNER et al. (1992), whose data reveals no particular advantage of a CRI of detomidine (0.18 µg kg⁻¹ minute⁻¹) in halothane anaesthetised horses during neurectomy. KALCHOFNER et al. (2006) investigated the use of medetomidine with isoflurane in a 300 horses’ trial and concluded that this combination results in a safe and cardiovascularly stable anaesthesia with an excellent recovery period. RINGER et al. (2007) showed that CI was significantly lower using isoflurane-medetomidine over the whole anaesthetic period than isoflurane-lidocaine balanced anaesthesia, but overall cardiovascular function was well maintained in both protocols with less isoflurane requirement during isoflurane-medetomidine anaesthesia. Other clinical studies failed to demonstrate an inhalation anaesthetic sparing effect of detomidine, romifidine or dexmedetomidine (DEVISSCHER et al. 2010; SCHAUVLIEGE et al. 2011; MARCILLA et al. 2012). However, recovery after isoflurane-alpha₂-agonist anaesthesia seems to be improved and maintenance of an adequate anaesthetic depth seems easier to be achieved (RINGER et al. 2007; MARCILLA et al. 2012) compared to control groups.

2.2.3 Ketamine

Ketamine, as a dissociative agent, which produces dissociation between the thalamic and the limbic system (MARTYN 1987), is a popular drug for induction (MUIR et al. 1977; WRIGHT 1982) or maintenance (MUIR et al. 1977) of general anaesthesia in horses. It provides sympathomimetic properties by stimulating the central nervous system directly (IVANKOVICH et al. 1974; WHITE et al. 1982) and it also exerts a noncompetitive antagonistic effect on N-methyl-D-aspartate (NMDA) receptors (KOHRS and DURIEUX 1998; MUIR 2010), through which ketamine might also have an inhibiting effect on the “wind-up” phenomenon (WOOLF and THOMPSON 1991). Especially by binding on NMDA-receptors (KOHRS and DURIEUX 1998), ketamine
induces analgesia, amnesia and immobility without depressing cardiovascular function (BETTSCHART-WOLFENSBERGER and LARENZA 2007). Ketamine seems to influence cardiovascular functions in different ways, as it provides centrally-mediated sympathomimetic properties, usually resulting in an increased HR, MAP and CO in a plasma concentration-related way (MUIR et al. 1977; MUIR and SAMS 1992; BETTSCHART-WOLFENSBERGER and LARENZA 2007). Improved CO is predominantly related to increased HR and cardiac contractility at plasma concentrations of ketamine above 1 µg ml\(^{-1}\) in horses and between 2 to 3 µg ml\(^{-1}\) in dogs (HASKINS et al. 1985; MUIR and SAMS 1992; BOSCAN et al. 2005). However, ketamine may also provide direct negative inotropic effects on the myocardium leading to depressed myocardial contractility, especially if sympathetic or parasympathetic control is absent (TRESESE et al. 1973; SCHWARTZ and HORWITZ 1975; DIAZ et al. 1976). Therefore, resultant cardiovascular effects may vary depending on concomitantly used drugs (HASKINS et al. 1985).

Generally, ventilation is not impaired by ketamine at clinically relevant doses. Respiration may be characterized by an apneustic (breath-holding) pattern of breathing (BENSON and THURMON 1990), but arterial blood gases such as PaO\(_2\) and PaCO\(_2\) are affected only mildly (MUIR et al. 1977). A study in humans proved the preservation of functional residual capacity, minute volume and tidal volume under anaesthetic doses of ketamine (MANKIKIAN et al. 1986).

Ketamine increases cerebral blood flow, metabolic rates and enhances intracranial pressure, when used as a single drug (HASKINS 2006), which can be reduced combining ketamine with anaesthetics or sedatives (HIMMELSEHER and DURIEUX 2005).

Ketamine also exhibits excitatory central nervous system effects (BETTSCHART-WOLFENSBERGER and LARENZA 2007). Thus during recovery, horses can suffer from muscle tremor and rigidity, excitation and ataxia, which can end in fatal injury of the horse (MUIR and SAMS 1992). Further side effects are sweating, hypertension, mydriasis, tachycardia and increased rectal temperature (MUIR 2010). To avoid those side effects in horses, ketamine has to be administered in combination with
sedative-hypnotics, muscle relaxants and analgesics to produce short-term
anaesthesia or to induce general anaesthesia (MIUR et al. 1977; LUNA et al. 1997). Due to its metabolism (active metabolite norketamine) in the liver (KNOBLOCH et al. 2006), redistribution in fat and muscles and elimination pathway, repeated administration of ketamine may result in accumulation of the drug (LANKVELD et al. 2006) leading to prolonged and poor recovery (MIUR and SAMS 1992) as metabolites and residues can be redistributed to the central compartment during the recovery process (BETTSCHART-WOLFENSBERGER et al. 1996). Two or more supplemental doses of xylazine-ketamine (0.3 and 0.68 mg kg\(^{-1}\), respectively) after induction with xylazine-ketamine or xylazine, guaifenesin and ketamine lead to significantly longer recovery periods (MCCARTY et al. 1990) compared to none or one supplemental injection. To reduce the risk of undesired side effects during recovery, ketamine infusions should be reduced or stopped 15 to 20 minutes before the end of anaesthesia (SPADAVECCHIA et al. 2002). BETTSCHART-WOLFENSBERGER and LARENZA (2007) recommended to avoid a 1 mg kg\(^{-1}\) hour\(^{-1}\) ketamine CRI for anaesthetic procedures exceeding two hours in horses, whereas ponies after two hours of approximately 10 mg kg\(^{-1}\) hour\(^{-1}\) ketamine recovered uneventfully (LEVIONNOIS et al. 2010).

Recently several studies investigated analgesic and antinociceptive effects of subanaesthetic doses of ketamine in horses. Doses up to 1.5 mg kg\(^{-1}\) hour\(^{-1}\) for up to six hours have been proved for safe use in conscious healthy horses (FIELDING et al. 2006; LANKVELD et al. 2006; PETERBAUER et al. 2008). Furthermore PETERBAUER et al. (2008) demonstrated an antinociceptive effect of a CRI at 20 \(\mu\)g kg\(^{-1}\) minute\(^{-1}\) of racemic ketamine after a bolus injection of 0.6 mg kg\(^{-1}\) ketamine over nearly 60 minutes, whereas FIELDING et al. (2006) failed to demonstrate an analgesic effect of 0.8 mg kg\(^{-1}\) hour\(^{-1}\) ketamine CRI over six hours. It seems that low-dose ketamine does not affect cardiovascular parameters since HR and MAP have not been changed significantly during administration of subanaesthetic CRIs. Horses recover with still up to 40 % of non metabolised ketamine remaining in the body due to a rapid redistribution phase (half-life ~ 3 minutes) from the central compartment, where ketamine induces the anaesthetic state, followed by a slower
terminal elimination phase with a half-life of approximately 66 minutes (WATERMAN et al. 1987). Plasma concentrations of ketamine, at which animals recovered from general anaesthesia, vary between species as rats and cats achieved consciousness at plasma levels between 2.5 and 2.9 µg ml\(^{-1}\), respectively (LIVINGSTON and WATERMAN 1978; WATERMAN 1983). In horses the anaesthetic level inducing plasma concentration is lower (1 µg ml\(^{-1}\)) (KAKA et al. 1979; MUIR and SAMS 1992). Duration of action after a single bolus injection of ketamine (2.2 mg kg\(^{-1}\) IV) after premedication with 1.1 mg kg\(^{-1}\) xylazine is approximately 10 to 12 minutes (WATERMAN et al. 1987). After induction with xylazine, guaifenesin and ketamine, a CRI of 150 µg kg\(^{-1}\) minute\(^{-1}\) ketamine was able to maintain a very light anaesthesia for one hour until infusion was stopped, but without facilitated a surgical plane of anaesthesia. Horses recovered after 33 minutes (MAMA et al. 2005).

Ketamine reduces the amount of halothane, isoflurane and sevoflurane required to maintain anaesthesia in horses and dogs proportionally to its plasma concentration (MUIR and SAMS 1992; BOSCAN et al. 2005; SOLANO et al. 2006; WILSON et al. 2008). The improvement of cardiovascular function observed in these cases might be explained either by reduction of the amount of inhalation agent or by centrally-mediated sympathomimetic effects (BETTSCHART-WOLFENSBERGER and LARENZA 2007).

Care must be taken in assessment of anaesthetic depths level due to the fact that ketamine produces an anaesthetic state often called as cataleptic (WHITE et al. 1982), where protective reflexes are preserved much more than under inhalation anaesthesia (SCHATZMANN and GIRARD 1984; BETTSCHART-WOLFENSBERGER and LARENZA 2007).

### 2.2.4 Midazolam

Classified as a benzodiazepine, midazolam provides anxiolytic, muscle relaxant and anticonvulsant effects by binding to inhibitory GABA\(_\alpha\)-receptor sites in the central nervous system (COSTA et al. 1975). Because of weak sedative effects, lack of analgesic properties and production of ataxia, midazolam should only be administered in combination with sedatives, opioids or anaesthetics in horses (MUIR
The muscle relaxant effect is strong enough to prohibit the increased muscle
tremor and rigidity elicited by ketamine (WHITE 1982) and therefore midazolam-
ketamine combinations are commonly used for induction of general anaesthesia,
leading to a smooth and safe induction quality (GANGL et al. 2001). Furthermore
sedative-hypnotic effects of anaesthetic drugs can be enhanced (MUIR 2009a). In
contrast to diazepam, midazolam is approximately twice as potent, shorter-acting and
water-soluble (REVES et al. 1985). Benzodiazepines produce no significant changes
of HR, CO, RR or arterial blood gas values in clinically relevant doses (MUIR et al.
1982) and are able to reduce the amount of inhalation agents in horses and ponies
(MATTHEWS et al. 1990; GANGL et al. 2001).

2.2.5 Acepromazine
Among phenothiazine tranquilizers acepromazine is the most commonly used drug in
horses (HUBBELL et al. 2010). It produces calming, sedation and indifference by
blocking dopamine-mediated receptors centrally (TOBIN and BALLARD 1979;
BALLARD et al. 1982; DRIESSEN et al. 2011). Further properties are anxiolytic and
anti-arrhythmic effects, inhibition of both opioid-induced excitement (COMBIE et al.
1981) and manic behaviour in horses. Due to antagonistic effects on
alpha_1-adrenoreceptors peripherally (MUIR 2009a; DRIESSEN et al. 2011), they
induce vasodilatation dose-dependently, which might result in severe hypotension
(TOBIN and BALLARD 1979), but also in an improved tissue and lung perfusion
(MARNTELL et al. 2005). The degree of hypotension depends on route of
administration and dose. Therefore the most seriously hypotensive effect is induced
at high IV doses (PARRY et al. 1982; DRIESSEN et al. 2011). The duration of action
is quite long, so systolic pressure remains below baseline values for more than six
hours after an IM injection of 0.05 mg kg^{-1} acepromazine (PARRY et al. 1982). A
dose of 0.05 to 0.1 mg kg^{-1} acepromazine can reduce MAP by about 26 to 34 mmHg
(MUIR et al. 1979).
Further circulatory effects are a significant and ongoing increase of CO and a
decreased total peripheral resistance (STEFFEY et al. 1985). During general
anaesthesia arterial oxygenation might be impaired by increased shunt and
ventilation-perfusion mismatch, which can be prevented partially by administration of acepromazine prior to anaesthesia (MARNEELL et al. 2005). Acepromazine decreases haematocrit (HTC) up to 25 % dose-related at low doses (0.01 mg kg\(^{-1}\)). If dosage is increased to 0.05 mg kg\(^{-1}\), the HTC is not depressed any further, but the duration of the effect persists much longer (BALLARD et al. 1982). Furthermore DOHERTY et al. (1997) and HEARD et al. (1986) proved a halothane MAC-reducing effect of up to 36.9 % and up to 40 % of 0.05 mg kg\(^{-1}\) and 0.02 mg kg\(^{-1}\) acepromazine in ponies and dogs, respectively.

A rare, but severe side effect is the potential to provoke persistent penile prolaps and priapism in stallions and geldings (BALLARD et al. 1982). Published prevalence was 0.56% in the past (GERRING 1981), whereas a recently study has reported an prevalence below 0.015 % (DRIESSEN et al. 2011). Decreased prevalence over the years may be associated with reduced doses of acepromazine (< 30 \(\mu\)g kg\(^{-1}\)) combined with other sedatives as part of premedication today compared to doses of acepromazine at 50 \(\mu\)g kg\(^{-1}\) and higher used more frequently in the past (DRIESSEN et al. 2011). The authors discussed abolishing the restricted use of acepromazine in geldings and stallions because expected beneficial properties seem to overwhelm possible side effects.

Finally, it is unknown which of the previously described properties are causal, but acepromazine reduces the mortality rate in anaesthetised horses (JOHNSTON et al. 2002) and administration prior to anaesthesia is therefore strongly recommended aside from haemodynamically depressed horses.

### 2.2.6 Butorphanol

Butorphanol belongs to the group of opioid analgesics, interacting with different opioid receptors (\(\mu\), \(\kappa\) and \(\delta\)). Depending on binding properties, opioids are classified as full agonist, partial agonist, agonist-antagonist or full antagonist. Butorphanol, a synthetic morphine derivative, is defined as an opioid agonist-antagonist, which provides strong analgesic properties by binding as agonist at \(\kappa\)-receptors, but also has weak antagonistic \(\mu\)-receptor properties (HEEL et al. 1978; ILKIW et al. 2002). In contrast to that, butorphanol provides strong \(\mu\)-receptor properties with only weak \(\kappa\)-
receptor binding properties in humans and primates (KÄSTNER 2008). It provides dose-related superficial as well as visceral analgesia over 30 to 90 minutes (KALPRAVIDH et al. 1984a, b) with an elimination half-life of 44 minutes after a single IV injection (SELLON et al. 2001).

Different studies investigated cardiopulmonary properties, analgesia and synergistic effects of butorphanol in horses. They all documented no or only minor effects on cardiopulmonary function at clinical doses (ROBERTSON et al. 1981; KALPRAVIDH et al. 1984b; SELLON et al. 2001; HOFMEISTER et al. 2008).

Opioids enhance sedative and analgesic effects of alpha2-agonists. Different studies evaluated the drug combinations detomidine, xylazine or romifidine each with butorphanol and concluded an increase in the degree of sedation and a decreased response to external stimuli (ROBERTSON and MUIR 1983; CLARKE and PATON 1988; TAYLOR et al. 1988; CLARKE et al. 1991).

As applied to almost every opioid, butorphanol induces different side effects including adverse gastrointestinal effects as risk of constipation is increased due to depressed intestinal propulsion (BOSCAN et al. 2006), behavioural changes and increased locomotor activity seen in shivering, ataxia and restlessness (COMBIE et al. 1981; KALPRAVIDH et al. 1984b; NOLAN et al. 1994). If increased locomotor activity occurs, it might be minimised by administering a sedative drug (KALPRAVIDH et al. 1984a) or can be partially blocked by either acepromazine or naloxone (COMBIE et al. 1981). Effects are transient and can be seen especially following high IV doses (0.1 to 0.5 mg kg\(^{-1}\)) of butorphanol (SELLON et al. 2001).

Experimental studies failed to demonstrate an inhalation anaesthetic sparing effect of butorphanol in horses (MATTHEWS and LINDSAY 1990; DOHERTY et al. 1997; STEFFEY et al. 2003), which could have been expected considering its analgesic properties (BENNETT and STEFFEY 2002). Moreover, studies in other species have proved an inhalation agent sparing effect for butorphanol. In these studies the minimal alveolar concentration of isoflurane could be reduced by butorphanol by up to 20 % in dogs (KO et al. 2000) and up to 19 % in cats (ILKIW et al. 2002).

BENNETT and STEFFEY (2002) speculated that the dose-related central nervous system stimulation in horses might be the reason for the differences between
species, overwhelming any MAC-reducing effect due to analgesic properties. These findings of experimental studies were confirmed under clinical conditions as horses, premedicated with butorphanol, did not benefit from any MAC-sparing nor any other beneficial effect considering both cardiopulmonary function and recovery quality during isoflurane-medetomidine (3.5 µg kg\(^{-1}\) hour\(^{-1}\)) anaesthesia (BETTSCHART-WOLFENSBERGER et al. 2011).

2.2.7 Dobutamine

Dobutamine, a synthetic catecholamine, consists of two enantiomers. The (-)-isomer provides potent alpha\(_1\)-agonistic properties with only weak action on beta-adrenoreceptors, whereas the more potent (+)-isomer is characterized by strong beta\(_1\)- and beta\(_2\)-agonistic effects (RUFFOLO et al. 1981). It increases HR and cardiac contractility while reducing vascular resistance and diastolic pressure (LAWSON 1994). An increase of CO in man is primarily due to the positive inotropic mechanism and secondarily caused by reduced afterload (LAWSON 1994). The decrease of SVR (and therefore afterload) in horses seems to be less important, as studies reported only a small and often insignificant influence on SVR at clinically relevant doses (SWANSON et al. 1985; RAISIS et al. 2000b). However, at low to moderate infusion rates, dobutamine seems to provide predominantly beta\(_2\)-adrenoreceptor activation (DAUNT 1990).

The use of dobutamine is recommended in hypotensive horses under general anaesthesia to avoid post-anaesthetic myopathy (SWANSON et al. 1985; DONALDSON 1988) since dobutamine is able to improve arterial blood pressure and intramuscular blood flow (LEE et al. 1998). Because half-life is only about two minutes application needs to be given as CRI and can easily be controlled (LAWSON 1994).

Several previous studies investigated the action on cardiovascular function of dobutamine in anaesthetised horses in prospective, experimental trials (SWANSON et al. 1985; GASTHUYS et al. 1991; LEE et al. 1998; YOUNG et al. 1998; RAISIS et al. 2000b). Overall results are conflicting and effects seem to be dose-related. LEE et al. (1998) published an increase of CI, MAP and intramuscular
blood flow for doses above $2.5 \mu g \text{ kg}^{-1} \text{ minute}^{-1}$. GASTHUYS et al. (1991) was able to demonstrate a significantly increased CO, CI and MAP already at lower doses ($1.25 \mu g \text{ kg}^{-1} \text{ minute}^{-1}$) of dobutamine, whereupon increased CO was due to increased SV because HR remained unchanged. RAISIS et al. (2000b) demonstrated an increase of MAP at a dose of $0.5 \mu g \text{ kg}^{-1} \text{ minute}^{-1}$ without changes in cardiac contractility or CO. A clinical study performed by DE VRIES et al. (2009) showed an increased MAP after starting dobutamine infusion ($\sim 1.0 \mu g \text{ kg}^{-1} \text{ minute}^{-1}$), but CO only increased after 30 minutes in combination with surgical stimulation. The authors hypothesised the increase of MAP might be related to peripheral alpha$_1$-mediated vasoconstriction. Moreover a positive chronotropic effect at dosages higher than $2.5 \mu g \text{ kg}^{-1} \text{ minute}^{-1}$ can be seen (SWANSON et al. 1985; GASTHUYS et al. 1991), with increased risk of severe tachycardia and cardiac arrhythmia at doses above $5 \mu g \text{ kg}^{-1} \text{ minute}^{-1}$ (SWANSON et al. 1985; GASTHUYS et al. 1991; YOUNG et al. 1998), including sinus bradycardia, second-degree atrioventricular block, premature ventricular depolarization and isorhythmic dissociation (DONALDSON 1988).

### 2.2.8 Thiopental

Thiopental produces dose-dependent sedation, general anaesthesia, cortical depression and finally death by enhancing the action of gamma-aminobutyric acid (GABA) at the GABA$_A$ receptors (MUIR 2009b). Barbiturates had been used for a long time period to induce and maintain short-term anaesthesia, until most of them have been replaced by other drugs with a wider margin of safety than those. Due to chemical properties (BRODIE et al. 1950) and pharmacokinetics (ABASS et al. 1994), thiopental is characterized by a rapid onset and short duration of action (5 – 15 minutes) and is therefore an ideal drug to deepen anaesthesia extremely fast if required, e.g. in the case of movement during surgery in horses. Most common side effect is a severe respiratory depression, seen in periods of apnoea followed by irregular breathing (TYAGI et al. 1964). As barbiturates accumulate over time (BUTLER et al. 1954), repeated administration has to be accomplished with caution, as this may result in prolonged recovery and severe cortical depression, cardiovascular collapse and death. An adverse impact on
cardiovascular function is seen in increased HR and decreased MAP, as well as decreased CO by myocardial depression following bolus administration (4.4 to 17 mg kg\(^{-1}\)) of thiopental (TYAGI et al. 1964; BUTERA et al. 1980).

After premedication with 0.5 mg kg\(^{-1}\) xylazine an anaesthetic induction dose of 5 - 8 mg kg\(^{-1}\) (BUTERA et al. 1980) in horses results in a 20 minutes lasting anaesthesia. If horses are premedicated with guaifenesin (1 litre of 5 %) 1- 2 g of thiopental leads to lateral recumbency for 15 to 30 minutes (MUIR 2009b). Repeated administration to maintain anaesthesia for a longer period of time can not be recommended (MUIR 2009b).

For adjunctive use during general anaesthesia (“top-up” bolus administration) 0.2 - 0.5 mg kg\(^{-1}\) thiopental are used.
2.3 Monitoring anaesthesia

The assessment of both haemodynamic and respiratory functions and protective and autonomic reflexes during general anaesthesia are the most important measures to improve anaesthetic quality, to evaluate and adapt anaesthetic depth and thus to reduce perioperative morbidity and mortality in horses (RIEBOLD 1990). Basic monitoring parameters are HR, RR and respiratory rhythm, capillary refill time, mucous membrane colour, assessment of peripheral pulse and absence or presence of protective reflexes. Depending on duration of anaesthesia, clinical health status of the horse and used anaesthetic drugs more invasive and advanced techniques may be required. Especially if volatile agents are used, invasive measurement of MAP, electrocardiogram and capnometry seem to be beneficial. Lately the possibility of cardiac output measurement has become appreciable under clinical conditions, which may improve assessment and quality of perfusion further (EDNER et al. 2002; HALLOWELL and CORLEY 2005).

2.3.1 Respiratory function

Respiratory rate can be easily assessed by observing both chest wall and reservoir bag movements and by auscultation. Tidal volume of each breath can be estimated by the degree of collapse of the rebreathing bag if horses are anaesthetised with inhalation agents (MUIR and HUBBELL 2009). To achieve more pronounced information on ventilation more advanced methods, such as capnography and blood gas analysis, are recommended. Blood gas analysis (PaO₂, PaCO₂) is the best method to evaluate and manage anaesthesia in such a way that both hypoventilation and hyperventilation can be avoided and adequate oxygenation can be provided (SCHATZMANN 1995a; MUIR and HUBBELL 2009).
2.3.2 Circulation

Heart rate and rhythm can be easily assessed by auscultation. Further information is provided by an electrocardiogram (ECG), as cardiac arrhythmias and dysrhythmias can be detected (RIEBOLD 1990). Palpation of peripheral pulse can also be performed to evaluate HR if auscultation is not possible due to recumbency of the horse, but it does not provide an adequate information about blood pressure or peripheral perfusion and should not be over-interpreted (MUIR and HUBBELL 2009).

Capillary refill time (CRT) can be used to estimate both perfusion and CO as prolonged CRTs indicate poor perfusion and low CO values. However, the colour of mucous membranes can be influenced differently by anaesthetic drugs (e.g. vasoconstriction by alpha2-agonists versus vasodilation by isoflurane) (MUIR and HUBBELL 2009).

The best, but also the most invasive method is to evaluate circulation in clinical practice by measuring MAP invasively, which should not be lower than 70 mmHg to prevent postoperative myopathy (RICHEY et al. 1990; RIEBOLD 1990; YOUNG and TAYLOR 1993). Therefore an arterial catheter is placed in a peripheral artery and connected to a pressure-sensing device, zeroed at the level of the heart. Best accessible arteries are the facial, the transverse faciei and the metatarsal arteries. Catheters have to be flushed regularly to maintain patency and, therefore, to avoid dampening of the arterial waveform.

2.3.2.1 Cardiac output measurement

A more detailed evaluation of circulation can be provided by measuring cardiac output (CO; l minute⁻¹), which is defined as the total amount of blood that is pumped by the heart in one minute and thus depends on heart rate (HR; beats minute⁻¹) and stroke volume (SV; l minute⁻¹). Furthermore it is inversely related to systemic vascular resistance (SVR; mmHg l⁻¹ minute⁻¹, simplified equation by KLABUNDE et al. (2005)) (SCHAUVLIEGE et al. 2008).
Cardiac index (CI; ml kg\(^{-1}\) minute\(^{-1}\)) is described as CO divided by body weight (bwt; kg).

\[
CI = \frac{\text{CO} \times 1000}{\text{bwt}}
\]

Normal cardiac indices for healthy, adult and awake horses (400-500 kg) are reported to be between 56 – 88 ml kg\(^{-1}\) minute\(^{-1}\) (MUIR et al. 1976; CLARK et al. 1991; BONAGURA and REEF 1998; SCHWARZWALD et al. 2005). In anaesthetised horses CO depends on applied drugs for both premedication and anaesthetic protocol, used dose, mode of ventilation and depth of anaesthesia as volatile agents depress cardiovascular function dose-dependently (STEFFEY and HOWLAND 1978, 1980). Mechanical ventilation reduces CO further due to increased thoracic pressure, resulting in a decreased venous return and less diastolic filling, leading to lower cardiac output values (MIZUNO et al. 1994a). Therefore, published CO or cardiac index values may vary a lot. However, for anaesthesia maintained with volatile agents (isoflurane or halothane), reported cardiac indices range between 51 to 72 ml kg\(^{-1}\) minute\(^{-1}\) (HILLIDGE and LEES 1975; HALLOWELL and CORLEY 2005; BLISSITT et al. 2008), but values may decrease below 40 ml kg\(^{-1}\) minute\(^{-1}\) depending on MAC multiples (STEFFEY and HOWLAND 1980).

Cardiac output is the most important determinant of muscle perfusion and therefore oxygen delivery to the tissues (EDNER et al. 2002). Though monitoring of CO during general anaesthesia might improve perfusion quality due to a better control of peripheral perfusion and might therefore prevent horses suffering from postoperative myopathy as amounts of anaesthetics can be titrated exactly to the individual required dose (EDNER et al. 2002). Unfortunately measurement of cardiac output has been very challenging in equine medicine over many years because available methods have been expensive, invasive, complicated to perform and/or have been
associated with complications. Therefore, measurement of CO was not possible to accomplish in clinical practice and its use was limited to experimental study designs.

2.3.2.1.1 The Fick principle

The Fick principle was firstly introduced 1870 (FICK) and validated in horses in 1898 (ZUNTZ and HAGEMANN). Until now it represents the "gold standard" and whenever new methods for CO measurement are investigated, they should be compared to this principle (HARYADI et al. 2000). The principle bases on oxygen consumption (VO$_2$) and the difference between arterial (CaO$_2$) and venous (CvO$_2$) oxygen blood content with the underlying theory that all oxygen is removed from inspired air by the blood whenever it passes the lung (CORLEY et al. 2003):

$$CO = \frac{VO_2}{CaO_2 - CvO_2}$$

Measurements of those variables are partially difficult. Oxygen consumption can be measured non-invasively over a face mask or intubation, but with requirement of a long equilibration time, whereas CaO$_2$ can quite easily be measured by blood gas analysis of arterial blood. A crucial factor for clinical use is the need of right heart catheterization for a pulmonary arterial catheter to measure CvO$_2$, which can implicate complications: Pulmonic valve lesions, dysrhythmias during insertion and septicemia traced to the catheter are only a few published examples for complications in man (ELLIOTT et al. 1979).

To avoid invasive right heart catheterization, an indirect method was developed by using carbon dioxide as parameter, based on partial carbon dioxide rebreathing. Using this “indirect Fick technique” a non-invasive cardiac output monitoring system (NICO) has been validated in people and dogs (HARYADI et al. 2000; ODENSTEDT et al. 2002). Indirect measurement has also been used in anaesthetised foals (GIGUERE et al. 2005; VALVERDE et al. 2007) representing one of the currently available non-invasively methods to measure cardiovascular function, which is extremely interesting and important particularly in critically ill neonatal foals.
Unfortunately, results were not such as accurate as compared to other methods to estimate cardiac output.

2.3.2.1.2 Indicator Dilution Methods

New techniques are indicator dilution methods, which are named based on the used indicator (dye dilution, thermodilution and lithium dilution). By measuring concentration of a known marker in the arterial blood (as for example a dye, cold solution or other chemical substances), which has been injected intravenously, cardiac output can be estimated as the marker is diluted by the blood passing the heart (CORLEY et al. 2003). Thus quantity of dilution reflects amount of blood pumped by the heart in a defined time unit as the higher the CO values, the greater the dilution in a certain volume of blood, the less amount of indicator is measured in the artery and the smaller is the “area under the curve” of a the time-concentration curve (CORLEY et al. 2003).

Calculation of CO can be performed by the following equation (CORLEY et al. 2003):

$$CO \ (l \ minute^{-1}) = \frac{\text{amount of indicator injected (mg)}}{\int (\text{concentration} \ [mg \ l^{-1}] \times \text{time} \ [minute])}$$

Use of indicator dilution techniques is limited in the presence of intracardiac shunts as indicator gets lost between injection and detection and measurement is becoming inaccurate (JONAS and TANSER 2002; CORLEY et al. 2003).

2.3.2.1.2.1 Dye dilution

In the past dye dilution has been used in horses quite often in experimental studies designed to measure CO (HILLIDGE and LEES 1975; MUIR et al. 1976) or to compare accuracy of newer techniques with this older, established method (MIZUNO et al. 1994b). Indicator is a dye, commonly indocyanine green as it is nontoxic, rapidly metabolised and measurable by using a photodensitometer (LUND-JOHANSEN 1990). Unfortunately this technique provides some disadvantages, too.
The photodensitometer has to be calibrated to the animals’ blood, a time-consuming process. Moreover, repeated measurements can lead to inaccuracy as the dye might accumulate or might recirculate through the heart (CORLEY et al. 2003).

2.3.2.1.2.2 Thermodilution

Thermodilution, a commonly used method, has been investigated in adult horses and foals (MIZUNO et al. 1994b; LINTON et al. 2000; CORLEY et al. 2002). After injection of a cold solution, for example saline, measured blood temperature in a pulmonary artery changes related to CO. Benefits are both inexpensive materials and the lack of indicator accumulation and thus the possibility of repeated measurements. Unfortunately thermodilution offers no advantage over the original “Fick principle” clinically as it also requires right heart catheterization and should therefore be avoided in clinical cases because of being relatively invasive, associated with already mentioned complications (CORLEY et al. 2003). Besides that, correct placement of a pulmonary artery catheter can be time-consuming (LINTON et al. 2000). Inaccuracy of estimation can occur if syringe with cold solution is warmed during handling prior to injection (CORLEY et al. 2003).

2.3.2.1.2.3 Lithium dilution

With the development of lithium dilution, there is now a technique available that can be applied in clinical practice as right heart catheterization is avoided. Lithium dilution represents a safe, non-invasive and simple method, already validated in horses and foals (LINTON et al. 2000; CORLEY et al. 2002; HALLOWELL and CORLEY 2005). This technology requires no pulmonary artery catheter only a venous and an arterial line access both already inserted in the anaesthetised horse as receiving a catheter in one jugular vein for drug administration and one in a peripheral artery for MAP measurement. After venous injection of a lithium chloride bolus and transpulmonary pass, concentration of lithium is measured by an arterial ion-selective electrode attached to the arterial manometer system (JONAS and TANSER 2002). The cardiac output can
then be determined, as with other indicator techniques, mathematically by the “area under the curve” of a time-concentration curve (JONAS and TANSER 2002). Such a curve, generated by the LiDCO™ plus system, is presented in Figure 2.1.

Lithium dilution and its accuracy has been tested, established and compared to older methods (thermodilution, electromagnetic flowmetry, transoesophageal Doppler echocardiography and partial carbon dioxide rebreathing) in many species like man, pigs, adult horses and foals (LINTON et al. 1997; KURITA et al. 1999; LINTON et al. 2000; CORLEY et al. 2002; VALVERDE et al. 2007). All authors concluded that lithium dilution is at least as accurate as thermodilution with the great advantage of being applicable in clinical cases because of its safety and easy handling. HATFIELD et al. (2001) was also able to demonstrate the lack of any toxic effects of lithium up to 60 mmol horse⁻¹ in a 60-minute period, which is a multiple of required dose since a single cardiac output determination requires only 2.250 mmol of lithium (LINTON et al. 2000). Disadvantages are based on the potential of lithium accumulation in the case of repeated measurements resulting in higher background levels of lithium leading to an underestimation of CO and additionally on the need of haemodynamic stability during indicator distribution from venous to arterial vessels. As applied to all indicator dilution methods, measurement is getting inaccurate in patients suffering from intracardiac shunts, as described above, leading to an overestimation of CO (JONAS and TANSER 2002; CORLEY et al. 2003).
Figure 2.1 Lithium dilution curve in a three-year-old thoroughbred generated by the LiDCO™plus system (LiDCO Ltd., London, UK). The X-axis represents time in seconds, whereas Y-axis demonstrates the measured concentration of lithium. Using the area under the curve, cardiac output can be calculated using the Stewart-Hamilton equation (CORLEY et al. 2003).

2.3.2.1.3 Pulse contour analysis (PulseCO)

“Pulse contour analysis” bases on the theory that the area under the curve of the arterial waveform (Figure 2.2) is related to CO since, during systole, blood is ejected into the catheterised arterial vessel, increasing the arterial pressure (GRAVES et al. 1968; CORLEY et al. 2003). It is established under clinical conditions in man, especially during, or rather after cardiac surgery in intensive care units (RÖDIG et al. 1999; LINTON and LINTON 2001; GÖDJE et al. 2002). With the aid of pulse contour analysis and development of a commercial machine using this technique in conjunction with lithium dilution calibration (LiDCO™plus; LiDCO Ltd., London, UK) it is now possible to give a beat-by-beat estimate of cardiac output by calculating stroke volume from the arterial pressure waveform using an autocorrelation algorithm without the need of cardiovascular stability as required for other dilution techniques.
Blood ejected by the systole discharges the aortic vessel depending on quantity (stroke volume). Thus the higher the stroke volume is the greater is the increased pressure. Therefore CO can be calculated by the following equation developed for use in man (GÖDJE et al. 2002; CORLEY et al. 2003):

$$CO = cal \times HR \times \int \left( \frac{P(t)}{SVR} + C(p) \times \frac{dP}{dt} \right) dt,$$

where cal is a patient-specific calibration factor, HR represents heart rate (beats minute$^{-1}$); $P(t)$ = pressure against time; SVR = systemic vascular resistance; $P(t)/SVR$ represents the area of the pressure curve; $C(p)$ = describes the compliance; $dP$ = change in pressure; $dt$ = change in time; and $dP/dt$ reflects the shape of the pressure curve (GÖDJE et al. 2002; CORLEY et al. 2003).

Thus this technique has to be calibrated for each patient or animal once, as the shape of arterial waveform is individually due to differences in arterial elasticity depending on several, different factors like age, gender and subject size (MCVEIGH et al. 1999; WINER et al. 2001). Calibration can be performed with either lithium dilution (CORLEY et al. 2003), as used in the LiDCO$^\text{TM}$plus system (LiDCO Ltd.,
Review of literature

London, UK), or by transpulmonary thermodilution (SHIH et al. 2009), as utilised in another system (PiCCO®, Pulsion Medical Systems, Munich, Germany). As based on a human algorithm, suitability and accuracy in animals remain questionable, although use has been adopted and evaluated in horses, foals and dogs (CHEN et al. 2005; HALLOWELL and CORLEY 2005; SHIH et al. 2009). Indeed authors have concluded that PulseCO is comparable with results estimated by lithium dilution, but accuracy seems to weaken especially with strong haemodynamic changes after initial calibration in critically ill humans as well as in dogs and horses (TANNENBAUM et al. 1993; CHEN et al. 2005; SCHAUVLIEGE et al. 2009), whereby continuous recalibrations are strongly recommended.

2.3.2.1.4 Other cardiac output measurement methods

Both transthoracic and transoesophageal Doppler echocardiography can be performed during general anaesthesia in horses (RAISIS et al. 2000a; CORLEY et al. 2003). It provides a sensitive and non-invasive estimation of cardiac output, but also requires some experience to perform and the need of expensive technical equipment. Transthoracic bioimpedance seems not to provide satisfactory results in animals as the human algorithm is not sufficiently accurate for use in horses (CORLEY et al. 2003).
2.3.3 Determination of anaesthetic depths

Monitoring of palpebral reflexes, corneal responses, eye position and the presence or absence of nystagmus is suitable to estimate anaesthetic depth in horses correctly (MUIR and HUBBELL 2009).

Historically depth of gas anaesthesia was described and classified into stages and planes defined and published by Guedel (GUEDEL 1927; GUEDEL 1951). Physical signs for each stage of anaesthesia (analgesia, excitation, tolerance with four planes from light to deep and finally the stage of asphyxia) were described for anaesthesia with increasing doses of diethyl ether in unpremedicated humans. Those stages and planes have been modified in various species and with the development of other anaesthetic drugs and for anaesthesia maintained with intravenous drugs as physical responses are influenced differently by various anaesthetic agents (MUIR and HUBBELL 2009; STEFFEY 2009). Especially dissociative anaesthetics, as e.g. ketamine, may preserve reflexes much more than classical inhalation agents (SCHATZMANN and GIRARD 1984; MUIR and HUBBELL 2009), which can be seen in centrally positioned globe, unstimulated blinking, lacrimation and oculogyric activity (MUIR and HUBBELL 2009). Today general characteristics of horses at three levels of general anaesthesia, which are premedicated, ketamine-based induced and maintained with an inhalation agent, are described by STEFFEY (2009).

If different anaesthetic drugs are combined as for example during balanced anaesthesia, anaesthetists have to learn estimation of anaesthetic depth depending on applied drugs (SCHATZMANN and GIRARD 1984; KALCHOFNER et al. 2006).

Anaesthetic depth can also be estimated by other physical signs like muscle tone, movement, response to surgical stimulation or changes in MAP, HR and RR. Last mentioned points can again be influenced and accordingly depressed by anaesthetic drugs (WAGNER et al. 1992; MUIR and HUBBELL 2009).
3 Material and Methods

3.1 Animals

Fifty-one client-owned horses of various ages, breeds (see Table 3.1) and body weight (bwt) undergoing elective surgery at the Clinic for Horses of the University of Veterinary Medicine Hannover, Foundation, were included into this study. Animals were determined to be healthy by clinical examination before inclusion. Furthermore a minimum age of 12 months, a minimum body weight of 300 kg and an anticipated anaesthetic duration of at least 90 and at the most 180 minutes were required for including horses in this study. Surgeries where eyes were covered (head and eye surgery) were excluded as well as horses with cardiac murmurs. The experimental protocol was approved by the State Office for Consumer Protection and Food Safety in accordance to the German Animal Welfare Law.

3.2 Assignment of animals to groups

Horses were randomly assigned to one of three treatment groups, but matched according to type of surgery and recumbency. Anaesthesia in group isoflurane (I) was maintained with isoflurane only in oxygen, whereas horses in both other groups received additionally a constant rate infusion (CRI) of either ketamine at 1 mg kg\(^{-1}\) hour\(^{-1}\) (IK) or xylazine (IX) at 1 mg kg\(^{-1}\) hour\(^{-1}\). Finally, each group consisted of seventeen horses.
### Table 3.1.1. Demographic data of horses anaesthetised with isoflurane (group I)

<table>
<thead>
<tr>
<th>No.</th>
<th>Recumbency</th>
<th>Breed</th>
<th>Age [years]</th>
<th>Bwt [kg]</th>
<th>Type of surgery</th>
<th>Duration of anaesthesia [minute]</th>
</tr>
</thead>
<tbody>
<tr>
<td>I 1</td>
<td>dorsal</td>
<td>WB</td>
<td>2</td>
<td>480</td>
<td>Castration</td>
<td>90</td>
</tr>
<tr>
<td>I 2</td>
<td>dorsal</td>
<td>WB</td>
<td>3</td>
<td>552</td>
<td>Arthroscopy</td>
<td>180</td>
</tr>
<tr>
<td>I 3</td>
<td>lateral</td>
<td>WB</td>
<td>1</td>
<td>365</td>
<td>Fistula excision</td>
<td>180</td>
</tr>
<tr>
<td>I 4</td>
<td>dorsal</td>
<td>WB</td>
<td>9</td>
<td>545</td>
<td>Septic funiculitis</td>
<td>110</td>
</tr>
<tr>
<td>I 5</td>
<td>dorsal</td>
<td>WB</td>
<td>2</td>
<td>534</td>
<td>Arthroscopy</td>
<td>130</td>
</tr>
<tr>
<td>I 6</td>
<td>dorsal</td>
<td>WB</td>
<td>4</td>
<td>512</td>
<td>Castration</td>
<td>90</td>
</tr>
<tr>
<td>I 7</td>
<td>lateral</td>
<td>WB</td>
<td>14</td>
<td>587</td>
<td>Neurectomy</td>
<td>120</td>
</tr>
<tr>
<td>I 8</td>
<td>lateral</td>
<td>WB</td>
<td>6</td>
<td>547</td>
<td>Tendon surgery</td>
<td>90</td>
</tr>
<tr>
<td>I 9</td>
<td>lateral</td>
<td>WB</td>
<td>4</td>
<td>533</td>
<td>Tendon surgery</td>
<td>90</td>
</tr>
<tr>
<td>I 10</td>
<td>lateral</td>
<td>WB</td>
<td>3</td>
<td>548</td>
<td>Tendon surgery</td>
<td>90</td>
</tr>
<tr>
<td>I 11</td>
<td>lateral</td>
<td>WB</td>
<td>5</td>
<td>602</td>
<td>Arthroscopy</td>
<td>180</td>
</tr>
<tr>
<td>I 12</td>
<td>lateral</td>
<td>WB</td>
<td>16</td>
<td>541</td>
<td>Bursoscopy</td>
<td>110</td>
</tr>
<tr>
<td>I 13</td>
<td>dorsal</td>
<td>WB</td>
<td>2</td>
<td>480</td>
<td>Arthroscopy</td>
<td>120</td>
</tr>
<tr>
<td>I 14</td>
<td>dorsal</td>
<td>WB</td>
<td>2</td>
<td>465</td>
<td>Arthroscopy</td>
<td>90</td>
</tr>
<tr>
<td>I 15</td>
<td>dorsal</td>
<td>WB</td>
<td>2</td>
<td>480</td>
<td>Arthroscopy</td>
<td>100</td>
</tr>
<tr>
<td>I 16</td>
<td>dorsal</td>
<td>F</td>
<td>4</td>
<td>408</td>
<td>Castration</td>
<td>120</td>
</tr>
<tr>
<td>I 17</td>
<td>dorsal</td>
<td>WB</td>
<td>2</td>
<td>460</td>
<td>Arthroscopy</td>
<td>170</td>
</tr>
</tbody>
</table>

WB, warmblood horse; F, Frisian
Table 3.1.2 Demographic data of horses anaesthetised with isoflurane and a constant rate infusion of ketamine (group IK)

<table>
<thead>
<tr>
<th>No.</th>
<th>Recumbency</th>
<th>Breed</th>
<th>Age [years]</th>
<th>Bwt [kg]</th>
<th>Type of surgery</th>
<th>Duration of anaesthesia [minute]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IK 1</td>
<td>dorsal</td>
<td>WB</td>
<td>5</td>
<td>550</td>
<td>Castration</td>
<td>100</td>
</tr>
<tr>
<td>IK 2</td>
<td>dorsal</td>
<td>WB</td>
<td>3</td>
<td>500</td>
<td>Arthroscopy</td>
<td>90</td>
</tr>
<tr>
<td>IK 3</td>
<td>lateral</td>
<td>WB</td>
<td>11</td>
<td>613</td>
<td>Neurectomy</td>
<td>180</td>
</tr>
<tr>
<td>IK 4</td>
<td>dorsal</td>
<td>GP</td>
<td>19</td>
<td>430</td>
<td>Phallectomy</td>
<td>140</td>
</tr>
<tr>
<td>IK 5</td>
<td>dorsal</td>
<td>WB</td>
<td>3</td>
<td>530</td>
<td>Arthroscopy</td>
<td>90</td>
</tr>
<tr>
<td>IK 6</td>
<td>dorsal</td>
<td>WB</td>
<td>3</td>
<td>542</td>
<td>Castration</td>
<td>90</td>
</tr>
<tr>
<td>IK 7</td>
<td>lateral</td>
<td>WB</td>
<td>3</td>
<td>498</td>
<td>Bone surgery</td>
<td>120</td>
</tr>
<tr>
<td>IK 8</td>
<td>lateral</td>
<td>WB</td>
<td>3</td>
<td>502</td>
<td>Tendon surgery</td>
<td>90</td>
</tr>
<tr>
<td>IK 9</td>
<td>lateral</td>
<td>WB</td>
<td>3</td>
<td>555</td>
<td>Tendon surgery</td>
<td>90</td>
</tr>
<tr>
<td>IK 10</td>
<td>lateral</td>
<td>WB</td>
<td>3</td>
<td>482</td>
<td>Tendon surgery</td>
<td>90</td>
</tr>
<tr>
<td>IK 11</td>
<td>lateral</td>
<td>WB</td>
<td>2</td>
<td>400</td>
<td>Arthroscopy</td>
<td>90</td>
</tr>
<tr>
<td>IK 12</td>
<td>lateral</td>
<td>WB</td>
<td>4</td>
<td>537</td>
<td>Arthroscopy</td>
<td>100</td>
</tr>
<tr>
<td>IK 13</td>
<td>dorsal</td>
<td>WB</td>
<td>3</td>
<td>551</td>
<td>Arthroscopy</td>
<td>135</td>
</tr>
<tr>
<td>IK 14</td>
<td>dorsal</td>
<td>WB</td>
<td>2</td>
<td>480</td>
<td>Arthroscopy</td>
<td>100</td>
</tr>
<tr>
<td>IK 15</td>
<td>dorsal</td>
<td>WB</td>
<td>3</td>
<td>484</td>
<td>Arthroscopy</td>
<td>90</td>
</tr>
<tr>
<td>IK 16</td>
<td>dorsal</td>
<td>WB</td>
<td>4</td>
<td>565</td>
<td>Castration</td>
<td>90</td>
</tr>
<tr>
<td>IK 17</td>
<td>dorsal</td>
<td>WB</td>
<td>2</td>
<td>480</td>
<td>Arthroscopy</td>
<td>180</td>
</tr>
</tbody>
</table>

WB, warmblood horse; GP, German riding pony
Table 3.1.3 Demographic data of horses anaesthetised with isoflurane and a constant rate infusion of xylazine (group IX)

<table>
<thead>
<tr>
<th>No.</th>
<th>Recumbency</th>
<th>Breed</th>
<th>Age [years]</th>
<th>Bwt [kg]</th>
<th>Type of surgery</th>
<th>Duration of anaesthesia [minute]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IX 1</td>
<td>dorsal</td>
<td>Polo</td>
<td>5</td>
<td>470</td>
<td>Arthroscopy</td>
<td>90</td>
</tr>
<tr>
<td>IX 2</td>
<td>dorsal</td>
<td>WB</td>
<td>2</td>
<td>500</td>
<td>Arthroscopy</td>
<td>170</td>
</tr>
<tr>
<td>IX 3</td>
<td>lateral</td>
<td>WB</td>
<td>3</td>
<td>515</td>
<td>Arthroscopy</td>
<td>90</td>
</tr>
<tr>
<td>IX 4</td>
<td>dorsal</td>
<td>F</td>
<td>3</td>
<td>565</td>
<td>Castration</td>
<td>100</td>
</tr>
<tr>
<td>IX 5</td>
<td>dorsal</td>
<td>GP</td>
<td>2</td>
<td>300</td>
<td>Septic funiculitis</td>
<td>135</td>
</tr>
<tr>
<td>IX 6</td>
<td>dorsal</td>
<td>WB</td>
<td>7</td>
<td>593</td>
<td>Castration</td>
<td>90</td>
</tr>
<tr>
<td>IX 7</td>
<td>lateral</td>
<td>WB</td>
<td>2</td>
<td>480</td>
<td>Arthrodesis</td>
<td>160</td>
</tr>
<tr>
<td>IX 8</td>
<td>lateral</td>
<td>WB</td>
<td>3</td>
<td>555</td>
<td>Tendon surgery</td>
<td>90</td>
</tr>
<tr>
<td>IX 9</td>
<td>lateral</td>
<td>WB</td>
<td>4</td>
<td>533</td>
<td>Tendon surgery</td>
<td>90</td>
</tr>
<tr>
<td>IX 10</td>
<td>lateral</td>
<td>WB</td>
<td>4</td>
<td>552</td>
<td>Tendon surgery</td>
<td>90</td>
</tr>
<tr>
<td>IX 11</td>
<td>lateral</td>
<td>WB</td>
<td>2</td>
<td>508</td>
<td>Arthroscopy</td>
<td>140</td>
</tr>
<tr>
<td>IX 12</td>
<td>lateral</td>
<td>WB</td>
<td>3</td>
<td>530</td>
<td>Arthroscopy</td>
<td>140</td>
</tr>
<tr>
<td>IX 13</td>
<td>dorsal</td>
<td>WB</td>
<td>17</td>
<td>695</td>
<td>Arthroscopy</td>
<td>140</td>
</tr>
<tr>
<td>IX 14</td>
<td>dorsal</td>
<td>WB</td>
<td>3</td>
<td>484</td>
<td>Arthroscopy</td>
<td>100</td>
</tr>
<tr>
<td>IX 15</td>
<td>dorsal</td>
<td>WB</td>
<td>2</td>
<td>467</td>
<td>Arthroscopy</td>
<td>120</td>
</tr>
<tr>
<td>IX 16</td>
<td>dorsal</td>
<td>WB</td>
<td>2</td>
<td>480</td>
<td>Castration</td>
<td>90</td>
</tr>
<tr>
<td>IX 17</td>
<td>dorsal</td>
<td>WB</td>
<td>2</td>
<td>545</td>
<td>Arthroscopy</td>
<td>90</td>
</tr>
</tbody>
</table>

WB, warmblood horse; F, Frisian; GP, German riding pony; Polo, Polo pony
3.3 Experimental setup

3.3.1 Preoperative examination and preparations

Horses were starved overnight for at least six hours prior to induction of anaesthesia, but access to water was always guaranteed. In addition to a physical examination at the day of surgery, a haematological examination of each horse was performed as well. Haematocrit (HTC [%]), count of white blood cells (WBC [G/l]) and the total amount of plasma protein (PP [g/l]) were measured. The HTC and WBC were specified by a blood analyser (Sysmex KX-21; Sysmex Deutschland GmbH, Norderstedt, Germany) and PP was determined using a hand refractometer (Hand Refraktometer; Euromex Microscopen BV, Arnhem, Netherlands).

The hair over the proximal third of one jugular vein was clipped, skin aseptically prepared and an indwelling venous catheter was placed (12 SWG; EquiCath™ Fastflow; Braun Vet Care GmbH, Tuttlingen, Germany) after local infiltration anaesthesia with mepivacaine hydrochloride (Scandicain 2%; AstraZeneca GmbH, Wedel, Germany).

3.3.2 Premedication and induction of general anaesthesia

Thirty minutes before induction of anaesthesia all animals were premedicated with a non-steroidal anti-inflammatory drug (flunixin meglumine (Flunidol®; CP-Pharma GmbH, Burgdorf, Germany); 1.1 mg kg\(^{-1}\) IV) and antimicrobial agents if required depending on the surgical case. At that time point horses received acepromazine (Vetranquil®; Albrecht GmbH, Aulendorf, Germany) (0.03 mg kg\(^{-1}\) IM) as well.

Before induction of anaesthesia horses were sedated with xylazine (Xylazin 2 %®; CP-Pharma GmbH, Burgdorf, Germany) (0.5 mg kg\(^{-1}\) IV) and butorphanol (Alvegesic®; CP-Pharma GmbH, Burgdorf, Germany) (0.025 mg kg\(^{-1}\) IV) and restrained behind a swinging door. A rope in front of the horses’ chest was clamped to avoid horses falling forward. If sedation was inadequate after five to eight minutes for smooth induction additional bolus of 0.15 mg kg\(^{-1}\) xylazine IV were given to effect and the final amount recorded. Once horses were adequately sedated, anaesthesia
was induced with ketamine (Narketan®; Vetoquinol GmbH, Ravensburg, Germany) and midazolam (Midazolam-ratiopharm®; Ratiopharm GmbH, Ulm, Germany) at a dose of 2.2 mg kg\(^{-1}\) IV and 0.06 mg kg\(^{-1}\) IV, respectively. Once the horse was laterally recumbent, the halter was removed, a mouth gag inserted and the trachea was intubated using a cuffed endotracheal tube (SurgiVet™; Smiths medical ASD, St. Paul, USA). Horses were hoisted on the surgery table in lateral or dorsal recumbency depending on the surgical case.

### 3.3.3 Anaesthetic protocol and ventilation
Immediately after intubation horses were connected to a large animal anaesthesia machine (Vet.-Tec. Model JAVC 2000 J.D. Medical Distributing Company Phoenix, USA) and ventilated using a pressure limited large animal respirator (modified Bird® Mark 7; Bird® Products Corporation, Palm Springs, USA). Intermittent positive pressure ventilation (IPPV) was performed with a peak inspiratory pressure (PIP) between 20 and 30 cmH\(_2\)O and the frequency was adjusted to maintain ETCO\(_2\) between 4.7 and 6 kPa (35 and 45 mmHg).

Anaesthesia was maintained using isoflurane (Isoflurane CP®; CP-Pharma GmbH, Burgdorf, Germany; Isoflurane Vapor 2000; Drägerwerk AG, Lübeck, Germany) in oxygen (6 l minute\(^{-1}\); reduced to 1 litre 100 kg\(^{-1}\)). Additionally horses in group IK and IX received a CRI of either ketamine (1 mg kg\(^{-1}\) hour\(^{-1}\)) or xylazine (1 mg kg\(^{-1}\) hour\(^{-1}\)), respectively. Ketamine infusion in group IK was reduced to 50% after an anaesthetic duration of two hours and stopped after a three hour administration, as well as 20 minutes before the end of general anaesthesia. All constant rate infusions were administered by an automatic infusion pump (Perfusor® compact; Braun Melsungen AG, Melsungen, Germany).

### 3.3.4 Cardiovascular support
Ringer's solution (Ringer®, Braun Melsungen AG, Melsungen, Germany) was infused for the duration of anaesthesia at a rate of 5 ml kg\(^{-1}\) hour\(^{-1}\). Each horse received a CRI of dobutamine (Dobutamin-ratiopharm®; Ratiopharm GmbH, Ulm, Germany) at a
dose of 0.3 µg kg\(^{-1}\) minute\(^{-1}\) until an arterial catheter was placed and connected for blood pressure monitoring. After the first blood pressure measurement, the dobutamine dose was adjusted (gradually increased or decreased) every 5 minutes to maintain MAP above 70 mmHg. If MAP remained below 70 mmHg after achieving 1.25 µg kg\(^{-1}\) minute\(^{-1}\) dobutamine, the Ringer's solution infusion rate was increased to 10 ml kg\(^{-1}\) hour\(^{-1}\) and patients received additionally hydroxyethyl starch (Tetraspan 10\(^{\circledast}\), Braun Melsungen AG, Melsungen, Germany) until the MAP recovered above 70 mmHg.

3.3.5 Recovery

At the end of surgery horses were weaned from IPPV and isoflurane. After regaining spontaneous respiration, horses were placed in a padded recovery box, where they recovered unassisted. Extubation was performed when swallowing and/or nystagmus was observed. Horses in group I and IK received a bolus of 0.25 mg kg\(^{-1}\) IV xylazine, whereas group IX received an additional bolus (0.1 mg kg\(^{-1}\) IV) if they showed early nystagmus if still being padded on the surgery table. Phenylephrine hydrochloride (Phenylephrin-Lösung\(^{\circledast}\); Löwen-Apotheke, Hanover, Germany) was instilled into the ventral nasal meatus to reduce nasal mucosal swelling. During recovery oxygen was insufflated at 15 l minute\(^{-1}\) as long as patients were recumbent and tolerated insufflation.
3.4 Determination of anaesthetic depth

Depth of anaesthesia was assessed and consequently isoflurane administration was adjusted using a scoring system published previously by ENDERLE et al. (2008) (see flow-chart presented in Figure 3.1) every five minutes. Based upon clinical signs like presence or absence of the palpebral reflex, nystagmus, body movements and variations in MAP the ETISO (vol %) was adjusted as required. For this purpose ENDERLE et al. developed a scoring system (see Figure 3.1), from score -1 (very deep anaesthesia) to score 4 (very light anaesthesia), where score 0 was desired as this was assumed to provide an adequate anaesthetic depth. Horses with a score between 2 and 4 received an additional bolus of thiopental-sodium (Trapanal®2.5g; Nycomed Deutschland GmbH, Konstanz, Germany) (0.5 mg kg\(^{-1}\) to 1.5 mg kg\(^{-1}\) IV) to deepen anaesthesia extremely fast. The amount of thiopental required was recorded.

**Figure 3.1:** Flow chart presenting the algorithm for evaluation of anaesthetic depth and adaption of isoflurane administration using a scoring system from -1 to 4 previously published by ENDERLE et al. (2008). Mean arterial pressure (MAP) reference implied the measured MAP immediately prior to first surgical stimulation. THIO = thiopental; ISO = isoflurane.
3.5 Intraoperative monitoring

After complete instrumentation (approximately ten minutes) data acquisition at predetermined intervals was started. Time points were defined as follows: $T_0$ (immediately after induction), $T_{10}$ (10 minutes after induction), $T_{20}$ (20 minutes after induction) and so on until a maximum anaesthesia time of 180 minutes after induction ($T_{180}$).

Measurement of HR, respiratory rate (RR), MAP, ETISO was performed by a multiparameter monitor (Datex-Ohmeda Cardiocap/5; GE Healthcare, Wisconsin, USA).

3.5.1 Heart rate

Heart rate (HR) and possible arrhythmias were monitored continuously by an electrocardiogram (ECG). The ECG was performed using a base-apex lead, where one electrode was set on the left chest and another one dorsally of the right jugular vein. If horses were laterally recumbent on the right side of the body, electrodes were placed the other way round. HR was recorded every ten minutes.

3.5.2 Respiratory rate and end-expiratory concentration of isoflurane

Respiratory rate (RR) was measured via a capnogram. The ETCO$_2$ and the end-expiratory concentration of isoflurane (ETISO) were analysed by side stream capnography and infrared spectroscopy, respectively. Gas was sampled from the Y-piece and measured CO$_2$ was displayed as a waveform of partial pressure as well as numerical as ETCO$_2$ and RR. ETISO was displayed as number (vol %) on the monitor. Based on ETCO$_2$ measurement, ventilation was adjusted to maintain ETCO$_2$ between 35 and 45 mmHg (4.7 – 6 kPa) by changing peak inspiratory pressure (PIP) between 20 and 30 cmH$_2$O and by adapting frequency between 5 and 8 breaths minute$^{-1}$. RR (breaths minute$^{-1}$) and ETISO (vol %) were recorded every ten minutes.
3.5.3 Mean arterial pressure
Systemic arterial pressure was measured invasively. A 20 SWG catheter (Venocan™ IV Catheter; Jørgen Kruuse AG, Langeskov, Denmark) was placed in the facial or transverse facial artery after hair had been clipped and skin aseptically prepared. The arterial catheter was connected via a three-way stopcock and a non compliant pressure tubing to a precalibrated electronic pressure transducer (BD DTXPlus™ Transducer; Becton Dickinson Critical Care Systems, Singapore, Singapore). Pressure curves were displayed via the multiparameter monitor (Datex-Ohmeda Cardiocap/5; GE Healthcare, Wisconsin, USA). The transducer was positioned and zeroed against the atmosphere at the level of the sternal manubrium. To prevent clotting and damping of the arterial waveform, artery line was flushed intermittently with heparinised saline (5 IU ml⁻¹). On the remaining outlet of the three-way stopcock the lithium-sensitive sensor for CO measurement was connected (see chapter 3.5.5). A continuous measurement of diastolic, mean and systolic arterial blood pressure occurred and arterial waveform was displayed on the monitor over the whole anaesthetic period. MAP (mmHg) was recorded every ten minutes.

3.5.4 Arterial blood gas analysis
For sampling arterial blood a second three-way stopcock was placed between the pressure tubing and the electronic pressure transducer. Using this valve, blood samples were anaerobically taken from the arterial line at each CO determination time point (T₃₀, T₆₀, T₉₀, T₁₂₀, T₁₅₀). The samples were analysed for arterial partial pressure of oxygen (PaO₂; mmHg) and arterial partial pressure of carbon dioxide (PaCO₂; mmHg) by a commercial, stationary machine (ABL 800 Flex; Radiometer GmbH, Willich, Germany) immediately operated by an auxiliary person. Arterial saturation of oxygen (SaO₂; %) was calculated based on system inbuilt algorithms using PaO₂ and pH (ABL 800 Flex; Radiometer GmbH, Willich, Germany) with a preset p50 of 37 mmHg (the PaO2 level at which 50 % of haemoglobin is saturated). Parameters PaO₂ and PaCO₂ were also expressed in kPa using following equation: kPa= mmHg x 0.133.
3.5.5 Cardiac output

Cardiac output (CO; l minute⁻¹) measurement was performed by lithium dilution using a commercial machine (LiDCO™ cardiac sensor systems; LiDCO™ plus; LiDCO Ltd., London, UK) every thirty minutes (T₃₀, T₆₀, T₉₀, T₁₂₀, T₁₅₀). Equipment consisted of a computer software, included in the LiDCO™ plus Hemodynamic Monitor (LiDCO Ltd., London, UK) (Figure 3.3), a sensor (LiDCO™- Sensor; LiDCO Ltd., London, UK) (Figure 3.4) implying a lithium-selective electrode positioned in a flow-through cell, a battery-powered peristaltic pump (Figure 3.5) and a collection container for waste. The basic principle can be seen in Figure 3.2 published previously by JONAS and TRANSER (2002).

Prior to each measurement, haemoglobin ([Hb]) and sodium ([Na⁺]) concentration (ABL 800 Flex; Radiometer GmbH, Willich, Germany) was measured in order to adjust the lithium dilution monitor as lithium chloride is only dissolved in the plasma, but CO pertains to the amount of whole blood pumped by the heart (CORLEY et al. 2003). [Na⁺] determines baseline voltage in the absence of lithium chloride and therefore needs to be corrected for, before measurements (HALLOWELL and CORLEY 2005). Blood for lithium analysis was sampled from the arterial line at the same time as the collection of arterial blood for blood gas analysis occurred.

As the lithium-selective sensor was connected to the arterial line by a three-way stopcock, blood flow was achieved by opening the three-way stopcock prior to CO estimation. To maintain a consistent blood flow through the cell, blood was rinsed with 4 ml minute⁻¹ across the electrode into the waste powered by the peristaltic pump. The lithium electrode analysed the baseline voltage coming across the blood passing the electrode, voltage was digitised on-line and stored on the LiDCO™ plus computer. If the voltage was declared as stable by the computer, measurement could be started manually and five seconds later a bolus of 2.250 mmol (15 ml of 150 mmol l⁻¹) lithium chloride (produced by the pharmacy “Löwen”; Hanover, Germany) was injected by rapid bolus injection into the venous catheter (LINTON et al. 2000). This approach is contrary to the advance in humans as there the lithium chloride has to be injected immediately after starting measurement. The reason for this five seconds delay in horses between start of measurement and injection was founded in findings
by Hallowell and Corley (2005) using the facial or transverse facial arteries as the system required 12 seconds of stable baseline for accurate CO calculation and as the indicator needs a variable length of time to reach the sensor depending on both used artery and circulation conditions (Hallowell and Corley 2005). Afterwards the venous catheter was flushed immediately with 20 ml of sodium chloride. After measuring, changed voltage by the lithium chloride, computer calculated CO as described above (2.3.2.1.2.3). To remove blood the sensor was flushed with heparinised saline afterwards and the three-way stopcock was positioned in such a way that the arterial pressure was connected to the pressure transducer again.

![Diagram]

**Figure 3.2:** Set up used for measurement of cardiac output by lithium dilution with the LiDCO™plus system (LiDCO Ltd., London, UK) published by Jonas and Transer (2002).
Figure 3.3: LiDCO™ plus Hemodynamic Monitor (LiDCO Ltd., London, UK). The monitor is transportable by being fitted on a movable framework.
**Figure 3.4:** LiDCO-Sensor consisting of a lithium-selective electrode in a flow-through cell (*) used for determination of lithium concentration in the blood during cardiac output measurement using the LiDCO™ plus system (LiDCO Ltd., London, UK).  
A Connection to battery-powered peristaltic pump and waste.  
B Connection attached to arterial catheter by a three-way stopcock for blood sampling.  
C Adapter for pressure transducer to monitor.

**Figure 3.5:** Battery-powered peristaltic pump providing a constant blood flow (4 ml minute⁻¹) through the sensor into the waste (A).  
B Connection to lithium sensor and artery line access.
3.5.6 Dobutamine amount

The required dose of dobutamine was assessed continuously and adjusted to an essential minimum as described above (3.3.4). At the end of anaesthesia the total amount of dobutamine, needed by each horse, was recorded and expressed as $\mu g \text{ kg}^{-1} \text{ minute}^{-1}$ [total dobutamine ($\mu g \text{ kg}^{-1}$)/ duration of anaesthesia (minutes)]. Dose of dobutamine during the first hour of anaesthesia, as well as between $T_{65}$ and $T_{90}$ were recorded and expressed as $\text{dob}_p1$ ($\mu g \text{ kg}^{-1} \text{ minute}^{-1}$) [total dobutamine during the first hour of anaesthesia ($\mu g \text{ kg}^{-1}$)/ 60 (minutes)] and as $\text{dob}_p2$ ($\mu g \text{ kg}^{-1} \text{ minute}^{-1}$) [total dobutamine between $T_{65}$ and $T_{90}$ ($\mu g \text{ kg}^{-1}$)/ 25 (minutes)].
3.6 Postoperative monitoring

The unassisted recovery phase was monitored continuously and scored always by the same person (NFP). Recovery was assessed in relation to quality and duration.

3.6.1 Duration of recovery

Measurement of recovery time started after horses were separated from isoflurane. Time [minutes] to first movement, to achieve sternal recumbency and to stand was recorded.

3.6.2 Recovery quality

Assessment of recovery quality was scored by a 100-point standardized form published previously (CLARK-PRICE et al. 2008) by the same grader (NFP) for all horses (Table 3.2). Eleven different parameters had to be assessed. Nine points allegorised a subjective assessment of quality, whereas two parameters were scored objectively as the scorer had to number the attempts to stand and to sternal recumbency. For each of the eight quality parameters there were different specifications characterising these points. The most excellent recovery phase was able to achieve 11 summed up points and the worst one 100 points.
**Table 3.2:** Recovery quality scale (100-point-scale) published by CLARK-PRICE et al. (2008). Nine objects were scored from one to ten and two parameters could be scored with a maximum of five points. Descriptions of points are given below.

<table>
<thead>
<tr>
<th>No.</th>
<th>Object (maximal score)</th>
<th>Points</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Activity in recumbency (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>quiet, occasional stretch, head lift</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>tense, waiting to explode</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>failing</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Move to sternal (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>smooth, methodical</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>fighting mat but controlled</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>crashing, flopping over</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Number of attempts to sternal (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 -1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>10</td>
<td>&gt; 5</td>
</tr>
</tbody>
</table>
### Table 3.2.a Prosecution

<table>
<thead>
<tr>
<th>No.</th>
<th>Object (maximal score)</th>
<th>Points</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Points</td>
<td>Description</td>
</tr>
<tr>
<td>4</td>
<td>Sternal phase (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td>an organized pause</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td>nonexistent</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
<td>prolonged</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td></td>
<td>multiple sternal phases</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
<td>continues to struggle to maintain sternal</td>
</tr>
<tr>
<td>5</td>
<td>Move to stand (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td>methodical</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td>an organized scramble</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
<td>used walls for support</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
<td>ricocheting off walls</td>
</tr>
<tr>
<td>6</td>
<td>Strength (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td>near full</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td>mildly rubbery</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
<td>dog sitting before standing</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
<td>repeated attempts because of weakness</td>
</tr>
<tr>
<td>7</td>
<td>Number of attempts to stand (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
<td>&gt; 5</td>
</tr>
</tbody>
</table>
### Table 3.2.b  Prosecution

<table>
<thead>
<tr>
<th>No.</th>
<th>Object (maximal score)</th>
<th>Points</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Balance and coordination (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>solid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>moderate dancing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>reflex saves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>careening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>falls back down</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Knuckling (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>none</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>hind limb only – mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>hind limb only – marked</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>all four – moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>excessive, prolonged</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Overall attitude (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>calm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>calm / determined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>anxious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>confused, dizzy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>angry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>frantic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Overall recovery (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>excellent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>fair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>unacceptable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.7 Calculated parameters after anaesthesia

After general anaesthesia further cardiopulmonary variables were calculated by standard formulas described below for T_{30}, T_{60}, T_{90}, T_{120}, T_{150} and T_{180}: Cardiac index (CI), stroke volume (SV), arterial oxygen content (CaO_2), oxygen delivery (DO_2) and systemic vascular resistance (SVR). In parts, equations were published recently by KALCHOFNER et al. (2009).

\[ \text{CI (ml kg}^{-1} \text{ minute}^{-1}) = \frac{\text{CO} \times 1000}{\text{bwt}}, \] where bwt was declared in kilograms (kg).

\[ \text{SV (l beat}^{-1}) = \frac{\text{CO}}{\text{HR}} \]

\[ \text{CaO}_2 \text{ (ml dl}^{-1}) = \text{Hb} \times 1.36 \times \text{SaO}_2 + (0.0031 \times \text{PaO}_2) \]

where \( \text{Hb} = \text{g dL}^{-1} \); \( \text{SaO}_2 \) is declared as decimal; \( \text{PaO}_2 = \text{mmHg} \); the constant (Hüfner’s constant) 1.36 represents the amount of oxygen (ml at 1 atmosphere) bound per gram of Hb; the constant 0.0031 represents the amount of oxygen dissolved in plasma at 1 atmosphere. Hb concentration was analysed (3.5.5).

\[ \text{DO}_2 \text{ (ml kg}^{-1} \text{ minute}^{-1}) = \text{CI} \times \left( \frac{\text{CaO}_2}{100} \right) \]

\[ \text{SVR (mmHg l}^{-1} \text{ minute}^{-1}) = \frac{\text{MAP}}{\text{CO}}, \] simplified by KLABUNDE et al. (2005) as accurate calculation of SVR would have required central venous pressure (CVP).
3.8 Statistical analysis

Statistical analysis was performed using SAS (SAS® 9.2; SAS Inc., Cary, North Carolina, USA). Measurements after T\textsubscript{90} were excluded because of incomplete data due to end of anaesthesia in many horses afterwards. For variables CO, CI, SV, SVR, DO\textsubscript{2} and CaO\textsubscript{2} only T\textsubscript{30}, T\textsubscript{60} and T\textsubscript{90} were included in analysis. Gaussian distribution was tested by visual inspection of a histogram and the Kolmogorov-Smirnov test. For HR, RR, MAP, ETISO, PaO\textsubscript{2}, PaCO\textsubscript{2} mean average over the whole anaesthetic period for each patient was calculated [sum of measurements/ number of measurements] and analysed by a one-way analyse of variance (ANOVA) to eliminate differences in duration of anaesthesia. In order to investigate influences by group and time, continuously and normally distributed data were analysed using a two-way ANOVA for repeated measurements. Non-parametric data were analysed using Kruskal-Wallis test, with following Wilcoxon-Mann-Whitney test, if significance level had been reached in Kruskal-Wallis analysis. For non-parametric data, influences by time (repeated measurements) were detected using Wilcoxon signed-rank test. Categorical data (amount of thiopental and hydroxyethyl starch) were analysed by Fisher's exact test. Significance level was set at 5% (p< 0.05).

Significant differences over time are depicted by asterisks. Letters indicate significance between groups (Table 9.1). Normally distributed data are presented as mean ± standard deviation (SD) and non-parametric data are shown as median [range].
Influence of ketamine or xylazine supplementation on isoflurane anaesthetised horses- a controlled clinical trial

Nina F Pöppel, med. vet.
Klaus Hopster Dr med vet, DiplECVAA
Sabine B R Kästner, MVetSci, Prof Dr med vet, DiplECVAA

Clinic for horses, University of Veterinary Medicine Hannover, Bünteweg 9, 30559 Hanover, Germany

Correspondence: Klaus Hopster, Clinic for horses, University of Veterinary Medicine Hannover, Bünteweg 9, 30559 Hanover, Germany

Email: klaus.hopster@tiho-hannover.de
Abstract
The influence of ketamine or xylazine constant rate infusion on isoflurane anaesthesia in fifty-one horses undergoing elective surgery was studied. After premedication with acepromazine, xylazine, butorphanol anaesthesia was induced with ketamine-midazolam and maintained with isoflurane alone (I), isoflurane with either 1 mg kg\(^{-1}\) hour\(^{-1}\) ketamine (IK) or xylazine (IX). End tidal isoflurane (ETISO) was adjusted according to a score always by the same anaesthetist. Dobutamine was infused to maintain mean arterial pressure (MAP) ≥ 70 mmHg. Arterial blood gases, heart rate (HR), respiratory rate, MAP, cardiac output were measured and cardiovascular indices calculated. Groups I and IK received xylazine before recovery. Recovery quality was scored.
Mean ± sd averaged ETISO (volume %) was significantly lower in IX (0.95 ± 0.07) and IK (0.97 ± 0.08) than in I (1.16 ± 0.13). In group IX mean averaged MAP (90 ± 13 mmHg) was significantly higher without dobutamine in combination with lower HR than in I and IK with 71 ± 7 mmHg and 76 ± 7 mmHg, respectively. Differences in other cardiopulmonary parameters did not reach statistical significance. All horses recovered well.
Cardiopulmonary function could be maintained with each protocol. Xylazine results in pronounced reduction of anaesthetic requirements and blood pressure support.
Introduction

Anaesthesia in horses carries a much higher risk of mortality than in humans and small animals (Johnston and others 2002; Bidwell and others 2007; Brodbelt 2009). Myopathies and fractures are the reason for death in 30.4 % (Johnston and others 2002). A major risk factor for post-anaesthetic myopathy is reduced muscle perfusion during anaesthesia (Weaver and others 1984; Lindsay and others 1989), which is closely related to MAP and cardiac output (CO) (Richey and others 1990; Lee and others 1998; Edner and others 2002). Therefore, maintenance of cardiovascular function is the basis of a safe anaesthetic protocol and smooth recovery.

Common practice for prolonged equine anaesthesia is the use of inhalation agents like isoflurane, which allow easy control of anaesthetic depth and fast recovery due to rapid elimination (Steffey and others 1977), but unfortunately they are accompanied by dose-related cardiovascular depression affecting CO (Steffey and Howland 1978, 1980). Therefore, ideally isoflurane concentrations should be kept as low as possible to improve cardiopulmonary function. This could be achieved by additional administration of sedatives and/ or analgesics during inhalation anaesthesia (Bettschart-Wolfensberger and Larenza 2007).

Ketamine is a dissociative agent with analgesic, anaesthetic and central sympathomimetic properties (Muir 2010), usually resulting in an increase of HR, MAP and CO in a plasma concentration-related way (Muir and others 1977; Muir and Sams 1992). It is also known to reduce the minimal alveolar concentration (MAC) of inhalation agents in dogs (Solano and others 2006) and horses (Muir and Sams 1992). However, ketamine and its metabolite accumulate with time (Lankveld and others 2006) leading to a prolonged elimination time and effects like muscle tremor and rigidity, excitation and ataxia during recovery, which can lead to fatal injury in horses (Muir and Sams 1992).

Xylazine is an alpha2-agonist with sedative, analgesic and muscle relaxant effects (Daunt and Steffey 2002). Studies demonstrated the potential to reduce the MAC of inhalation agents in horses (Steffey and others 2000) and dogs (Tranquilli and others 1984) dose- and time-dependently. Xylazine produces cardiopulmonary changes in horses with decreased HR and an increased incidence of second-degree
atrioventricular block (England and Clarke 1996), a reduction of CO up to 40% (Kerr and others 1972) and transient hypertension, followed by hypotension (Wagner and others 1991). Thus respiratory and circulatory effects could be enhanced when administering alpha₂-agonists in addition to inhalation anaesthesia (Teixeira Neto and others 2004).

The aim of this study was to compare the influence of ketamine or xylazine constant rate infusion (CRI) on cardiopulmonary function, anaesthetic requirements and recovery in isoflurane anaesthetised horses under clinical conditions.

Materials and methods

Animals

Fifty-one client-owned horses of various ages (1 to 19 years), breeds (46 warmbloods, two Frisian, two German riding ponies and one polo pony) and a minimum body weight of 300 kg scheduled for elective surgery with an anticipated anaesthetic duration between 90 and 180 minutes were used for the study. The horses were determined to be healthy based on clinical examination before inclusion into this study. Surgeries where the eyes were covered were excluded. The experimental protocol was approved by the State Office for Consumer Protection and Food Safety in accordance to the German Animal Welfare Law.

Anaesthetic protocol and instrumentation

The horses were randomly assigned to one of three treatment groups: isoflurane alone (I), isoflurane in combination with a CRI of either ketamine (IK) or xylazine (IX). Food was withheld over night for at least 6 hours, but access to water was always given. A catheter was placed into one jugular vein (EquiCathTM Fastflow; Braun Vet Care) under local anaesthesia (mepivacaine; Scandicain®; AstraZeneca). Thirty minutes before anaesthesia induction all patients were premedicated with acepromazine (Vetranquil®; Albrecht) (0.03 mg kg⁻¹ intramuscularly), flunixin meglumin (Flunidol®; CP-Pharma) (1.1 mg kg⁻¹ intravenously) and antimicrobial agents depending on the surgical case.
Horses were sedated with xylazine (Xylazin 2®; CP-Pharma) (0.5 mg kg\(^{-1}\)) and butorphanol (Alvegesic®, CP-Pharma) (0.025 mg kg\(^{-1}\)) intravenously. If sedation was inadequate additional bolus of 0.15 mg kg\(^{-1}\) xylazine were given to effect and the final dose recorded. Anaesthesia was induced intravenously with ketamine (Narketan®, Vetoquinol) and midazolam (Midazolam-ratiopharm®; Ratiopharm) at a dose of 2.2 mg kg\(^{-1}\) and 0.06 mg kg\(^{-1}\), respectively. Once the horse was laterally recumbent, the trachea was intubated and the horse hoisted on the surgery table in lateral or dorsal recumbency.

At time point zero (T\(_{0}\)) horses were connected to a large animal anaesthesia machine (Vet.-Tec. Model JAVC 2000; J.D. Medical Distributing Company) and ventilated using a pressure limited large animal respirator (modified Bird®Mark 7; Bird® Products Corporation). Intermittent positive pressure ventilation (IPPV) was performed with a peak inspiratory pressure between 20 and 30 cm H\(_2\)O. The respiratory frequency was adjusted to maintain end-expiratory concentration of carbon dioxide (ETCO\(_2\)) between 4.7 and 6 kPa. Anaesthesia was maintained with isoflurane (Isofluran CP®, CP-Pharma) (Isofluran Vapor 2000; Drägerwerk AG) in oxygen (6 litres minute\(^{-1}\)). Horses in group IK and IX received a CRI of 1 mg kg\(^{-1}\) hour\(^{-1}\) ketamine or 1 mg kg\(^{-1}\) hour\(^{-1}\) xylazine in addition. In IK ketamine infusion was reduced to 50% after an anaesthetic duration of 2 hours and totally stopped after 3 hours of infusion or at least 20 minutes before the end of anaesthesia.

A 20 SWG catheter (Venocan™; Jørgen Kruuse) was placed in the facial or transverse facial artery. The arterial catheter was connected to an electronic pressure transducer (BD DTXPlus™ Transducer; Becton and Dickinson) positioned and zeroed at the level of the sternal manubrium. To prevent clotting and dampening of the arterial waveform, the arterial line was flushed intermittently with heparinised saline (5 IU ml\(^{-1}\)).

Ringer’s solution (Ringer®; Braun) was infused for the duration of anaesthesia at rate of 5 ml kg\(^{-1}\) hour\(^{-1}\). All horses received a CRI of dobutamine (Dobutamin-ratiopharm®, Ratiopharm) at a dose of 0.3 µg kg\(^{-1}\) minute\(^{-1}\) until blood pressure monitoring was connected. After the first arterial pressure reading the dose was adjusted every 5 minutes to maintain MAP above 70 mmHg. If MAP remained < 70 mmHg after
reaching 1.25 μg kg⁻¹ minute⁻¹ dobutamine, the rate of Ringer’s solution was increased to 10 ml kg⁻¹ hour⁻¹. At the end of anaesthesia the total amount of dobutamine given was recorded and expressed as μg kg⁻¹ minute⁻¹ [total dobutamine (μg kg⁻¹)/ anaesthetic duration (minutes)]. In addition, the dobutamine amount during the first hour [total dobutamine between T₀ and T₆₀ (μg kg⁻¹)/ 60 (minutes)] and between T₆₅ and T₉₀ [total dobutamine between T₆₅ and T₉₀ (μg kg⁻¹)/ 25 (minutes)] was recorded. All CRIs were delivered by an automatic syringe infusion pump (Perfusor® compact; Braun).

Depth of anaesthesia and isoflurane administration were evaluated and adjusted always by the same anaesthetist (NFP) using a previously published scoring system (Enderle and others 2008). Based upon clinical signs like presence or absence of palpebral reflex, nystagmus, body movements and variation in MAP the ETISO was adjusted as required. The scoring system comprised scores from score -1 (very deep anaesthesia) to score 4 (very light anaesthesia), where score 0 demonstrated the adequate anaesthetic level. Horses with a score between 2 and 4 received a bolus of thiopental-sodium (Trapanal® 2.5g; Nycomed) (0.5 to 1.5 mg kg⁻¹ intravenously) to deepen anaesthesia and the amount of thiopental was recorded.

At the end of surgery the horses were weaned from IPPV and isoflurane. After return of spontaneous breathing, the horses were placed in a recovery box and horses in groups I and IK received 0.25 mg kg⁻¹ xylazine intravenously, whereas horses in IX received 0.1 mg kg⁻¹ xylazine intravenously if they showed early nystagmus if still being padded on the surgery table. Phenylephrine-hydrochloride (Phenylephrin-Lösung®; Löwen-Apotheke) was instilled into the ventral nasal meatus to reduce mucosal swelling. During recovery oxygen was insufflated at 15 litres minute⁻¹ as long as patients were recumbent. Times to first movement, to achieve sternal recumbency and to standing were recorded. Quality of the recovery phase was scored by a 100-point standardised form published previously (Clark-Price and others 2008) by the same grader for all horses. The most excellent recovery could achieve 11 points and the worst possible one 100 points.
**Experimental protocol**

Technical monitoring was carried out with a multiparameter monitor (Datex-Ohmeda Cardiocap/5; GE Healthcare). HR, respiratory rate (RR), MAP and ETISO were recorded every 10 minutes. The CO (litres minute\(^{-1}\)) was measured every 30 minutes by lithium dilution method using a commercial machine (LiDCO\textsuperscript{TM} plus; LiDCO Ltd.) (Hallowell and Corley 2005). Lithium chloride (2.25 mmol) was compounded by a local pharmacy (Löwen-Apotheke). Haemoglobin concentration (Sysmex KX-21; Sysmex) and sodium concentration were measured before premedication and during anaesthesia (ABL 800 Flex; Radiometer) to adjust the lithium dilution equipment. During anaesthesia blood samples were anaerobically taken from the arterial line at each CO determination time point and were additionally analysed for saturation of oxygen in arterial blood (SaO\(_2\); calculated) and arterial partial pressure of carbon dioxide (PaCO\(_2\)) and oxygen (PaO\(_2\)) (ABL 800 Flex; Radiometer).

Cardiac index (CI), arterial oxygen content (CaO\(_2\)), oxygen delivery (DO\(_2\)), stroke volume (SV) and systemic vascular resistance (SVR) were calculated based on previously published formulas (Klabunde 2005, Kalchofner and others 2009).

**Statistical analysis**

Statistical analysis was performed with a computer software (SAS\textsuperscript{®} 9.2; SAS Inc.). Different time points were denominated as T\(_0\) (immediately after induction), T\(_{10}\) (10 minutes after induction), T\(_{20}\) (20 minutes after induction) and so on. Time points after T\(_{90}\) were not analysed to obtain balanced data sets. Gaussian distribution was tested by visual inspection of histograms and the Kolmogorov-Smirnov test. For HR, RR, MAP, ETISO, PaO\(_2\) and PaCO\(_2\) mean average over the whole anaesthetic period for each patient was calculated [sum of measurements/ number of measurements] and analysed by an one-way analysis of variance (ANOVA) to eliminate differences in length of anaesthetic duration. Normally distributed data were analysed using a two-way ANOVA for repeated measurements. Non-parametric data were analysed by the Kruskal-Wallis test, followed by the Wilcoxon-Mann-Whitney test, if significance level had been reached before. For non-parametric data influences by time were detected using Wilcoxon signed-rank test. Categorical data were analysed by the Fisher’s
exact test. Significance level was set at \( p < 0.05 \). Normally distributed data are presented as mean \( \pm \) sd and non-parametric data are shown as median [range].

Results

There were no significant differences between the three groups in age, body weight, onset of surgery and duration of anaesthesia (Table 1). All groups required a mean averaged dose of xylazine of \( 0.6 \pm 0.1 \) mg kg\(^{-1}\) before induction of anaesthesia. Additional boli of thiopental to deepen anaesthesia were required in nine and seven horses in group I and group IK, respectively. Both groups were statistically different to IX in which none of the horses required additional thiopental. Horses received thiopental at a maximum of three times per anaesthesia, but never in quick succession. Median [range] total additional doses of thiopental in I and IK were 0.831 [0- 2.99] mg kg\(^{-1}\) and 0 [0- 2.77] mg kg\(^{-1}\), respectively.

Group IX had significantly \( (p < 0.0022) \) lower values for mean averaged HR (beats minute\(^{-1}\)) and significantly \( (p < 0.0001) \) higher values for mean averaged MAP compared to group I and IK, respectively (Table 2). Group IX and IK required significantly \( (p < 0.001) \) less isoflurane than group I (Table 2). Horses in IX also required significantly less \( (p < 0.0001) \) dobutamine than in group I and IK (Table 3). No differences in RR, CO, CI, SV, SVR, DO\(_2\), CaO\(_2\) and arterial blood gases occurred between groups (Table 2-4).

In group I a significant \( (p < 0.0042) \) increase in HR from \( T_{20} \) (35 ± 5) to \( T_{50-70} \) (39 ± 8) was seen (Figure 1). Twenty minutes after induction of anaesthesia MAP increased from 64 and 68 mmHg to 71 mmHg and 78 mmHg at \( T_{60} \) in groups I and IK, respectively. Thereafter MAP remained unchanged until end of anaesthesia (Figure 2).

Isoflurane requirements (ETISO) increased in I between \( T_{20} \) (1.1 ± 0.18) and \( T_{90} \) (1.26 ± 0.16) continuously with end tidal values during the last 30 minutes being significantly \( (p < 0.0005) \) higher than the mean average (1.16 ± 0.13) over whole anaesthetic period (Figure 3).

In groups I and IK CO \( (p < 0.023) \), CI \( (p < 0.013) \), SV \( (p < 0.05) \) and DO\(_2\) \( (p < 0.0022) \) decreased significantly between \( T_{60} \) and \( T_{90} \) (Table 3). At \( T_{30} \) SVR was significantly
higher in IX than in I (p< 0.0055) and IK (p< 0.0085). A significant increase of SVR over the course of anaesthesia (T₃₀ to T₉₀) occurred in I (p< 0.0038) and IK (p<0.0011) (Table 3).

Arterial blood gases and CaO₂ were not different between groups. PaO₂ and CaO₂ decreased (p< 0.0001) over anaesthesia time in all groups, whereas PaCO₂ significantly increased only in IX (p< 0.0018) between T₃₀ and T₉₀ (Table 4).

There was an influence of the anaesthetic period on dobutamine requirements, with the highest values during the first period of anaesthesia (T₀ to T₆₀) in each group. After instrumentation only six horses in IX received still a small amount of dobutamine, whereas dobutamine could be stopped only in two horses in IK and in none of the horses in I during period 1 (Figure 4).

All horses recovered well. For statistical analysis two horses (one of IK and one of I) were excluded due to prolonged anaesthesia (260 minutes) and another one due to a fire alert once the horse got padded in the recovery box. None of the horses in IX required additional sedation after general anaesthesia. There were no differences between groups in any of the recovery time parameters, but recovery quality was significantly (p< 0.0407) better in IX compared to IK, respectively (Table 5).

**Discussion**

All three tested anaesthetic protocols were able to maintain cardiopulmonary function within a clinically acceptable range without differences in recovery quality. Isoflurane requirements to maintain an adequate level of anaesthesia were reduced with both balanced anaesthesia protocols.

Cardiac output in all three groups was in the range of previously published data in horses, with a dose dependent effect of isoflurane on CO (Edner and others 2005; Blissitt and others 2008). With xylazine as supplemental drug, CO was comparable to balanced protocols with dexmedetomidine (Marcilla and others 2012) or medetomidine (Kalchofner and others 2009).

Cardiac output and CI significantly decreased over time in groups I and IK similar to studies by Raisis and others (2005) and Blissitt and others (2008). This decrease over time was mainly carried by a decrease in SV probably related to the increase in
Isoflurane requirements towards the end of the anaesthetic period reflecting the dose-dependent reduction in myocardial contractility by isoflurane (Steffey and Howland 1980).

Standard calculation of SVR requires central venous pressure (CVP) to be measured. However, CVP has only a small influence on the calculated SVR. Therefore, CVP was neglected and a simplified formula (Klabunde 2005) used instead in these clinical cases. In I and IK, SVR increased over time in conjunction with MAP which might be attributed to sympathetic nervous activation by surgical stimulation. In horses, MAP should be maintained above 70 mmHg to provide adequate muscle perfusion (Richey and others 1990). This preset value was only achieved in animals receiving a CRI of xylazine without increased fluid requirements or dobutamine infusion. In contrast, hypotension occurred quite often during the first 40 minutes in I and IK before surgical stimulation began. The subsequent increase of MAP might be contributed to cardiovascular support (Ringer’s solution and dobutamine), waning effects of premedication, onset of surgery or a combination of all of them. In groups I and IK, there has been no significant difference in CO between T₃₀ and T₆₀, despite significantly lower MAP values, which underlines findings by Wagner and others (1992) and Edner and others (2002), that MAP may be inversely related to CO and therefore does not predict muscle perfusion in clinical practice.

Isoflurane-xylazine anaesthesia was characterised by high consistency of cardiopulmonary variables, even during surgical stimulation. Marcilla and others (2012) hypothesised that additional sedation and analgesia provided by infusion of alpha₂-agonists might blunt the autonomic response to noxious stimulation. Furthermore, xylazine supplementation reduced isoflurane requirements in the current study up to 21 % compared to I, which lead to ETISO values comparable with a previously published study using a CRI of medetomidine (3.5 µg kg⁻¹ hour⁻¹) in isoflurane anaesthetised horses (Kalchofner and others 2009), but is in contrast to other clinical studies using detomidine and romifidine, in which the authors failed to demonstrate any isoflurane sparing effects (Devisscher and others 2010; Schauvliege and others 2011).
Other authors (Kalchofner and others 2006; Ringer and others 2007) have already raised the question if xylazine may produce strong peripheral vasoconstriction resulting in increased SVR and high blood pressures but low CO by a drop in HR due to baroreceptor response. However, despite lower HR and highest values for SVR at the beginning of anaesthesia in IX, CO was not different from the other groups. It is also possible that cardiovascular depression by xylazine is compensated by the lower dose of isoflurane in this group (Steffey and Howland 1980).

In the current study we failed to demonstrate an improvement of cardiovascular function during isoflurane-ketamine anaesthesia due to sympathomimetic or isoflurane sparing effects of ketamine. Centrally mediated indirect sympathomimetic properties of ketamine (Muir and others 1977) can be seen at plasma concentrations above 1 µg ml$^{-1}$ (Muir and Sams 1992) in halothane anaesthetised horses, which is also reported being the required plasma concentration to induce anaesthesia in horses (Muir and Sams 1992; Fielding and others 2006; Lankveld and others 2006; Peterbauer and others 2008). Antinociceptive effects of ketamine occurred with a subanaesthetic dose of 1.2 mg kg$^{-1}$ hour$^{-1}$ (Peterbauer and others 2008), whereas Fielding and others (2006) failed to demonstrate an analgesic effect of 0.8 mg kg$^{-1}$ hour$^{-1}$ ketamine. However, in our study some antinociceptive or anaesthetic sparing effects of ketamine are evident by the reduction of isoflurane requirements up to 19.6% compared to the control group. As we did not measure plasma concentrations we do not know which levels were achieved with used doses as during general anaesthesia volume of distribution and metabolism of drugs are changed leading to altered pharmacokinetics (Thomasy and others 2005, 2007). Whether higher doses of ketamine would lead to more pronounced isoflurane sparing effects or more central sympathomimetic activation with improved cardiovascular function is not known. However, increasing doses of ketamine decrease recovery quality with muscle tremor and rigidity, excitation and ataxia (Muir and Sams 1992). With our data we cannot explain the lack of cardiovascular improvement despite the decrease in isoflurane requirements, but direct negative inotropic effects of ketamine on the myocardium (Treese and others 1973; Diaz and others 1976) might have disguised the isoflurane sparing effect.
In IK and I isoflurane requirements during the first 40 minutes of anaesthesia were very low, probably related to ongoing effects of induction agents and absence of surgical stimulation. After start of surgical stimulation, isoflurane doses had to be increased due to insufficient anaesthetic depth and contemporaneous thiopental administration in many horses. Because of the low concentrations at the beginning of anaesthesia, mean averaged ETISO (1.16 ± 0.13) over the whole anaesthetic period were much lower than published data for MAC (1.3 to 1.6) in isoflurane-anaesthetised horses (Steffey and others 1977; Steffey and others 2000).

Blood gases, CaO$_2$ and DO$_2$ changed minimally over time and changes were without clinical relevance. As there were no differences between groups, the changes seemed to be drug-independent and mainly influenced by anaesthesia time.

The quality of unassisted recovery was good and unremarkable for all tested protocols, but sedation with a xylazine bolus in I and IK before recovery might have minimised differences between groups. As sedation for recovery has become general practice (Clark-Price and others 2008) we decided to include xylazine for recovery in the client-owned horses. The slightly better recovery quality of IX compared to IK seems not to be clinically relevant as all horses recovered well and a median score of 22 in IK was still low on a scale from 11 to 100 points.

The study design had some limitations. The aim was to evaluate three different anaesthetic protocols in a clinical setting. Therefore, results can be influenced by premedication, induction, use of inotropes and fluids and different degree and time span of surgical stimulation.

Another limitation of this clinical study was the adjustment of anaesthetic depth and determination of isoflurane sparing effects by the same, but not blinded anaesthetist. If balanced anaesthesia techniques are used, eye reflexes, eye movement and eye position differ from those seen under plain inhalation anaesthesia (Kalchofner and others 2006; Bettschart-Wolfensberger and Larenza 2007; Ringer and others 2007). Eye reflexes are more active and horses appear more lightly anaesthetised even if adequate anaesthesia is provided. Therefore, it can be questioned whether all horses have been anaesthetised to the same anaesthetic level. With the scoring system we tried to achieve an objective evaluation of anaesthetic depth, but a comparison to
MAC determinations with assessment of immobility in response to a standardised stimulation cannot be made.

Two horses in IX (two stallions, three and seven years old, presented for castration) showed exceedingly high CO measurements with CI values of 130 - 240 ml kg\(^{-1}\) minute\(^{-1}\). Reasons for those high values remained unclear, as no technical problem has been observed and the dilution curve appeared to be accurate. Sympathetic stimulation (due to insufficient analgesia or anaesthesia during castration) has not been evident in these horses, as both HR and MAP were within normal limits. Such high values (200 ± 25 ml kg\(^{-1}\) minute\(^{-1}\)) have only been reported for neonatal foals resulting from high HR (Thomas and others 1987: Corley 2002; Corley and others 2002). A possible explanation might be the observation that the lithium sensor used in the LiDCO\(^{TM}\) technique might be influenced by several drugs (especially xylazine and ketamine) in a dose-dependent way (Ambrisko and others 2012). After performing experimental “in-vitro” studies, they speculated that changes in baseline voltage by different drugs might result in an overestimation of CO data by about 10\%.

Clinically we observed that the sensor tended to need a lot of time to achieve stable baseline voltages in IX, whereas it took only a few seconds in I and IK. So we cannot preclude the possibility of falsely high CO values in some horses in IK and IX. But up to now it is not known at which drug plasma concentrations the sensor will be affected. When we excluded the two outliers from statistical analysis, results did not change. However, it is possible that differences between groups in cardiovascular values were not detected due to the high variability in CO measurements.

In conclusion, it was possible to maintain cardiopulmonary parameters with all three protocols without clinically relevant differences in recovery quality, but with pronounced differences in blood pressure support. Xylazine supplementation resulted in a pronounced reduction of anaesthetic requirements to maintain an adequate anaesthetic level and less blood pressure support. Further studies are warranted to investigate higher doses of ketamine or the effects of xylazine in horses suffering from colic, to determine if xylazine still exerts positive effects on blood pressure and global perfusion under these conditions.
Tables and figures

**Figure 1** Heart rate (HR) measured at different time points (T<sub>20-90</sub>; minutes after induction) during isoflurane anaesthesia (I) or isoflurane anaesthesia balanced with a continuous rate infusion (CRI) of either ketamine (IK) or xylazine (IX). * Significantly different from T<sub>20</sub>. Letter indicates significant differences from both other groups (p < 0.05).

**Figure 2** Mean arterial pressure (MAP) at different time points (T<sub>20-90</sub>; minutes after induction) during isoflurane anaesthesia (I) or isoflurane anaesthesia balanced with a continuous rate infusion (CRI) of either ketamine (IK) or xylazine (IX). * Significantly different from T<sub>20</sub>. a Significantly different from group I. Significance was set at p < 0.05.
Figure 3 End tidal of isoflurane (ETISO) measured at different time points (T\textsubscript{20-90}; minutes after induction) during isoflurane anaesthesia (I) or isoflurane anaesthesia balanced with a constant rate infusion (CRI) of either ketamine (IK) or xylazine (IX). * Significantly different from T\textsubscript{20}. ** Significantly different from T\textsubscript{50}. Letters indicates significant differences between groups: a Significantly different from both other groups, c from group IK, d from group IX. Significance was set at p < 0.05.

Figure 4 Median dose of dobutamine during anaesthetic period 1 (p1; T\textsubscript{0} - T\textsubscript{60}) and anaesthetic period 2 (p2; T\textsubscript{65} - T\textsubscript{90}) during isoflurane anaesthesia (I) or isoflurane anaesthesia balanced with a constant rate infusion of either ketamine (IK) or xylazine (IX) in horses. Whiskers represent 95% of data. * Significantly different from p1. a Significantly different from both other groups within same anaesthetic period. Significance was set at p < 0.05.
Table 1 Demographic data and information about recumbency, type of surgery and anaesthetic duration of horses undergoing isoflurane (I) anaesthesia and isoflurane with a constant rate infusion (CRI) of either ketamine (IK) or xylazine (IX)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I</th>
<th>Group IK</th>
<th>Group IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horses included</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>3 [1 – 16]</td>
<td>3 [2 – 19]</td>
<td>3 [2 – 17]</td>
</tr>
<tr>
<td>Recumbency position</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Lateral</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthroscopies</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Castration</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tendon surgeries</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Other soft tissue surgeries</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other orthopaedic surgeries</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Anaesthetic duration (minutes)</td>
<td>110 [90 – 260]</td>
<td>90 [90 – 180]</td>
<td>100 [80 – 170]</td>
</tr>
</tbody>
</table>

No significant differences between three treatment groups (p < 0.05). Values are expressed as median [range] (age, body weight, anaesthetic duration and onset of surgery) or number of horses (type of surgery and recumbency).
**Table 2** Mean averaged cardiopulmonary parameters and median dose of dobutamine in isoflurane anaesthetised horses (I) and isoflurane anaesthesia balanced with either ketamine (IK) or xylazine (IX)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I</th>
<th>Group IK</th>
<th>Group IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats minute(^{-1}))</td>
<td>37 ± 5</td>
<td>35 ± 4</td>
<td>31 ± 3 (^a)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>71 ± 8</td>
<td>76 ± 7</td>
<td>91 ± 13 (^a)</td>
</tr>
<tr>
<td>RR (breaths minute(^{-1}))</td>
<td>7 ± 1</td>
<td>6 ± 1</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>ETISO (volume %)</td>
<td>1.16 ± 0.13 (^a)</td>
<td>0.97 ± 0.08</td>
<td>0.96 ± 0.07</td>
</tr>
<tr>
<td>PaO(_2)</td>
<td>334 ± 101</td>
<td>377 ± 105</td>
<td>367 ± 92</td>
</tr>
<tr>
<td>PaCO(_2)</td>
<td>44.5 ± 13.4</td>
<td>50.2 ± 13.9</td>
<td>48.8 ± 12.3</td>
</tr>
<tr>
<td>dob (µg kg(^{-1}) minute(^{-1}))</td>
<td>0.38 [0.16 – 1.00]</td>
<td>0.22 [0.07 – 1.20]</td>
<td>0.07 [0.02 – 0.32] (^a)</td>
</tr>
<tr>
<td>dob(_p1) (µg kg(^{-1}) minute(^{-1}))</td>
<td>0.50 [0.23 – 1.35] (^a)</td>
<td>0.35 [0.15 – 1.03] (^a)</td>
<td>0.10 [0.05 – 0.30] (^a)</td>
</tr>
<tr>
<td>dob(_p2) (µg kg(^{-1}) minute(^{-1}))</td>
<td>0.42 [0.00 – 1.21]</td>
<td>0.00 [0.00 – 1.62]</td>
<td>0.00 [0.00 – 0.30] (^a)</td>
</tr>
</tbody>
</table>

HR, heart rate; MAP, mean arterial pressure; ETISO, end tidal of isoflurane; PaO\(_2\), arterial partial pressure of oxygen; PaCO\(_2\), arterial partial pressure of carbon dioxide; dob, dose of dobutamine; dob\(_p1\), dose of dobutamine during p1 (= T\(_0\) – T\(_60\)); dob\(_p2\), dose of dobutamine during p2 (=T\(_65\) – T\(_90\)); Normally distributed data are presented as mean ± sd. Non-parametric data are presented as median [range]. \(^a\) Significantly different from other groups (p < 0.05).
**Table 3** Cardiac output and other calculated cardiovascular indices in isoflurane anaesthetised horses (I) and isoflurane anaesthesia balanced with a constant rate infusion (CRI) of either ketamine (IK) or xylazine (IX)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>T&lt;sub&gt;30&lt;/sub&gt;</th>
<th>T&lt;sub&gt;60&lt;/sub&gt;</th>
<th>T&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO (litres minute&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>I</td>
<td>36 [13 - 60]</td>
<td>40 [20 - 76]</td>
<td>33 [17 - 63]  *</td>
</tr>
<tr>
<td>CI (ml kg&lt;sup&gt;-1&lt;/sup&gt; minute&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>I</td>
<td>75.3 [23.9 - 112.4]</td>
<td>70.8 [36.7 - 165.2]</td>
<td>69.8 [31.2 - 115.0]</td>
</tr>
<tr>
<td></td>
<td>IK</td>
<td>77.5 [32.1 - 128.0]</td>
<td>76.5 [47.8 - 145.0]</td>
<td>65.1 [40.0 - 130.0]</td>
</tr>
<tr>
<td></td>
<td>IX</td>
<td>62.4 [43.5 - 129.9]</td>
<td>66.0 [36.2 - 187.0]</td>
<td>80.0 [40.4 - 241.0]</td>
</tr>
<tr>
<td>SV (litres beat&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>I</td>
<td>1.03 [0.34- 1.62]</td>
<td>1.03 [0.57- 1.53]</td>
<td>0.81 [0.50- 1.62]  *</td>
</tr>
<tr>
<td></td>
<td>IK</td>
<td>1.06 [0.58- 2.11]</td>
<td>1.04 [0.66- 1.87]</td>
<td>0.94 [0.68- 1.45]  * ***</td>
</tr>
<tr>
<td></td>
<td>IX</td>
<td>1.01 [0.69- 2.57]</td>
<td>1.21 [0.77- 3.31]</td>
<td>1.44 [0.69- 4.25]  a</td>
</tr>
<tr>
<td>DO&lt;sub&gt;2&lt;/sub&gt; (ml kg&lt;sup&gt;-1&lt;/sup&gt; minute&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>I</td>
<td>11.5 [3.4- 17.5]</td>
<td>12.4 [4.3- 27.5]</td>
<td>10.2 [4.3- 18.3]  *</td>
</tr>
<tr>
<td></td>
<td>IK</td>
<td>12.4 [5.8- 17.3]</td>
<td>12.4 [7.7- 20.3]</td>
<td>8.6 [6.5- 18.1]  *</td>
</tr>
<tr>
<td></td>
<td>IX</td>
<td>9.6 [5.5- 23.6]</td>
<td>10.2 [4.9- 30.2]</td>
<td>10.2 [5.5- 36.7]</td>
</tr>
<tr>
<td>SVR (mmHg litre&lt;sup&gt;-1&lt;/sup&gt; minute&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>I</td>
<td>1.72 [0.80- 4.69]</td>
<td>1.85 [0.93- 4.30]</td>
<td>2.24 [1.06- 4.35]  ***</td>
</tr>
<tr>
<td></td>
<td>IK</td>
<td>1.76 [1.16- 3.33]</td>
<td>2.27 [1.08- 3.52]</td>
<td>2.22 [1.33- 3.83]  ***</td>
</tr>
<tr>
<td></td>
<td>IX</td>
<td>2.67 [1.00- 5.45]  a</td>
<td>2.62 [0.86- 4.33]</td>
<td>2.14 [0.68- 4.40]</td>
</tr>
</tbody>
</table>

CO, cardiac output; CI, cardiac index; SV, stroke volume; DO<sub>2</sub>, oxygen delivery; SVR, systemic vascular resistance. Data are presented as median [range]. a Significantly different from other groups; * Significantly different from T<sub>60</sub>; ** Significantly different from T<sub>30</sub>. Significance was set at p < 0.05. Because of technical problems during CO measurement, parameters were analysed with n = 16 at T<sub>30</sub> and T<sub>60</sub> or rather n = 15 at T<sub>90</sub> in group IX.
Table 4 Arterial blood gases and arterial oxygen content in isoflurane anaesthetised horses (I) and isoflurane anaesthesia balanced with either ketamine (IK) or xylazine (IX)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>T&lt;sub&gt;30&lt;/sub&gt;</th>
<th>T&lt;sub&gt;60&lt;/sub&gt;</th>
<th>T&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO&lt;sub&gt;2&lt;/sub&gt; (mmHg)</td>
<td>I</td>
<td>354 ± 95</td>
<td>350 ± 94</td>
<td>326 ± 114 **</td>
</tr>
<tr>
<td></td>
<td>IK</td>
<td>396 ± 104</td>
<td>403 ± 118</td>
<td>366 ± 112 * **</td>
</tr>
<tr>
<td></td>
<td>IX</td>
<td>394 ± 97</td>
<td>364 ± 90 **</td>
<td>359 ± 95 **</td>
</tr>
<tr>
<td>PaO&lt;sub&gt;2&lt;/sub&gt; (kPa)</td>
<td>I</td>
<td>47 ± 13</td>
<td>46 ± 13</td>
<td>43 ± 15 **</td>
</tr>
<tr>
<td></td>
<td>IK</td>
<td>53 ± 14</td>
<td>54 ± 16</td>
<td>49 ± 15 * **</td>
</tr>
<tr>
<td></td>
<td>IX</td>
<td>52 ± 13</td>
<td>48 ± 12 **</td>
<td>48 ± 13 **</td>
</tr>
<tr>
<td>PaCO&lt;sub&gt;2&lt;/sub&gt; (mmHg)</td>
<td>I</td>
<td>44 ± 4</td>
<td>46 ± 5</td>
<td>46 ± 6</td>
</tr>
<tr>
<td></td>
<td>IK</td>
<td>44 ± 7</td>
<td>44 ± 6</td>
<td>45 ± 5</td>
</tr>
<tr>
<td></td>
<td>IX</td>
<td>43 ± 5</td>
<td>45 ± 5</td>
<td>47 ± 6 **</td>
</tr>
<tr>
<td>PaCO&lt;sub&gt;2&lt;/sub&gt; (kPa)</td>
<td>I</td>
<td>5.9 ± 0.5</td>
<td>6.2 ± 0.7</td>
<td>6.1 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>IK</td>
<td>5.9 ± 0.9</td>
<td>5.9 ± 0.8</td>
<td>6.0 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>IX</td>
<td>5.7 ± 0.6</td>
<td>5.9 ± 0.7</td>
<td>6.3 ± 0.8 **</td>
</tr>
<tr>
<td>CaO&lt;sub&gt;2&lt;/sub&gt; (ml dl&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>I</td>
<td>16.2 ± 1.6</td>
<td>16.4 ± 1.4</td>
<td>15.3 ± 1.4 * **</td>
</tr>
<tr>
<td></td>
<td>IK</td>
<td>16.0 ± 1.7</td>
<td>16.0 ± 1.6</td>
<td>15.0 ± 1.5 * **</td>
</tr>
<tr>
<td></td>
<td>IX</td>
<td>15.5 ± 1.4</td>
<td>14.8 ± 1.9 **</td>
<td>14.3 ± 2.0 **</td>
</tr>
</tbody>
</table>

No differences were observed between groups. PaO<sub>2</sub>, arterial pressure of oxygen; PaCO<sub>2</sub>, arterial pressure of carbon dioxide; CaO<sub>2</sub>, arterial oxygen content. Data are presented as mean ± sd. * Significantly different from T<sub>60</sub>; ** Significantly different from T<sub>30</sub>. Significance was set at p < 0.05.
Table 5 Recovery times and scores after three different anaesthetic protocols in horses

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I</th>
<th>Group IK</th>
<th>Group IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>movement</td>
<td>20 [7- 34]</td>
<td>16 [5- 36]</td>
<td>20 [7- 40]</td>
</tr>
</tbody>
</table>

Recovery times (minutes) and recovery score (points 11 - 100; 11 = best, 100 = worst) in isoflurane anaesthetised horses (I) and isoflurane anaesthesia balanced with a continuous rate infusion (CRI) of either ketamine (IK) or xylazine (IX). Values are presented as median [range]. \(^c\) Significantly different from group IK; \(^d\) Significantly different from group IX. Significance was set at \(p < 0.05\).
References


TREESE, N., NIEMCZYK, H. & REUTHER, P. (1973) [Animal experiments on the effect of ketamine on the cardiovascular system as produced by the myocardium and central nervous system]. Anaesthesist 22, 117-120


5 Discussion

5.1 Discussion of Materials and Methods

5.1.1 Animals

Horses were randomly assigned to one of three treatment groups. As no statistically significant differences concerning age, bwt, onset of surgery and duration of anaesthesia were present, groups seem to be comparable concerning cardiovascular function and recovery. At the end of the study only seven horses in each group were operated in lateral recumbency, whereas ten horses in each group were dorsally recumbent during surgery. Type of recumbency can influence cardiovascular function, and as there has been an inequality within each group, results of this study might have been impaired (STEFFEY et al. 1990; RAISIS et al. 2005; BLISSITT et al. 2008). However, statistical analysis for cardiovascular functions revealed no significant differences in relation to recumbency and the uneven distribution was the same in all 3 groups, all results were pooled independent of type of recumbency.

Because of differences in length of surgical procedures, intraoperatively measured parameters after T90 were not included in statistical analysis. As duration of anaesthesia is correlated with recovery score (YOUNG and TAYLOR 1993), one horse had to be excluded from statistical analysis for recovery as anaesthesia did exceed the determinant time of 180 minutes. Data of recovery of another horse was also excluded due to a fire alert once the horse got padded in the recovery box.

5.1.2 Premedication, induction and maintenance of anaesthesia

Horses were premedicated with acepromazine, xylazine and butorphanol. Sedation with different alpha2-agonists followed by induction with ketamine and a benzodiazepine has been tested manifold and has been approved being safe and appropriate (RAISIS et al. 2000a; GANGL et al. 2001; KALCHOFNER et al. 2006; DEVISSCHER et al. 2010; SCHAUVLIEGE et al. 2011). Adding acepromazine seems to improve anaesthetic quality as mortality rates can be reduced, as seen in a large multicentre retrospective trial as well (JOHNSTON et al. 2002). To reduce the
requirement of xylazine and therefore its influence on cardiovascular effects, especially at the beginning of general anaesthesia, butorphanol was added to the sedative protocol. The combination of butorphanol with an alpha2-agonist increases the degree of sedation and decreases the response to external stimuli (ROBERTSON and MUIR 1983; CLARKE et al. 1991), but without providing further cardiovascular or MAC-sparing effects (HOFMEISTER et al. 2008; BETTSCHART-WOLFENSBERGER et al. 2011). Moreover, butorphanol was administered to provide additionally analgesia (KALPRAVIDH et al. 1984a, b). Since required dose of xylazine for premedication has been similar between groups, an influence on the results seems to be unlikely.

All horses received isoflurane in oxygen to maintain general anaesthesia as it currently is the only licensed volatile anaesthetic drug for horses in Germany (LÖSCHER 2010).

All horses were mechanically ventilated by IPPV to maintain both normocapnia and stable experimental conditions. Isoflurane depresses respiratory function seriously, which can be seen in a reduced RR, resulting in irregular isoflurane uptake and increased PaCO$_2$ (STEFFEY et al. 1977). Increasing PaCO$_2$ values can affect haemodynamics differently (KHANNA et al. 1995) and both horses and groups would not have been comparable anymore. However, cardiovascular functions could have been impaired by IPPV (EDNER et al. 2005) as well, but as all groups were mechanically ventilated, all horses were influenced equally.

In contrast to group IX, dose of ketamine in IK was reduced after an anaesthetic duration of two hours and CRI was stopped twenty minutes before the end of anaesthesia, at latest. Due to the fact that ketamine accumulates over time and can impair recovery quality, this procedure and dosage is recommended for clinical cases (BETTSCHART-WOLFENSBERGER and LARENZA 2007). Thus it remains unknown whether differences between groups concerning recovery might have been more pronounced in the case of not withdrawing ketamine early on.
5.1.3 Cardiovascular support

Horses have received a CRI of dobutamine if MAP has been below 70 mmHg, which was defined as hypotension, as dobutamine can increase MAP at even low doses (DONALDSON 1988; RAISIS et al. 2000b). Dose was gradually adjusted every five minutes and actually there were differences between groups in required doses. Due to the fact that dobutamine can affect haemodynamics in several ways, cardiovascular results could have been influenced, especially CO measurement, as doses above 1.25 µg kg\(^{-1}\) minute\(^{-1}\) have been shown to increase CO by positive inotropic effects (GASTHUYS et al. 1991). So actually CO might have been affected in some horses receiving high dosages of dobutamine, especially in groups I and IK, where five horses and one horse received between 1.0 and 1.35 µg kg\(^{-1}\) minute\(^{-1}\) dobutamine during period 1, respectively.

Chronotropic effects can be seen at doses above 2.5 µg kg\(^{-1}\) minute\(^{-1}\), resulting in severe tachycardia and cardiac dysrhythmias (SWANSON et al. 1985; GASTHUYS et al. 1991). As the maximum dobutamine infusion dose has been 1.62 µg kg\(^{-1}\) minute\(^{-1}\) in the recent study, a chronotropic influence on the heart seems to be minimal in this study.

However, in our opinion it would have been unethical to waive dobutamine, as hypotension is the most important risk factor for the development of post-anaesthetic myopathy (GRANDY et al. 1987; RICHEY et al. 1990) and only client-owned horses were included in this clinical trial. In addition, the study tried to reflect clinical practice, where dobutamine is given in cases of hypotension as well (DONALDSON 1988; LEE et al. 1998).

5.1.4 Determination of anaesthetic depth

Anaesthetic depth and consequentially isoflurane requirement was evaluated by clinical signs as movement, nystagmus, presence or absence of both palpebral and corneal reflex and changes in MAP (ENDERLE et al. 2008). Determination of anaesthetic depth by those signs is suitable (MUIR and HUBBELL 2009), but as reflexes are preserved or blocked differently by different drugs (SCHATZMANN and
GIRARD 1984; KALCHOFNER et al. 2006; BETTSCHART-WOLFENSBERGER and LARENZA 2007; RINGER et al. 2007), horses in the different groups might not have been in a comparable anaesthetic state. With using the flow chart developed by ENDERLE et al. (2008) to determine anaesthetic depth exactly, we tried to achieve the most objective evaluation of anaesthetic depth as possible. However, it has to be discussed whether results might have been influenced by either too deep or too light planes of anaesthesia in some cases, especially if considered that there actually was a significant difference in thiopental requirement between group IX and the other groups.

Consumption of volatile agents can be very individual and depends on age, gender and clinical health status of a horse, type of surgery, duration of anaesthesia and concomitantly used drugs (STEFFEY and HOWLAND 1978; PETERSEN-FELIX et al. 1993; STEFFEY et al. 2000; BENNETT et al. 2004; LEVIONNOIS et al. 2009). For definitive estimation of isoflurane sparing effects of either ketamine or xylazine in the used dose, individual MAC determination would have been necessary at the beginning of anaesthesia, which is not possible under clinical conditions (STEFFEY et al. 1977).

5.1.5 Intraoperative monitoring

Measurement of CO was performed only every thirty minutes as background accumulation of lithium and thus incorrect measurements should be avoided (HATFIELD et al. 2001). Estimation of CO using lithium dilution in anaesthetised horses has been evaluated, approved and adopted in several experimental and clinical studies over the last decade (LINTON et al. 2000; HALLOWELL and CORLEY 2005; RINGER et al. 2007; KALCHOFNER et al. 2009; MARCILLA et al. 2010; SCHAUVLIEGE et al. 2011). However, recently an abstract has been published (AMBRISCO et al. 2012), which describes that the sensor used in the LiDCO™ technique might be influenced directly by different drugs dose-dependently and CO values may become variable, with an overestimation of obtained CO with xylazine and ketamine. This study used plain drug solutions, not comparable to clinical drug concentrations in blood in an in-vitro approach and results under clinical
conditions (in-vivo trials) are outstanding, but it has to be discussed whether results of the recent study might have been influenced by administration of either ketamine or xylazine. Since plasma concentrations of the used drugs have not been measured, it remains speculatively if infusion rates were able to achieve such plasma concentrations at which the sensor might be influenced at all. Actually some technical problems occurred during CO measurements, especially in group IX, as the sensor tended to need a lot of time to achieve stable baseline voltages in this group, whereas it only took a few seconds in both other groups. Additionally after using a sensor with xylazine often replacement was necessary.

There were two outliers (two stallions, three and seven years old, presented for castration) in group IX which had exceeding values for CI (130 – 240 ml kg\(^{-1}\) minute\(^{-1}\)). We could not see any technical problem nor did dilution curves appear inaccurate in both cases. Furthermore no visible sympathetic stimulation (due to an insufficient analgesia or anaesthesia during castration) was evident in these horses, as both HR and MAP ranged within normal limits as we could measure in other horses of group IX as well. The two horses did not receive any dobutamine at the time of measurements. Actually, those high values (200 ± 25 ml kg\(^{-1}\) minute\(^{-1}\)) have only been reported for neonatal foals yet (THOMAS et al. 1987; CORLEY 2002; CORLEY et al. 2002), resulting from high HR values. However, when outliers were excluded from statistical analysis, results remained the same.

The use of indicator dilution techniques is limited in the presence of intracardiac shunts as indicator gets lost between injection and detection and measurement is becoming inaccurate, or rather falsely high (JONAS and TANSER 2002; CORLEY et al. 2003). In order to avoid disproportionate costs and considerable technical efforts we refrained from echocardiography, but only horses with unremarkable cardiac auscultation without exhibiting cardiac murmurs, which is associated with intracardiac shunts (BONAGURA and REEF 1998), were included in the study.

Postoperatively, SVR was calculated using a simplified equation published by KLABUNDE (2005). This formula neglects the influence of central venous pressure (CVP) on SVR as measurement of CVP would have been necessary to calculate SVR correctly, but would have also required right heart catheterization or at least a
central venous catheter. So actually the results of SVR are only an approximation, but this approach has been used several times in previously published studies and is able to assess changes over time (EDNER et al. 2005; KALCHOFNER et al. 2009; SCHAUVLIEGE et al. 2011).

5.1.6 Recovery

The whole recovery period was assessed by the same person who was able to observe horses directly from an elevation higher than the walls of the recovery box. Overall, objective evaluation is challenging and thus evaluation should be based on several different aspects, defined as "recovery quality", summarized below: Behaviour during lateral and sternal recumbency, number of attempts required to sternal recumbency and to stand, and coordination while arising (DONALDSON et al. 2000; CLARK-PRICE et al. 2008).

Scoring of quality was carried out by the same person who had anaesthetised the horses beforehand, so unfortunately was not unaware of treatment. Another approach for scoring of recovery quality by different graders using video recording after general anaesthesia would have improved objectivity of assessment.

As there is still no universal standardized scale for evaluation recovery, different clinical studies are using a variety of different recovery scores (RINGER et al. 2007; CLARK-PRICE et al. 2008; LARENZA et al. 2009; DEVISSCHER et al. 2010). In the recent study a previously published score has been used (CLARK-PRICE et al. 2008) and is a modification of a score reported by DONALDSON et al. (2000). It is a multidimensional scale in which different aspects have to be scored according to grade of activity described in one or more sentences (PORTIER et al. 2010), which is in contrast to more simple descriptive scales whose scores range from 1= best/excellent to 5= worst (GROSENBAUGH and MUIR 1998; RINGER et al. 2007; LARENZA et al. 2009). Evaluating different aspects may improve objective assessment of quality, as even more individual components can be included in analysis (CLARK-PRICE et al. 2008).

Measurements of duration and number of attempts to achieve sternal recumbency and standing are included in the assessment, as time is a quite important factor in
returning to pre-anaesthetic cardiovascular conditions (YOUNG and TAYLOR 1993). Especially prolonged lateral recumbency can be detrimental as circulation is reduced and muscle function can be impaired by both reduced blood flow and oxygen content leading to muscle metabolic changes (RICHEY et al. 1990; YOUNG and TAYLOR 1993; RAISIS et al. 2000a; EDNER et al. 2002). On the other hand, horses may benefit from prolonged recovery as time to stand has been correlated with recovery score in unsedated horses after isoflurane and halothane anaesthesia (DONALDSON et al. 2000). The longer horses tended to remain down, the better was the recovery quality. If horses are recumbent for a longer period of time, they can eliminate volatile anaesthetics, regain a better degree of consciousness, muscles become strong enough to carry the whole bodyweight and horses can arise less ataxic (DONALDSON et al. 2000; HUBBELL and MUIR 2009a), whereby risk of injuries may be extremely decreased (SANTOS et al. 2003). Therefore, improved recovery might be associated with horses remaining longer in sternal recumbency, but still without making a step to arise too early, since sternal recumbency is associated with better cardiopulmonary performance compared to dorsal or lateral recumbency (SCHATZMANN 1995b; HUBBELL and MUIR 2009b). In order to achieve those conditions and to restrain horses on the ground, groups I and IK received additional boli of xylazine as recovery after administration of alpha2-agonists is reported to be improved and therefore application is recommended (MATTHEWS et al. 1998; SANTOS et al. 2003; CLARK-PRICE et al. 2008; ENDERLE et al. 2008). Horses of group IX have not received additional sedation after general anaesthesia, except they would have shown signs of nystagmus or movement too early in the recovery phase, e.g. if horses were still recumbent on the surgery table. It was hypothesised that the CRI of xylazine would be sufficient to provide an adequate sedation level by maintaining still adequate plasma concentrations of xylazine even during the recovery phase. According to the result, since none of the horses in group IX have required additional sedation, this hypothesis seems to be approved. Finally, differences between groups concerning quality and duration of recovery might be influenced and probably be minimised by adding an alpha2-agonist to the
recovery protocol. As all horses were client-owned an abdication of chemical restraint was not considered for ethical reasons.

5.2 Discussion of results

5.2.1 Heart rate

Heart rates (at an average between 30 – 45 beats minute\(^{-1}\)) were within clinically reported ranges for anaesthetised horses (RAISIS et al. 2005; MUIR and HUBBELL 2009; SCHAUVLIEGE et al. 2011). Horses in group IX tended to be bradycardic, a typical side effect of alpha\(_2\)-agonists (ENGLAND and CLARKE 1996), which has already been reported in previous studies using balanced anaesthesia with different alpha\(_2\)-agonists (KALCHOFNER et al. 2006; SCHAUVLIEGE et al. 2011). As CO was always maintained adequately it was not necessary to treat those low values in this study. Unlike in group I, HR remained stable over the whole anaesthetic period in group IX as well as IK. The significant increase of HR around T\(_{50}\) in group I might be due to waning effects of premedication, but could also represent an autonomic response to surgical stimulation, as mean onset of surgery was between T\(_{50}\) and T\(_{55}\) (ILKIW 1999). Theoretically, significantly higher infusion rates of dobutamine in this group at that time point could also be the reason for higher heart rates, as dobutamine provides chronotropic effects, but this is usually only seen at higher doses than those used in this study (SWANSON et al. 1985; GASTHUYS et al. 1991).

In contrast to other studies (MUIR et al. 1977; MUIR and SAMS 1992), an increase of HR (and also MAP and CO) due to direct central sympathomimetic properties of ketamine over time was not observed in the current study. An explanation might be the low dosed CRI of ketamine, with plasma concentrations of ketamine remaining below 1 \(\mu\)g ml\(^{-1}\), which is the reported concentration providing those sympathomimetic properties (MUIR and SAMS 1992). As we have not measured any plasma concentrations, this aspect remains speculatively.
5.2.2 Mean arterial pressure

Untreated hypotension is one of the main risk factors for postoperative myopathy. Thus MAP is the most important parameter, which should be monitored in prolonged equine general anaesthesia (RICHEY et al. 1990; YOUNG and TAYLOR 1993). It was possible to maintain MAP above 70 mmHg with all three protocols, but with pronounced differences in required blood pressure support (e.g. dobutamine request). Especially horses in groups I and IK suffered from hypotension at the beginning of anaesthesia quite often, whereas MAP of IX was well maintained and extraordinarily constant over the whole anaesthetic period. During anaesthesia MAP did not differ between I and IK. In both these groups MAP reached the pre-determinant value of 70 mmHg at an average of 40 to 50 minutes after induction, which might be due to infusion and cardiovascular support (Ringer’s solution, HES or dobutamine), waning effects of premedication, onset of surgery or a combination of all of them. Overall, differences between groups might have been more pronounced if no additional cardiovascular support would have been applied. However, as described above, this was not possible as this was a clinical study.

5.2.3 Cardiac output

A main focus of this study was the measurement of cardiac output, as it accounts for muscle perfusion and reflects global circulation (EDNER et al. 2002). Under these study conditions it was able to maintain CO in clinically acceptable ranges with all anaesthetic protocols tested without differences between groups (MUIR and HUBBELL 2009). Generally comparison to other studies is difficult as CO depends much on anaesthetic protocol, used drugs, used dose of drugs, premedication and recumbency (STEFFEY et al. 1990; RAISIS et al. 2000a; JOHNSTON et al. 2002; EDNER et al. 2005). As volatile agents depress cardiovascular function dose-dependently, mainly the dose of isoflurane seems to affect CO (STEFFEY and HOWLAND 1978, 1980). Anyway, the values of CO in the current study are comparable or even somewhat better compared to other studies in horses (BLISSITT et al. 2008; KALCHOFNER et al. 2009; MARCILLA et al. 2012). Values of group I are
even much higher than those reported for isoflurane-anaesthetised, mechanically ventilated horses by EDNER et al. (2005), probably due to much higher ETISO (1.4 – 1.7 vol%) values required compared to our control group. As CO is the product of HR x SV, the decreased SV between T₆₀ and T₉₀ in groups I and IK seems to account for decreased CO between T₆₀ and T₉₀, which might be due to significantly increased ETISO during this time unit in these two groups as isoflurane provides negative inotropic effects (STEFFEY et al. 1977; DAVIES et al. 2000).

It has to be considered that despite significantly lower MAP values at T₃₀ compared to T₆₀, CO was not significantly different in group I, or between T₃₀ and T₆₀ in group IK. This supports findings by WAGNER et al. (1992) and EDNER et al. (2002), that MAP might be inversely related to CO and consequently high MAP values (e.g. due to increased SVR) might not necessarily translate to high CO values as well. Mainly for this reason, CO monitoring could improve quality of equine anaesthesia in practice, but until now this technique is still sensitive to errors and quite expensive making it not suitable for routine clinical use.

With ketamine supplementation an improvement of cardiovascular function in group IK due to sympathomimetic properties directly, or by reduction of isoflurane requirements had been expected (MUIR and SAMS 1992; BETTSCHART-WOLFENSBERGER and LARENZA 2007), but we failed to demonstrate that hypothesis. Quite contrary, to maintain MAP above 70 mmHg dobutamine requirement did not differ between group I and group IK. An improvement of cardiovascular function due to central sympathomimetic properties can be seen at plasma concentrations above 1 µg ml⁻¹ of ketamine and is reflected in increased HR, MAP and CO (due to raised HR and cardiac contractility) (MUIR and SAMS 1992). Therefore, those plasma concentrations have not been reached under our study conditions using 2.2 mg kg⁻¹ ketamine for induction, followed by a 1 mg kg⁻¹ hour⁻¹ dosed CRI. On the other hand, an improvement in CO due to less isoflurane would have been expected. Actually the used dose seemed to provide some antinociceptive properties as horses in group IK required less (19.6 %) isoflurane than horses in group I, but nevertheless improvement of cardiovascular function was still lacking.
However, ketamine itself can provide direct negative inotropic effects when indirect sympathetic stimulation is lacking (TREESE et al. 1973; DIAZ et al. 1976; WAXMAN et al. 1980). Therefore, effects on the heart concerning on CO, HR, contractility and preload might depend much on simultaneously used drugs for premedication and maintenance of anaesthesia (DOWDY and KAYA 1968; HASKINS et al. 1985). Further studies are warranted to investigate whether horses may benefit from higher dosed ketamine CRIs, but there is the potential of decreased recovery quality due to muscle tremor and rigidity, ataxia and excitation with increasing doses of ketamine (MUIR and SAMS 1992).

With xylazine supplementation, it was of interest if isoflurane requirements could be reduced and if so, whether cardiodepressive effects of the alpha2-agonist might disguise the anaesthetic sparing effect. Different experimental studies approved MAC-reducing effects for different alpha2-agonists (STEFFEY et al. 2000; BETTSCHEART-WOLFENSBERGER et al. 2001; BENNETT et al. 2004). In the current study xylazine reduced the required isoflurane up to 20.8 %, comparable to results of a CRI of medetomidine in a clinical trial by RINGER et al. (2007). In contrast, studies investigating romifidine, detomidine and dexmedetomidine (DEVISSCHER et al. 2010; SCHAUVLIEGE et al. 2011; MARCILLA et al. 2012) failed to demonstrate isoflurane reducing effects. On one hand, doses used in those studies (e.g. 40 µg kg⁻¹ hour⁻¹ romifidine) might be less antinociceptive or hypnotic than the dose of xylazine infused here and therefore insufficient in reducing isoflurane requirements, especially when considering that only 80 µg kg⁻¹ romifidine seems to be equipotent to 1 mg kg⁻¹ xylazine (ENGLAND et al. 1992). On the other hand, possible MAC-reducing effects might not have been detected in those studies because of very short anaesthetic periods being analysed. In these cases surgical stimulation occurred at a time when premedication drugs were still having an effect, diminishing responses to surgical stimulation. This hypothesis might be supported by observations in our study, where differences between groups have not become evident until T₅₀ (mean onset time of surgery).

We did not detect any clinically relevant difference between groups in cardiovascular function. Despite significantly lower HR over the whole time and significantly higher
SVR in group IX compared to groups I and IK, differences in CO did not reach statistical significance. Classic side effects of alpha$_2$-agonists seems to be less pronounced under steady state conditions than after bolus administration as has also been observed in ponies sedated with a CRI of medetomidine, where CI and SVR did not differ from baseline values after achieving steady-state conditions (BETTSCHART-WOLFENSBERGER et al. 1999). Finally, it remains questionable, if differences between groups have not been detected by statistical analysis due to high variability of CO measurements mainly in group IX.

5.2.4 Other cardiopulmonary parameters

Administration of xylazine may result in hypertension (ENGLAND and CLARKE 1996). In the present study, MAP was also higher in group IX compared to both other groups. However, SVR has not been different between groups indicating that vasoconstriction induced by xylazine was not severe. But it has to be considered that acepromazine has been part of the anaesthetic protocol and possible vasoconstrictive effects of xylazine might be counteracted by this potent alpha$_1$-antagonist (DRIESSEN et al. 2011).

Whereas SVR in group IX remained constant during the whole anaesthetic period, SVR in groups I and IK increased over time, which might be attributed to sympathetic nervous activation by surgical stimulation. Theoretically less infusion of dobutamine after the first hour of anaesthesia (dose decreased over time) can also be accountable for higher values of SVR during period 2 as dobutamine is known to decrease total peripheral resistance in humans (LAWSON 1994). However, studies have either failed to demonstrate this effect in horses yet (SWANSON et al. 1985; RAISIS et al. 2000b).

Changes over time in blood gases, CaO$_2$ and DO$_2$ were minimal and not clinically relevant. Mean averaged PaO$_2$ values were above 300 mmHg, suggesting fully saturated haemoglobin, and mean averaged PaCO$_2$ values of below 48 mmHg indicated normocapnia in all horses (MUIR and HUBBELL 2009). As there were no differences between groups, the changes seemed to be drug-independent and mainly influenced by time. Decreased DO$_2$ in groups I and IK over time was
correlated with a decrease in CO at that point in time as well, demonstrating the strong association between both parameters (MARCILLA et al. 2010).

5.2.5 Isoflurane requirements and adaption of anaesthetic depth

Isoflurane requirements were reduced by up to 20 % in both balanced anaesthetic protocol groups compared to isoflurane alone. The overall required concentration of isoflurane in the control group (1.16 ± 0.13 vol %) was lower than previously published MAC-values (1.3 to 1.6 vol %) for isoflurane anaesthetised horses (STEFFEY et al. 1977; STEFFEY et al. 2000). This might be the result of several aspects: Especially during the first 40 minutes, horses in group I required less isoflurane than afterwards as there were still effects of the xylazine premedication and ketamine for induction of anaesthesia present. Both acepromazine and midazolam are known to reduce the MAC of isoflurane (MATTHEWS et al. 1990; DOHERTY et al. 1997; GANGL et al. 2001). However, because of insufficient depth of anaesthesia ETISO had to be increased after T₅₀ and concomitant onset of surgery in both groups other than IX. Aside from providing a continuously stable surgical plane of anaesthesia, all cardiovascular parameters were characterized by high consistency and stability over the whole anaesthetic period in group IX. It seems that a CRI of 1 mg kg⁻¹ hour⁻¹ xylazine may blunt the autonomic response to noxious stimulation, which are still present at ETISO values, which block motor responses (ZBINDEN et al. 1994), by providing additional hypnosis and analgesia (MARCILLA et al. 2012) or by vasopressor responses suppressing heart rate changes (KERR et al. 1972). Insufficient anaesthetic depth in group I and group IK after onset of surgery was also reflected by higher amounts of thiopental needed. Horses showed nystagmus or even gross movements, which did not occur at any point in time in group IX. The increase of HR after T₅₀ in group I might be a response to surgical stimulation. Different theories exist about the cardiovascular consequences of noxious stimulation and stress response. Some studies reported an increase of CO due to beta-receptor activation and therefore increased HR (RINGER et al. 2007), whereas a fall in CO was observed in other studies (WAGNER et al. 1992; RAISIS et al. 2005; BLISSITT
et al. 2008), probably due to an increased vascular tone by alpha-receptor activation in peripheral vessels leading to raised SVR and increased afterload. Last mentioned theory appears less likely to be present in this study as peripheral alpha-receptor activation has been inhibited or at least weakened by acepromazine, a potent alpha1-antagonist (DRIESSSEN et al. 2011).

5.2.6 Recovery
Several aspects like age, character of the horse, cardiovascular conditions, duration of anaesthesia, invasiveness of surgery and duration of recovery, are known to influence recovery quality (YOUNG and TAYLOR 1993). As horses were randomly assigned to treatment groups with special consideration to those aspects (“matched-pairs”), groups did not differ in duration of anaesthesia, age and types of surgery. Thereby impact on the results of recovery should be minimally.

Time to standing after 105-minutes of isoflurane anaesthesia in horses is reported to be between 17 to 22 minutes (MATTHEWS et al. 1992), which is quite fast compared to the present study. Prolonged recovery in the current study can be explained by additional sedation with xylazine after general anaesthesia. Horses have been calmed and have remained recumbent for a longer period of time, which is known to improve recovery quality (SANTOS et al. 2003; CLARK-PRICE et al. 2008). Time to standing after administration of an alpha2-agonist (0.1 to 0.2 mg kg\(^{-1}\)) is reported to be approximately thirty minutes (SANTOS et al. 2003; CLARK-PRICE et al. 2008), which is about ten minutes faster than horses in group I in this study. This difference can be explained by the higher dose of xylazine (0.25 mg kg\(^{-1}\)) used in our study. Compared to clinical studies using isoflurane and a CRI of medetomidine (KALCHOFNER et al. 2006; RINGER et al. 2007), horses in group IX recovered approximately ten minutes earlier, which might be due to the fact, that horses had received additional boli of medetomidine before recovery, increasing the plasma concentration and prolonging the effect.

Results of recovery quality were better compared to the score points given in the original study (approximately 40 points), where anaesthesia was maintained with isoflurane alone (CLARK-PRICE et al. 2008). Actually comparison of recovery quality
Discussion

to other studies is difficult due to different anaesthetic protocols and different animal populations (age, breed, gender). Compared to group I, horses in the last mentioned study received higher doses of isoflurane (1.3 vol %), a lower dose of xylazine after general anaesthesia and have still raised ten minutes earlier on average. These aspects can be responsible for worse recovery quality compared to group I in the present study, as horses might have tried to arise too early before regaining full muscle strength.

As all horses recovered well without signs of PAM, all tested anaesthetic protocols seem to be associated with a safe and unremarkable recovery. No significant differences between I and IX, or rather I and IK were observed. Anyway, recovery quality of group IX was better compared to group IK, even without receiving additional boli of xylazine after general anaesthesia. The adverse effects of ketamine (excitement and muscle rigidity) (KNOBLOCH et al. 2006) seemed to overwhelm the beneficial and calming properties of additional sedation after general anaesthesia, despite an early reduction of ketamine administration during surgery as previously recommended (BETTSCHART-WOLFENSBERGER and LARENZA 2007). However, the statistically significant difference seems not to be clinically relevant as all horses recovered well and a median score of 22 in group IK was still low considering that the worst recovery would have been scored with 100 points.

5.3 Conclusion

Under these study conditions it was possible to maintain cardiopulmonary parameters with all three protocols tested without clinically relevant differences in anaesthetic and recovery quality, but with pronounced differences in blood pressure support. As hypotension can occur during isoflurane and isoflurane-ketamine anaesthesia, monitoring of MAP and treatment of hypotension is strongly recommended in horses anaesthetised with those anaesthetic protocols. Xylazine supplementation resulted in a pronounced reduction of anaesthetic requirements, less top up thiopental to maintain an adequate anaesthetic level and less blood pressure support to provide haemodynamically stable conditions.
A CRI of 1 mg kg\(^{-1}\) hour\(^{-1}\) ketamine resulted in no improvement of cardiovascular function due to its sympathomimetic and MAC-reducing properties in isoflurane anaesthetised horses.

Despite only few differences in cardiovascular variables and recovery quality under these study conditions, from the practical point of view isoflurane-xylazine anaesthesia seems to be superior to isoflurane-ketamine balanced anaesthesia since it can be infused with less time limitations in contrast to ketamine with its cumulative effects. An adequate surgical level of anaesthesia can be achieved more easily with a xylazine combination.

Further studies are warranted to investigate the potential of higher doses of ketamine CRIs, as well as balanced anaesthesia using xylazine in haemodynamically depressed horses, such as those suffering from colic.
6 Zusammenfassung

Nina Pöppel

Einfluss zweier balancierter Anästhesieprotokolle mit Xylazin oder Ketamin für das Pferd im Hinblick auf die Narkosequalität, kardiopulmonale Stabilität, benötigte Isoflurankonzentration und die Qualität der Aufstehphase im kontrollierten klinischen Versuch

Ziel der Studie war es, sowohl die zwei balancierten Anästhesieprotokolle Isofluran-Ketamin und Isofluran-Xylazin untereinander, als auch jeweils mit einer Isofluranmononarkose hinsichtlich der kardiopulmonalen Stabilität, der dafür benötigten Isoflurankonzentration und der Qualität der Aufstehphase zu vergleichen.

Einundfünfzig klinisch gesunde Pferde, die elektiv an der Klinik für Pferde der Tierärztlichen Hochschule Hannover operiert werden sollten, wurden randomisiert einer von drei Anästhesiegruppen zugeteilt. Alle Tiere wurden mit Acepromazin (0,03 mg/kg i.m.), Xylazin (0,5-1,0 mg/kg i.v.) und Butorphanol (0,025 mg/kg i.v.) sediert und die Anästhesie mittels Ketamin (2,2 mg/kg i.v.) und Midazolam (0,06 mg/kg i.v.) eingeleitet. Die Aufrechterhaltung der Narkose erfolgte entweder mit Isofluran alleine (Gruppe I), oder mit Isofluran in Kombination mit einer Dauertropinfusion Ketamin (1 mg/kg/Stunde) (Gruppe IK) beziehungsweise Xylazin (1 mg/kg/Stunde) (Gruppe IX).

Spätestens nach einer Narkosedauer von zwei Stunden wurde die Dosierung der Ketamininfusion halbiert und diese jeweils spätestens 20 Minuten vor Narkoseausleitung beendet. Alle Pferde wurden mit intermittierender, positiver Druckbeatmung ventiliert (end-exspiratorischer Kohlenstoffdioxidgehalt zwischen 4,7 und 6 kPa) und die end-exspiratorische Isoflurankonzentration (ETISO) nach einem Anästhesietiefenpunktesystem (-1 bis 4) durch den gleichen Anästhesisten nach Bedarf eingestellt. Bei einer Punktzahl zwischen 2 und 4 (insuffiziente Narkosetiefe) wurde Thiopental zur unmittelbaren Anästhesievertiefung verabreicht und der Bedarf notiert. Der mittlere arterielle Blutdruck (MAD) wurde mit Hilfe von Dobutamin ≥ 70 mmHg gehalten. Herz- und Atemfrequenz, MAD, ETISO, arterielle Blutgase und das
Herzminutenvolumen (Lithiumdilution) wurden kontinuierlich gemessen. Im Anschluss an die Narkose wurden folgende weitere Parameter berechnet: Der Herzindex (CI), der systemisch vaskuläre Widerstand (SVR), das Schlagvolumen (SV), die arterielle Sauerstoffkonzentration (CaO₂) und die arterielle Sauerstoffaufnahme (DO₂). Die Gruppen I und IK erhielten 0,25 mg/kg Xylazin kurz vor der Aufstehphase. Die Beurteilung dieser hinsichtlich der Qualität erfolgte nach einem Punktesystem von 11 (ideal) bis 100 (sehr schlecht). Die Dauer bis zur ersten Bewegung, bis zum Erreichen der Brustlage und bis zum sicheren Stand wurde notiert.


Die Gruppen unterschieden sich statistisch signifikant in den Parametern Herzfrequenz, MAD, Dobutamin- und Isofluranbedarf voneinander. Die mittlere Herzfrequenz (31 ± 3 Schläge/Minute) war im Vergleich zu beiden anderen Gruppen in der Gruppe IX signifikant am niedrigsten. Beide balancierten Anästhesieprotokolle führten zu einer statistisch signifikanten Reduktion des Isofluranbedarfes (ETISO (Volumen %); IK: 0,97 ± 0,08; IX: 0,95 ± 0,07) um ca. 20 %, verglichen mit dem über die Anästhesiedauer gemitteltem ETISO (1,16 ± 0,13 Volumen %) der Gruppe I. Pferde in Gruppe IX zeigten einen MAD von durchschnittlich 90 ± 13 mmHg ohne Dobutamin. Sowohl der mittlere MAD (I: 71 ± 8 mmHg; IK: 76 ± 7 mmHg), als auch der mediane Dobutaminbedarf (I: 0,38 µg/kg/Minute; IK: 0,22 µg/kg/Minute) der anderen Gruppen unterschied sich hiervon hochsignifikant (p< 0,0001). Alle Gruppen haben in der ersten Stunde der Anästhesie statistisch signifikant (p< 0,05) mehr Dobutamin benötigt, als in der zweiten Hälfte der Narkose, um den MAD über 70
mmHg zu halten. Um eine ausreichend tiefe Narkose zu gewährleisten, benötigten neun (Gruppe I) bzw. sieben (Gruppe IK) Tiere zusätzliche Injektionen von Thiopental, wohingegen dies in der Gruppe IX nicht notwendig war. Keine Unterschiede zwischen den Gruppen zeigten sich hinsichtlich Atemfrequenz, Herzminutenvolumen, CI, SV, CaO2, DO2, SVR und arteriellen Blutgase, allerdings sanken das Herzminutenvolumen, der CI, der DO2 und das SV statistisch signifikant (p< 0,05) über den Narkosezeitraum in den Gruppen I und IK, wohingegen der SVR in diesen beiden Gruppen anstieg. Alle Pferde zeigten insgesamt eine gute Aufstehqualität, die in Gruppe IX (15 [11 – 42]) leicht (p< 0,0407) besser war als in Gruppe IK (22 [13 – 45]), ohne Unterschied in der Dauer der Aufstehphase zwischen den Gruppen.

Zusammenfassend konnte eine kreislaufstabile Narkose, gefolgt von einer guten Aufstehqualität, mit allen drei getesteten Anästhesieprotokollen erreicht werden, allerdings bedurften Pferde unter Isofluranmononarkose hierfür deutlich mehr kreislaufunterstützende Maßnahmen. Vor allem durch die Supplementierung von Xylazin zu einer Inhalationsnarkose konnte die benötigte Isoflurankonzentration reduziert und die Kreislaufsituations besser stabil gehalten werden. Zusätzlich zeichnete sich dieses Anästhesieprotokoll durch eine gute Steuerbarkeit und eine leichte Aufrechterhaltung der adäquaten Anästhesietiefe, bei gleichzeitig sehr konstanten und über die Zeit kaum veränderten Kreislaufverhältnissen, aus.
7 Summary

Nina Pöppel

Influence of ketamine or xylazine constant rate infusion on quality of anaesthesia, cardiopulmonary function and recovery in isoflurane anaesthetised horses- a controlled clinical trial

As balanced anaesthesia techniques have become common in equine anaesthesia, the aim of this study was to compare the effects of three different anaesthetic protocols on cardiopulmonary function, end-tidal isoflurane and quality of recovery in isoflurane anaesthetised horses under clinical conditions. Fifty-one clinically healthy horses undergoing elective surgery at the Clinic for Horses at the University of Veterinary Medicine, Hannover, Foundation, were randomly assigned to one of three treatment groups (n = 17). The horses were premedicated with acepromazine (0.03 mg kg\(^{-1}\) IM) 30-60 minutes before induction of anaesthesia, xylazine (0.5-1.0 mg kg\(^{-1}\) to effect) and butorphanol (0.025 mg kg\(^{-1}\)) IV. Anaesthesia was induced with midazolam (0.06 mg kg\(^{-1}\) IV) and ketamine (2.2 mg kg\(^{-1}\) IV) and maintained with isoflurane in oxygen alone (I), or isoflurane balanced with either a constant rate infusion (CRI) of ketamine (IK) (1 mg kg\(^{-1}\) hour\(^{-1}\), stopped 20 minutes before end of anaesthesia) or a CRI of xylazine (IX) (1 mg kg\(^{-1}\) hour\(^{-1}\)). All horses were mechanically ventilated (end-expiratory concentration of carbon dioxide between 4.6-6 kPa) using intermittent positive pressure ventilation. End-expiratory concentration of isoflurane (ETISO) was adjusted to an anaesthetic-depth-scoring system (-1 to 4) by the same anaesthetist. Additional boli of thiopental were injected if anaesthetic depth was considered as too light (score 2 to 4) and the total amount recorded. Mean arterial pressure (MAP) was maintained above 70 mmHg with dobutamine if required. Heart rate (HR), respiratory rate (RR), MAP, ETISO, cardiac output (CO; lithium dilution method) and arterial blood gases (\(\text{PaO}_2\), \(\text{PaCO}_2\)) were measured at set time intervals. After general anaesthesia the following parameters were calculated: Cardiac index (CI), systemic vascular resistance (SVR), stroke
volume (SV), arterial oxygen content (CaO₂) and oxygen delivery (DO₂). Groups I and IK received xylazine (0.25 mg kg⁻¹ IV) before recovery. Recovery was scored from 11 (best) to 100 (worst) and recovery times (time to first movement, sternal recumbency and standing) recorded. Normally distributed data were analysed using one-way analysis of variance (ANOVA) or two-way ANOVA for repeated measurements. Non-parametric data were analysed by either Kruskal-Wallis test, followed by Wilcoxon-Mann-Whitney test, if significance level had been reached, or Wilcoxon signed-rank test for repeated measurements. Normally distributed data are presented as mean ± standard deviation (SD), whereas non-parametric data are expressed as median [minimum – maximum]. Significance level was set at p < 0.05. Statistically significant differences between groups were detected in HR, MAP, and both dobutamine and isoflurane requirements. Mean averaged HR (31 ± 3 beats minute⁻¹) was significantly lowest and MAP (90 ± 13 mmHg) was significantly highest in group IX. Isoflurane requirement (ETISO, vol %) was significantly reduced up to 20% using balanced anaesthesia techniques (IK: 0.97 ± 0.08; IX: 0.95 ± 0.07) compared to group I (1.16 ± 0.13). To maintain MAP above 70 mmHg, groups I and IK required median [minimum – maximum] dose of dobutamine (µg kg⁻¹ minute⁻¹) at 0.38 [0.16 – 1.00] and 0.22 [0.07 – 1.20], respectively, which was significantly higher (p < 0.0001) compared to group IX, in which dobutamine was rarely infused. During the first hour of anaesthesia all groups achieved significantly (p < 0.05) higher doses of dobutamine as afterwards until the end of anaesthesia. To provide an adequate anaesthetic depth, nine horses (I) and seven horses (IK) required additional boli of thiopental, whereas none of the horses in group IX received thiopental. Differences in other cardiopulmonary parameters (CO, CI, SV, CaO₂, DO₂ and arterial blood gases) did not reach statistical significance. However, there was an influence by time in several parameters, mainly in groups I and IK, as CO, CI, DO₂ and SV decreased significantly (p < 0.05), whereas SVR significantly (p < 0.05) increased over time in these two groups. All horses recovered well, with a significant (p < 0.0407) difference between group IK (22 [13 – 45]) and IX (15 [11 – 42]). Recovery times did not differ among groups.
In conclusion, cardiopulmonary parameters were maintained with all three protocols without clinically relevant differences in recovery quality, but with pronounced differences in required blood pressure support. Especially xylazine supplementation resulted in a pronounced reduction of anaesthetic requirements and less blood pressure support without clinically adverse impact on cardiovascular function.
8 References


References


References


HALLOWELL, G. D. and K. T. CORLEY (2005):  
Use of lithium dilution and pulse contour analysis cardiac output determination in anaesthetized horses: a clinical evaluation.  
Vet Anaesth Analg 32, 201-211

Partial CO2 rebreathing indirect Fick technique for non-invasive measurement of cardiac output.  
J Clin Monit Comput 16, 361-374

Comparative cardiovascular and pulmonary effects of sedatives and anesthetic agents and anesthetic drug selection for the trauma patient.  
J Vet Emerg Crit Care 16, 300-328

HASKINS, S. C., T. B. FARVER and J. D. PATZ (1985):  
Ketamine in dogs.  
Am J Vet Res 46, 1855-1860

Pharmacokinetics and toxic effects of lithium chloride after intravenous adminstration in conscious horses.  
Am J Vet Res 62, 1387-1392

HEARD, D. J., A. I. WEBB and R. T. DANIELS (1986):  
Effect of acepromazine on the anesthetic requirement of halothane in the dog.  
Am J Vet Res 47, 2113-2115

Butorphanol: a review of its pharmacological properties and therapeutic efficacy.  
Drugs 16, 473-505

HILLIDGE, C. J. and P. LEES (1975):  
Cardiac output in the conscious and anaesthetised horse.  
Equine Vet J 7, 16-21

HIMMELSEHER, S. and M. E. DURIEUX (2005):  
Revising a Dogma: Ketamine for Patients with Neurological Injury?  
Anesth Analg 101, 524-534

Clinical evaluation of xylazine as a chemical restraining agent, sedative, and analgesic in horses.  
J Am Vet Med Assoc 164, 42-45
Effect of butorphanol administration on cardiovascular parameters in isoflurane-
anesthetized horses - a retrospective clinical evaluation.
Vet Anaesth Analg 35, 38-44

The use of sedatives, analgesic and anaesthetic drugs in the horse: an electronic
survey of members of the American Association of Equine Practitioners (AAEP).
Equine Vet J 42, 487-493

Considerations for induction, maintenance and recovery.
In: W.W. MUIR and J.A.E. HUBBELL:
Equine anaesthesia: Monitoring and Emergency Therapy
2nd, Saunders Elsevier, St. Louis, pp. 381- 396

Equine Anesthesia: Monitoring and Emergency Therapy
2nd, Saunders Elsevier, St. Louis

ILKIW, J. E. (1999):
Balanced anesthetic techniques in dogs and cats.
Clin Tech Small Anim Pract 14, 27-37

ILKIW, J. E., P. J. PASCOE and L. D. TRIPP (2002):
Effects of morphine, butorphanol, buprenorphine, and U50488H on the minimum
alveolar concentration of isoflurane in cats.
Am J Vet Res 63, 1198-1202

IVANKOVICH, A. D., D. J. MILETICH, C. REIMANN, R. F. ALBRECHT and B.
ZAHED (1974):
Cardiovascular effects of centrally administered ketamine in goats.
Anesth Analg 53, 924-933

The confidential enquiry into perioperative equine fatalities (CEPEF): mortality results
of Phases 1 and 2.
Vet Anaesth Analg 29, 159-170

Confidential enquiry of perioperative equine fatalities (CEPEF-1): preliminary results.
Equine Vet J 27, 193-200
Lithium dilution measurement of cardiac output and arterial pulse waveform analysis:
an indicator dilution calibrated beat-by-beat system for continuous estimation of
cardiac output.
Curr Opin Crit Care 8, 257-261

KAKA, J. S., P. A. KLAVANO and W. L. HAYTON (1979):
Pharmacokinetics of ketamine in the horse.
Am J Vet Res 40, 978-981

KALCHOFNER, K. S., S. PICEK, S. K. RINGER, M. JACKSON, M. HASSIG and R.
BETTSCHART-WOLFENSBERGER (2009):
A study of cardiovascular function under controlled and spontaneous ventilation in
isoflurane-medetomidine anaesthetized horses.
Vet Anaesth Analg 36, 426-435

and R. BETTSCHART-WOLFENSBERGER (2006):
Clinical assessment of anesthesia with isoflurane and medetomidine in 300 equidae.
Pferdeheilkunde 22, 301-308

Analgesic effects of butorphanol in horses: dose-response studies.
Am J Vet Res 45, 211-216

Effects of butorphanol, flunixin, levorphanol, morphine, and xylazine in ponies.

Zur Anwendung von Butorphanol in der Veterinärmedizin- Eine Übersicht.
Tierarztl Prax K 6, 393-398

The organ toxicity of inhaled anesthetics.
Anesth Analg 81, S51-66

Sedative and other effects of xylazine given intravenously to horses.
Am J Vet Res 33, 525-532

Cardiopulmonary effects of hypercapnia during controlled intermittent positive
pressure ventilation in the horse.
Can J Vet Res 59, 213-221
KLABUNDE, R. E. (2005):
Vascular Concepts.
In: R.E. KLABUNDE:
Cardiovascular Physiology Concepts
1st, Lippincott Williams & Wilkins, Philadelphia, p 102-103

Antinociceptive effects, metabolism and disposition of ketamine in ponies under target-controlled drug infusion.
Toxicol Appl Pharmacol 216, 373-386

Effects of butorphanol and carprofen on the minimal alveolar concentration of isoflurane in dogs.
J Am Vet Med Assoc 217, 1025-1028

Ketamine: teaching an old drug new tricks.
Anesth Analg 87, 1186-1193

Lithium dilution cardiac output measurements using a peripheral injection site comparison with central injection technique and thermodilution.
J Clin Monit Comput 15, 279-285

Pharmacodynamic effects and pharmacokinetic profile of a long-term continuous rate infusion of racemic ketamine in healthy conscious horses.
J Vet Pharmacol Ther 29, 477-488

Evaluation of anesthesia recovery quality after low-dose racemic or S-ketamine infusions during anesthesia with isoflurane in horses.
Am J Vet Res 70, 710-718

Catecholamines: the first messengers.
Baillière's Clin Anaes 8, 27-58


Narkotika.
In: W. LÖSCHER, F.R. UNGEMACH and R. KROKER:
Pharmakotherapie bei Haus- und Nutztieren
8th, Enke, Stuttgart, pp. 68-85

LUNA, S. P., P. M. TAYLOR and F. MASSONE (1997):
Midazolam and ketamine induction before halothane anaesthesia in ponies: cardiorepiratory, endocrine and metabolic changes.
J Vet Pharmacol Ther 20, 153-159

LUND-JOHANSEN, P. (1990):
The dye dilution method for measurement of cardiac output.
Eur Heart J 11 Suppl I, 6-12

LUNDY, J. (1926):
Balanced anaesthesia.
Minn Med 9, 399- 404

LUNN, J. N. and W. W. MUSHIN (1982):
Mortality associated with anesthesia.
Anaesthesia 37, 856

Evaluation of xylazine and ketamine for total intravenous anesthesia in horses.
Am J Vet Res 66, 1002-1007

Ventilatory pattern and chest wall mechanics during ketamine anesthesia in humans.
Anesthesiology 65, 492-499

Use of the bispectral index as a monitor of anesthetic depth in cats anesthetized with isoflurane.
Am J Vet Res 64, 1534-1541

Cardiopulmonary effects of two constant rate infusions of dexmedetomidine in isoflurane anaesthetized ponies.
Vet Anaesth Analg 37, 311-321
References

Influence of a constant rate infusion of dexmedetomidine on cardiopulmonary function and recovery quality in isoflurane anaesthetized horses.
Vet Anaesth Analg 39, 49-58

MARNTELL, S., G. NYMAN, P. FUNKQUIST and G. HEDENSTIERNA (2005):
Effects of acepromazine on pulmonary gas exchange and circulation during sedation and dissociative anaesthesia in horses.
Vet Anaesth Analg 32, 83-93

Burn care protocols: administration of ketamine. Ketamine pharmacology and therapeutics.
J Burn Care Rehabil 8, 146-148

MATTHEWS, N. S., N. S. DOLLAR and R. V. SHAWLEY (1990):
Halothane-sparing effect of benzodiazepines in ponies.
Cornell Vet 80, 259-265

Recovery from sevoflurane anesthesia in horses: comparison to isoflurane and effect of postmedication with xylazine.
Vet Surg 27, 480-485

MATTHEWS, N. S. and S. L. LINDSAY (1990):
Effect of low-dose butorphanol on halothane minimum alveolar concentration in ponies.
Equine Vet J 22, 325-327

Comparison of recoveries from halothane vs isoflurane anesthesia in horses.
J Am Vet Med Assoc 201, 559-563

Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia.
Anesthesiology 74, 581-605

MCCARTY, J. E., C. M. TRIM and D. FERGUSON (1990):
Prolongation of anesthesia with xylazine, ketamine, and guaifenesin in horses: 64 cases (1986-1989).
J Am Vet Med Assoc 197, 1646-1650

MCCASHIN, F. B. and A. A. GABEL (1975):
Evaluation of xylazine as a sedative and preanesthetic agent in horses.
Am J Vet Res 36, 1421-1429
Age-related abnormalities in arterial compliance identified by pressure pulse contour analysis: aging and arterial compliance. 
Hypertension 33, 1392-1398

MIZUNO, Y., H. AIDA, H. HARA and T. FUJINAGA (1994a): 
Cardiovascular effects of intermittent positive pressure ventilation in the anesthetized horse. 

Comparison of methods of cardiac output measurements determined by dye dilution, pulsed Doppler echocardiography and thermodilution in horses. 

Monitoring Anaesthesia. 
In: W. W. MUIR and J.A.E. HUBBELL: 
Equine anaesthesia: Monitoring and Emergency Therapy 
2nd, Saunders Elsevier, St. Louis, pp. 149-170

Balanced Anaesthesia: New emphasis on an old idea. 
Vet Anaesth Analg 21, 9-11

Anxiolytics, nonopioid sedative-analgesics and opioid analgesics. 
In: W. W. MUIR and J.A.E. HUBBELL: 
Equine anaesthesia: Monitoring and Emergency Therapy 
2nd, Saunders Elsevier, St. Louis, pp. 185-209

Intravenous anesthetic drugs. 
In: W. W. MUIR and J.A.E. HUBBELL: 
Equine anaesthesia: Monitoring and Emergency Therapy 
2nd, Saunders Elsevier, St. Louis, pp. 243-259

NMDA receptor antagonists and pain: ketamine. 
Vet Clin North Am Equine Pract 26, 565-578

Effects of ketamine infusion on halothane minimal alveolar concentration in horses. 
Am J Vet Res 53, 1802-1806
References


References


Effects of dobutamine on cardiovascular function and respiratory gas exchange after
enoximone in isoflurane-anaesthetized ponies.
Vet Anaesth Analg 35, 306-318

SCHAUVLIEGE, S., A. VAN DEN EEDE, L. DUCHATEAU, F. PILLE, L. VLAMINCK
and F. GASTHUYS (2009):
Comparison between lithium dilution and pulse contour analysis techniques for
cardiac output measurement in isoflurane anaesthetized ponies: influence of different
inotropic drugs.
Vet Anaesth Analg 36, 197-208

Effects of ketamine on left ventricular performance.
J Pharmacol Exp Ther 194, 410-414

SCHWARZWALD, C. C., J. D. BONAGURA and V. LUIS-FUENTES (2005):
Effects of diltiazem on hemodynamic variables and ventricular function in healthy
horses.
J Vet Intern Med 19, 703-711

Pharmacokinetics and adverse effects of butorphanol administered by single
intravenous injection or continuous intravenous infusion in horses.

SHIH, A. C., S. GIGUERE, L. C. SANCHEZ, A. VALVERDE, H. J. JANKUNAS and S.
A. ROBERTSON (2009):
Determination of cardiac output in anesthetized neonatal foals by use of two pulse
wave analysis methods.
Am J Vet Res 70, 334-339

SHORT, C. E., N. MATTHEWS, R. HARVEY and C. L. TYNER (1986):
Cardiovascular and pulmonary function studies of a new sedative/analgetic
(detomidine/Domosedan) for use alone in horses or as a preanesthetic.
Acta Vet Scand Suppl 82, 139-155

Effect of intravenous administration of ketamine on the minimum alveolar
concentration of isoflurane in anesthetized dogs.
Am J Vet Res 67, 21-25

Anaesthesia in horses using halothane and intravenous ketamine–guaiphenesin: a
clinical study.
Vet Anaesth Analg 29, 20-28
References


Effects of intravenous lidocaine, ketamine, and the combination on the minimum alveolar concentration of sevoflurane in dogs.
Vet Anaesth Analg 35, 289-296

Gender differences in vascular compliance in young, healthy subjects assessed by pulse contour analysis.
J Clin Hypertens (Greenwich) 3, 145-152

WOODBRIDGE, P. D. (1957):
Changing concepts concerning depth of anesthesia.
Anesthesiology 18, 536-550

The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states.
Pain 44, 293-299

Pharmacologic effects of ketamine and its use in veterinary medicine.
J Am Vet Med Assoc 180, 1462-1471

YOUNG, L. E., K. J. BLISSITT, R. E. CLUTTON and V. MOLONY (1998):
Temporal effects of an infusion of dobutamine hydrochloride in horses anesthetized with halothane.
Am J Vet Res 59, 1027-1032

YOUNG, S. S. and P. M. TAYLOR (1993):
Factors influencing the outcome of equine anaesthesia: a review of 1,314 cases.
Equine Vet J 25, 147-151

Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. II. Hemodynamic responses.
Anesthesiology 80, 261-267

ZUNTZ, N. and O. HAGEMANN (1898):
Untersuchungen über den Stoffwechsel des Pferdes bei Ruhe und Arbeit.
Landwirtsch Jahrb 27 Suppl. 3, 371-412
Table 9.1 Significant differences between groups

<table>
<thead>
<tr>
<th>Letter</th>
<th>Significantly (p&lt; 0.05) different from</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>both other groups</td>
</tr>
<tr>
<td>b</td>
<td>group I</td>
</tr>
<tr>
<td>c</td>
<td>group IK</td>
</tr>
<tr>
<td>d</td>
<td>group IX</td>
</tr>
</tbody>
</table>

Figure 9.1 Median heart rate (HR) averaged over the anaesthetic period in isoflurane anaesthetised horses (I) or in horses anaesthetised with both isoflurane and a constant rate infusion (CRI) of either ketamine (IK) or xylazine (IX). Whiskers represent 95 % of data. *Significantly different from other groups. Significance was set at p < 0.05.
Figure 9.2 Median mean arterial pressure (MAP) averaged over the anaesthetic period in isoflurane anaesthetised horses (I) or in horses anaesthetised with both isoflurane and a constant rate infusion (CRI) of either ketamine (IK) or xylazine (IX). Whiskers represent 95% of data. * Significantly different from other groups. Significance was set at p < 0.05.

Figure 9.3 Median end-expiratory concentration of isoflurane (ETISO) averaged over the anaesthetic period in isoflurane anaesthetised horses (I) or in horses anaesthetised with both isoflurane and a constant rate infusion (CRI) of either ketamine (IK) or xylazine (IX). Whiskers represent 95% of data. * Significantly different from other groups. Significance was set at p < 0.05.
Figure 9.4 Median stroke volume (SV) at different time points in isoflurane anaesthetised horses (I) or in horses anaesthetised with both isoflurane and a constant rate infusion (CRI) of either ketamine (IK) or xylazine (IX). Whiskers represent 95% of data. * Significantly different from $T_{60}$. ** Significantly different from $T_{30}$. a Significantly different from other groups. Significance was set at $p < 0.05$. 

Appendix
Figure 9.5 Median systemic vascular resistance (SVR) at different time points in isoflurane anaesthetised horses (I) or in horses anaesthetised with both isoflurane and a constant rate infusion (CRI) of either ketamine (IK) or xylazine (IX). Whiskers represent 95% of data. * Significantly different from T<sub>60</sub>. ** Significantly different from T<sub>30</sub>. a Significantly different from other groups. Significance was set at p < 0.05.
Figure 9.6 Median averaged dose of dobutamine in isoflurane anaesthetised horses (I) or in horses anaesthetised with both isoflurane and a constant rate infusion (CRI) of either ketamine (IK) or xylazine (IX). Whiskers represent 95 % of data. 

\( ^{a} \) Significantly different from other groups. Significance was set at \( p < 0.05 \).

Figure 9.7 Median recovery score after isoflurane anaesthesia in horses (I) or after anaesthesia maintained with both isoflurane and a constant rate infusion (CRI) of either ketamine (IK) or xylazine (IX). Whiskers represent 95 % of data. 

\( ^{c} \) Significantly different from IK. 

\( ^{d} \) Significantly different from IX. Significance was set at \( p < 0.05 \).
Danksagung

Mein herzlicher Dank geht an Prof. Dr. Sabine Kästner sowohl für das Überlassen der klinikbezogenen und lehrreichen Arbeit, als auch für die stets ausgezeichnete Unterstützung.

Des weiteren möchte ich mich herzlich bei Dr. Klaus Hopster und Dr. Christina Müller bedanken, die mir durch ihre fleißige Vorarbeit, ihre Erfahrungen mit den angewendeten Geräten und ihre tolle Einarbeitung in das Thema, die Technik und nicht zuletzt der Anästhesie eine sehr große Hilfe waren.

Ganz besonders möchte ich mich bei dem gesamten Chirugenteam der Klinik für Pferde bedanken, die meinen klinischen Versuchen mit sehr viel Geduld, Hilfe und Nachsicht begegnet sind. Danke an Paul für die moralische Unterstützung vor dem Ablegen!

Ein großes Dankeschön geht an meinen Bruder Jan, der in stundenlanger Feinarbeit und Geduld sein Wochenende den Korrekturen der Arbeit gewidmet hat.

Vielen Dank an meine Doktoranden- und Internkollegen, die mir stets eine moralische Stütze gewesen sind und mir eine unvergessliche und unterhaltsame Zeit besichert haben.

Thomas, tausend Dank für deine Aufmunterung, die Stunden der Auszeit und vor allem aber auch für die technische Unterstützung in jeder Stimmungslage und den berüchtigten „Word-Krisen-Zeiten“.

Mein größter Dank jedoch gilt meiner Familie, deren dauerhafte und aufopfernde Unterstützung und Tatkraft mir immer geholfen haben. Meinen Titel hab ich euch zu verdanken!! Vielen, vielen Dank!