Cardiopulmonary effects of anaesthesia maintained by propofol infusion versus isoflurane inhalation in cheetahs (*Acinonyx jubatus*)

By

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Submitted in partial fulfilment of the requirements for the degree of Masters of Veterinary Medicine (Anaesthesiology) in the Department of Companion Animal Clinical Studies in the Faculty of Veterinary Science, University of Pretoria

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Declaration of originality

Full name of student: Roxanne Kate Buck
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1. I understand what plagiarism is and am aware of the University's policy in this regard.

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List of abbreviations

%	percentage
>	greater than
<	less than
=	equal to
±	plus minus
^{o}C	degrees Celsius
µg	microgram(s)
CRI	constant rate infusion
ECG	electrocardiogram
Et-Iso	end-tidal isoflurane concentration
ET-tube	endotracheal tube
F_EO_2	fractional expired oxygen concentration
FiO_2	fractional inspired oxygen concentration
GABA	gamma-aminobutyric acid
G	gauge (needle and catheter bore measurement)
Group-I	cheetahs in isoflurane maintenance group
Group-P	cheetahs in propofol maintenance group
HCO_3^-	bicarbonate ion
IM	intramuscular
IV	intravenous
kg	kilogram(s)
kPa	kilo Pascal(s)
L	litre(s)
MAP	mean arterial blood pressure
mg	milligram(s)
mL	millilitre(s)
mmHg	millimetre(s) Mercury
mmol	millimole(s)
n	number of animals
NMDA	N-methyl-D-aspartate
p	estimation of statistical significance
$PaCO_2$	arterial carbon dioxide tension
PaO_2	arterial oxygen tension
$P_E'CO_2$	end-tidal carbon dioxide tension
pH	negative log of hydrogen ion concentration
SD	standard deviation
SpO_2	peripheral oxygen haemoglobin saturation
TCI	target controlled infusion
TIVA	total intravenous anaesthesia

Summary

Cardiopulmonary effects of anaesthesia maintained by propofol infusion versus isoflurane inhalation in cheetah (*Acinonyx jubatus*)

By

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Department: Companion Animal Clinical Studies

Degree: Master of Veterinary Medicine (Anaesthesiology)

Objective To compare the cardiopulmonary function of cheetahs (*Acinonyx jubatus*) undergoing propofol total intravenous anaesthesia (TIVA) to isoflurane maintenance in order to evaluate their feasibility for field use.

Study design Prospective clinical study

Animals 24 adult cheetahs

Materials and Methods Cheetahs were immobilised with tiletamine-zolazepam (1.2 mg kg^{-1}) and medetomidine (40 µg kg^{-1}) intramuscular by darting. A maintenance protocol of propofol

TIVA (Group-P) or isoflurane inhalation (Group-I) was randomly assigned to each cheetah. Anaesthesia was maintained for at least 60 minutes. Cheetah breathed spontaneously throughout anaesthesia. Oxygen was supplemented at 3 L minute^{-1}. Cardiopulmonary parameters were recorded at five minute intervals and three arterial blood gas samples analysed. Following maintenance, atipamezole was administered intramuscular (200 µg kg^{-1}) and recovery observed. Data is reported as mean ±SD; variables over time were compared using a linear mixed model (fixed: time, treatment; random: cheetah).

Results Lack of response to manipulations was maintained in all cases (end-tidal isoflurane 1.1 ± 0.1%, propofol infusion rate maintained at 0.1 mg kg^{-1} minute^{-1}). The heart rate and respiratory rate were 82 ± 10 beats minute^{-1} and 14 ± 4 breaths minute^{-1}, respectively for both groups overall. The end-tidal carbon dioxide tension increased slowly (to 44.0 ± 5.0 mmHg at the end of maintenance) with no differences between groups. All cheetahs were initially markedly hypertensive (mean arterial pressure (MAP) 163.3 ± 17 mmHg); MAP normalised for Group-I (125 ± 30 mmHg) but remained high for Group-P (161.0 ± 17 mmHg) ($p < 0.001$). The arterial carbon dioxide tension (48.9 ± 14.6 mmHg) never differed between groups. Recovery time was 10.8 ± 5.0 and 51.9 ± 23.5 minutes for Group-I and Group-P, respectively.

Conclusions and clinical relevance Both protocols provided acceptable cardiopulmonary values. Propofol may be an alternative to isoflurane for field use, but the prolonged recovery requires investigation.

Keywords *Acinonyx jubatus*, cheetah, isoflurane, propofol, TIVA

Literature review

Current practises in anaesthesia of cheetah and other wild felids

Working with wild mammals requires chemical or physical restraint to facilitate any handling to ensure safety to personnel and the animal. For large wild felids (cheetahs [*Acinonyx jubatus*], leopards [*Panthera pardus*], lions [*Panthera leo*], tigers [*Panthera tigris*] and panthers [*Panthera onca*]), chemical restraint is usually preferred. The approach to anaesthesia of domestic species usually comprises premedication to provide tranquilisation or light sedation to facilitate intravascular catheter placement, followed by intravenous induction and then maintenance with either inhalation or intravenous agents (Clarke et al. 2014). However, large wild felids cannot simply or safely be injected with pre-medicants and will not commonly tolerate catheter placement with only light sedation. Thus, to reduce patient stress and improve personnel safety, the general approach to wild felid anaesthesia is initial immobilisation (chemical capture with sedative and anaesthetic drug combinations to produce profound sedation, or even anaesthesia) so the animal is safe to approach and handle, followed by the administration of maintenance agents where needed (Chinnadurai et al. 2016). For short, non-invasive procedures, such as clinical examinations, or loading for transport, immobilisation may be sufficient. However, more invasive or longer procedures may require general anaesthesia rather than sedation due to increased stimuli and/or waning effects of the drug(s) used for immobilisation (through metabolism and elimination that decreases plasma and biophase concentration). In addition, a reliable method to extend the duration of anaesthesia, while maintaining cardiopulmonary stability is desirable. Thus, maintenance agents (volatile inhalation or intravenous anaesthetic agents) which do not cause dramatic alterations in cardiovascular (hypotension, bradycardia, negative inotropy, for example) and respiratory (hypoventilation or apnoea, for example) physiology should be pursued.

An ideal anaesthetic agent should allow flexible adjustment of anaesthetic depth while maintaining stable cardiopulmonary function (Clarke et al. 2014). Recovery from anaesthesia should be rapid and complete, particularly for wild animals where residual sedation or renarcotisation can result in injury following release, and where return to normal behaviour as soon as possible is essential (Chinnadurai et al. 2016). When working with wild animals, the ability to practically anaesthetise animals in a field setting is beneficial to the animal and care givers, as this decreases possible transport related stress and injury, and minimises the logistics behind veterinary care and interventions (movement permits, hospital biosecurity and patient/client confidentiality).

Immobilisation drugs are generally short acting injectable agents that can be administered intramuscularly and may or may not be reversible. As in domestic animals, anaesthesia may be maintained using either inhalation agents or through intravenous agents only (total intravenous anaesthesia or TIVA). Although there is extensive research on immobilisation agents in large felids (Bush et al. 1978, Deem et al. 1998, Lewandowski et al. 2002, Stegmann & Jago 2006), very little work has been done on maintenance agents in these species.

Inhalation anaesthesia

The inhalation anaesthetic agents are a group of gases and volatile liquids which bring about general anaesthesia when inhaled. Isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether) is a halogenated ether volatile anaesthetic agent that has been widely used in human and animal anaesthesia. It is supplied as a volatile liquid that requires vaporisation and delivery in a gas to the patient (Clarke et al. 2014).

Although many theories have been postulated, it is still unclear as to the exact mechanism of action of isoflurane, and the other volatile anaesthetics. It is thought that anaesthesia is induced

through enhancing inhibitory activity at $GABA_A$ receptors in the brain and glycine receptors in the spinal cord. $GABA_A$ receptors are pentameric membrane proteins found throughout the central nervous system that function as GABA-gated chloride channels. When activated, the neuron becomes hyperpolarised and subsequently there is decreased action potential transmission (Rudolph et al. 2001). Glycine receptors are also chloride channels and play important roles in motor reflex circuits in the spinal cord (Lynch 2004). Inhibition of excitatory effects at cholinergic and glutamate receptors has also been proposed as an additional mechanism of action (Clarke et al. 2014).

Isoflurane is administered and expelled via the respiratory system, allowing for rapid and precise adjustment of anaesthetic depth (Chinnadurai et al. 2016). Due to its high volatility and low blood solubility, induction and recovery from isoflurane anaesthesia are rapid (Clarke et al. 2014). Isoflurane undergoes only minimal (0.2%) hepatic metabolism (Keegan & Greene 1993).

Although, isoflurane generally maintains cardiovascular function, all the inhalation agents are known to cause some dose-dependent respiratory and cardiovascular depression. Thus use of these agents at concentrations higher than the minimum alveolar concentration is less desirable. The minimum alveolar concentration is defined as the alveolar concentration of inhalant anaesthetic agent required to prevent a response to a standardised noxious stimulus in 50% of patients, at a standardised atmospheric air pressure (Quasha et al. 1980). In addition, inhalation agents traditionally require bulky, equipment such as anaesthetic machines, which are impractical in field settings (Dzikiti 2013). Purpose-built field-ready anaesthetic machines are currently cost prohibitive for veterinarians only occasionally administering inhalation anaesthesia in the field. Further, the use of inhalant agents requires the transport of volatile liquids and oxygen cylinders, which may be prohibited by air and public land transportation

(trains, trams, busses etc.) (Chinnadurai et al. 2016). Inhalation anaesthesia is also associated with increased atmospheric pollution and unscavenged or incorrectly used machines pose occupational health hazards to personnel (Dzikiti 2013).

Reports on the use of inhalant anaesthetic agents in cheetahs have appeared irregularly in the literature. Walzer et al. (1996) reported isoflurane use to maintain anaesthesia in immobilised cheetahs to allow for ultrasonographic examination, with no reported adverse effects. Kimeli et al. (2014) reported stable cardiopulmonary function during fracture repair in a cheetah using isoflurane (end-tidal concentration 0.5-2%). Mwangi et al. (2016) reported stable cardiopulmonary function at isoflurane end-tidal concentrations between 0.5-1% during a femoral fracture repair; further, the cheetah recovered quickly and completely following a long anaesthetic procedure (over 2 hours and 40 minutes). However, there have been reports of emergence delirium and excitement during recovery from isoflurane maintenance in cheetah (Deem et al. 1998).

Total intravenous anaesthesia

Total intravenous anaesthesia (TIVA) is the use of only intravenous anaesthetic agents to achieve an adequate depth of anaesthesia (Clarke et al. 2014). Less equipment is needed for TIVA than for the delivery of inhalation anaesthetic agents (Dzikiti 2013). In fact, its simplest form, TIVA requires only the anaesthetic drugs of choice and an intravenous fluid administration set, although endotracheal intubation and oxygen supplementation are still recommended, and the use of electronic drip pumps or syringe drivers can improve accuracy of drug delivery (Dzikiti 2013).

TIVA can be performed by either intermittent bolus injection, by continuous rate infusion of a drug or by target controlled infusion (TCI). Intermittent bolus delivery is simple to perform –

incremental calculated doses are administered in reaction to patient's response to stimuli – but can result in high peak plasma concentrations and excessive depth of anaesthesia following bolus administration (Beier et al. 2015). A CRI targets a specific infusion rate of drug, while a TCI is designed to target a specific plasma (or biophase) concentration of the drug. Both infusions produce a more stable plane of anaesthesia than intermittent bolus administration. However, to perform TCI, specific pharmacokinetic data is required for the species and the drug being used (Joubert 2009).

Injectable drugs used to maintain anaesthesia should be short-acting, non-accumulating, easy to titrate, quickly redistributed from the central compartment or metabolised and have a high therapeutic index (Clarke et al. 2014). A number of different agents have been used alone, or in various combinations, to maintain anaesthesia.

Propofol (2,6-di-isopropylphenol) is an ultra-short acting hypnotic agent which acts by enhancing the effects of GABA by binding to the beta-subunit of cerebral $GABA_A$ receptors (Clarke et al. 2014). A direct depressant effect on the neurons of the spinal cord through actions on $GABA_A$ and glycine receptors has also been postulated (Clarke et al. 2014).

Propofol has been widely used for induction and maintenance of anaesthesia in a variety of species. Propofol is metabolised rapidly by both hepatic and extrahepatic pathways (primarily the kidneys and lungs) (Clarke et al. 2014). Propofol infusions are associated with a physiologically stable anaesthetic and calm, rapid recovery.

However, propofol can also cause decreased arterial blood pressure, through arterial and venous vasodilation, as well as decreased myocardial contractility and dose-dependent

respiratory depression which may result in hypoxia and hypercapnia (Clarke et al. 2014). Studies in domestic dogs, however, have shown better mean arterial blood pressure (MAP) with propofol infusion compared to isoflurane (Keegan & Greene 1993).

There are few reports on the use of propofol in cheetahs, generally for induction rather than maintenance. The use of propofol in other wild felids for induction or short-term maintenance of anaesthesia in individual cases has been documented (Bharathidasan et al. 2014). Also, Carstens et al. (2006) used propofol and halothane in an unspecified number of cheetahs to induce anaesthesia during an imaging study with no reported ill effects. Epstein et al. (2002) reported using propofol top-up boluses to maintain anaesthesia in tiletamine-zolazepam-medetomidine-immobilised lions. A dose of 1 mg kg^{-1} administered at 5 minute intervals was effective at maintaining anaesthesia without causing any adverse effects (giving an equivalent infusion rate of 0.2 mg kg^{-1} $minute^{-1}$). However, it has been suggested the infusions of propofol (0.05-0.2 mg kg^{-1} $minute^{-1}$) may lead to prolonged recovery when used for longer than 20 minutes of maintenance in cheetahs (Woc Colburn et al. 2009).

Outcome of literature review

To be effective and practical, an anaesthetic agent should allow for flexible control of anaesthetic depth to achieve a desired level of anaesthesia and to maintain stable cardiopulmonary function at effective doses. In addition, the agent should allow for easy extension of anaesthetic duration and provide a calm, complete and quick recovery to allow for immediate release of wild animals. The anaesthetic should also be practical to administer in a field setting. The current literature focus is on immobilisation of wild felids for transport and short management and husbandry procedures of these species. As a result, there is currently very little literature detailing strategies for anaesthetic maintenance in wild felids and none comparing the effects either propofol to isoflurane in cheetahs.

Introduction

Cheetahs (*Acinonyx jubatus*) are classified as vulnerable by the International Union for Conservation of Nature (International Union for Conservation of Nature 2016). The large decline in wild populations as a result of human population expansion, human-wildlife conflict and decreased availability of natural prey has led to increased emphasis being placed on captive cheetahs for potential maintenance of the species (Marker 2002).

With their increased numbers and value in zoo and conservation collections, the ability to safely anaesthetise cheetahs for veterinary procedures is increasingly important. Also, with the growing spectrum of invasive procedures being performed, both in the field and in-hospital setting, further investigation of maintenance protocols is warranted.

This study compared isoflurane inhalation maintenance, the cornerstone of anaesthetic maintenance, to maintenance by propofol infusion, a general anaesthetic agent commonly used for maintenance in a variety of species, to investigate the feasibility of using propofol TIVA for field anaesthesia.

To mimic field conditions, the cheetahs were first immobilised before undergoing anaesthetic maintenance. When assessing an anaesthetic protocol for field use, field practices should be noted. Thus, when wild cheetahs are usually chemically captured prior to anaesthesia, there is little value to investigating a maintenance protocol in isolation, as the capture drugs would have an effect (anaesthetic sparing effect, cardiovascular and respiratory effect). A commonly used immobilisation combination in cheetahs is tiletamine-zolazepam and medetomidine.

Tiletamine is a N-methyl-D-aspartate receptor antagonist and is usually provided in combination with the benzodiazepine zolazepam as Zoletil ® or Telazol®. Tiletamine provides immobilisation and analgesia while the zolazepam is included for its muscle relaxant and sedative properties (Lin et al. 1993). Large doses of tiletamine-zolazepam may be associated with adverse cardiorespiratory effects and prolonged recoveries that are associated with emergence delirium (Lin et al. 1993). Medetomidine is a selective alpha$_2$-adrenergic agonist that produces sedation, analgesia and muscle relaxation (Virtanen 1989). Medetomidine may cause bradycardia, hypertension and respiratory depression (Virtanen 1989). The use of the drugs in combination allows for significant dose sparing of tiletamine-zolazepam and results in deeper sedation of longer duration (Deem et al 1998).

The tiletamine-zolazepam-medetomidine combination has been widely studied in cheetahs (Deem et al. 1998; Stegmann and Jago 2006). It is associated with rapid onset of action and a duration of action of around 87 minutes (Deem et al. 1998). Atipamezole, an alpha$_2$-adrenergic antagonist, may be used as a partial reversal agent and recovery is generally calm and rapid (Deem et al. 1998).

Aims and objectives

The primary aim of this study was to compare isoflurane inhalation and propofol infusion for maintenance of anaesthesia in cheetah of at least 60 minutes duration. The comparison focussed on:

1. Ability to maintain stable and optimal cardiopulmonary function during light anaesthesia, as indicated by arterial blood pressure and end-tidal carbon dioxide ($P_E'CO_2$), respectively.
2. Ability to maintain adequate depth of anaesthesia for minimally invasive procedures, as assessed by palpebral reflexes and a lack of conscious movement despite procedural manipulations.
3. Ability to provide a recovery that is calm, rapid and allows immediate release and reintegration following termination of anaesthesia.

Hypotheses

Cardiopulmonary effects

H_0: The mean arterial blood pressure (MAP) and $P_E'CO_2$ in cheetahs anaesthetised by propofol infusion will be no different to that of cheetahs anaesthetised by isoflurane.

H_1: The MAP and $P_E'CO_2$ in cheetahs anaesthetised by propofol infusion will be different to that of cheetahs anaesthetised by isoflurane.

Anaesthetic maintenance

H_0: The number of purposeful conscious movements in response to procedural manipulation will be no different for cheetahs anaesthetised by a propofol infusion compared to cheetahs anaesthetised with isoflurane.

H_1: The number of purposeful conscious movements in response to procedural manipulation will be different for cheetahs anaesthetised by a propofol infusion compared to cheetahs anaesthetised with isoflurane.

Recovery characteristics

H_0: The recovery time (time from end of maintenance to "head-up") in cheetahs anaesthetised by propofol infusion will be no different to that for cheetahs anaesthetised by isoflurane.

H_1: The recovery time in cheetahs anaesthetised by propofol infusion will be different to that for cheetahs anaesthetised by isoflurane.

Benefits arising from the study

The principle benefit of this investigation was to expand our knowledge and understanding of the cardiopulmonary effects as well as the recovery characteristics of both propofol and isoflurane in cheetah. This will help to improve planning of field anaesthesia for both cheetah and other large felids. A safe and reliable TIVA protocol could improve the administration and safety of field anaesthesia for both cheetah and other large wild felids.

Materials and methods

Experimental design

The prospective, randomised, paired clinical trial was approved by the Animal Ethics and Research Committees of the University of Pretoria (V014-14 and V052-16).

Animals

Twenty four adult semi-captive cheetahs (8 female, 16 male) housed at the AfriCat Foundation near Otjiwarongo in Namibia (20°50'57.8" South, 16°38'51.6" East) were included in the study. The AfriCat Foundation is a carnivore care centre dedicated to long-term conservation of large carnivores. The foundation cares for orphaned, injured or displaced cheetahs prior to rehabilitation and release and also houses some animals that are too old or too tame to be released. Cheetahs are housed in groups of two to five in large camps of 48 000 to 200 000 m^2 in a natural environment. Each large "home" camp contains a smaller "management" camp which allows keeping a selected cheetah separate from the others. The cheetahs are fed a well-balanced diet of large pieces of donkey carcass (including skin and bone) and supplemented with carnivore powder. Cheetahs are fed and monitored daily.

Annual health evaluations are performed on all captive cheetahs at AfriCat. This study was performed during the annual health evaluation. The animals were immobilised and then anaesthetised to allow for annual health evaluations, which encompass a clinical examination, haematology and biochemistry, abdominal ultrasonography, gastroscopy and a dental examination (procedural manipulations causing stimulation).

Procedures

Data collection took place over a two week period during winter. The trial was conducted at the AfriCat Veterinary Clinic. Each cheetah was anaesthetised only once to facilitate health evaluation procedures. A maintenance protocol of either isoflurane in oxygen (Group-I) or propofol infusion (Group-P) was assigned to each cheetah using paired sampling, where at each data collection point of two cheetah, one was assigned to each group.

Data collection for the study comprised three phases, namely immobilisation, maintenance and recovery. An onsite data collection sheet was used for each animal (see Addendum I). Data included date of the trial, animal identification, sex and body weight. All clinical variables were recorded on this sheet for the duration of anaesthesia. In addition, dosages of all drugs, infusion rates and important times were recorded on the sheet. Any deviations from the protocol or rescue interventions were also recorded.

Immobilisation

Food was withheld for 24 hours prior to anaesthesia, although free access to water was allowed until darting. To facilitate capture, the preselected cheetah was moved from their large “home” camp into the adjacent smaller management camp prior to darting.

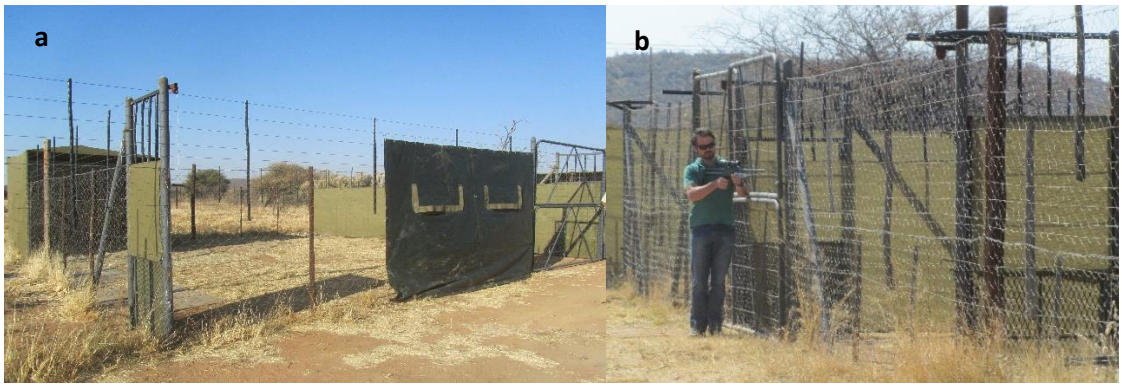


Photo 4a Small management camp visible as a section of the larger "home" camp. Note darting screens have been placed to shield darter from view. **1b** Darting a cheetah in its management camp.

All animals were captured with the same immobilisation protocol - a combination of tiletamine-zolazepam (1.2 mg kg^{-1} Zoletil; Virbac; South Africa) and medetomidine (40 µg kg^{-1}; Kyron

Laboratories; South Africa). Historical records and visual assessment were used to estimate current body weight for darting. The combination was delivered by a 1.5 mL air-pressurised dart delivered by a carbon dioxide powered dart rifle (Model JM Special; DanInject; Denmark) into a suitable muscle mass.

Once recumbent, the cheetah was approached from their rear and the tail was tugged and the ear flick reflex tested; absence of response was used to deem immobilisation sufficient to allow safe handling. The time from darting to safe handling was recorded as the "handling time". The cheetah was then blindfolded to reduce the effects of external stimuli. The cheetah was then transported by pickup truck to the procedure room (up to 10 minutes).

Instrumentation

Once in the procedure room, the cheetah was weighed using an electronic veterinary scale; this weight was used for all further drug dosages. The medial saphenous vein and dorsal pedal artery were aseptically catheterised (18G and 20G Jelco, respectively; Smith's Medical Ltd; South Africa). The venous catheter was used as the primary access for intravenous maintenance drugs and fluids. The arterial catheter served as a sampling port for arterial blood and facilitated direct blood pressure measurement.

The cheetah's trachea was intubated via the orotracheal route, using an illuminated laryngoscope (MacIntosh-blade 4; Welch Allyn; USA), with a cuffed polyvinyl chloride endotracheal (ET) tube (internal diameter 8.0 to 10.0 mm). If depth of anaesthesia was insufficient to allow intubation, ketamine was administered intravenously in 1 mg kg^{-1} boluses until anaesthetic depth was sufficient to allow intubation. The amount of ketamine administered was recorded.

Maintenance

General anaesthesia was maintained using either an intravenous infusion of propofol (Group-P) or isoflurane in oxygen (Group-I) for at least 60 minutes to allow for health evaluations. All cheetahs were connected to an anaesthetic machine via a Bain's (co-axial modified Mapleson D) breathing system and oxygen (3 L $minute^{-1}$) was provided. Cheetahs in both groups were allowed to breathe spontaneously throughout the anaesthetic maintenance period. Balanced isotonic crystalloid fluids (lactated Ringer's solution; Fresenius Kabi; South Africa) were administered via the medial saphenous vein at 5 mL kg^{-1} $hour^{-1}$ for the duration of anaesthetic maintenance.

For Group-I, anaesthesia was maintained using isoflurane (Forane; Abbot Laboratories; South Africa) delivered in oxygen. Isoflurane was delivered to the anaesthetic breathing system using a precision, out-of-circuit vaporiser (Ohmeda Isotec MK 3; BOC Healthcare; UK). An end-tidal isoflurane concentration (Et-Iso) of 1% was initially targeted and thereafter was adjusted according to anaesthetic depth.

For Group-P, propofol 1% (Propoven 50 mL; Fresenius Kabi; South Africa) was administered using a drip administration set and an electronic infusion pump (Infusomat Space; BBraun; Germany). The patient end of the administration set was connected directly to the intravenous catheter in the medial saphenous vein. The crystalloid infusion was administered via the Y-port connector of the propofol administration set. Propofol was initially delivered at 0.1 mg kg^{-1} $minute^{-1}$ and was adjusted according to anaesthetic depth.

Anaesthetic depth was judged on the basis of autonomic nervous reflex reactions to manipulation and scope placement, the degree of muscle relaxation present, the presence or

absence of palpebral and pedal withdrawal reflexes. Anaesthetic depth was assessed at five minute intervals. If the anaesthetic plane was deemed to be too light, the infusion or vaporiser setting was increased by 20%. Conversely, if anaesthetic depth became excessive, the maintenance agent was decreased by 20%. If any conscious movement (lifting of head, purposeful non-reflex movement away from the stimulation) occurred, a propofol bolus of 0.5 mg kg^{-1} for Group-P or a ketamine bolus of 0.5 mg kg^{-1} for Group-I was administered and the infusion or vaporiser setting was titrated upwards by 20%. Changes in vaporiser setting or infusion rate as well as any additional boluses of drugs required were recorded.

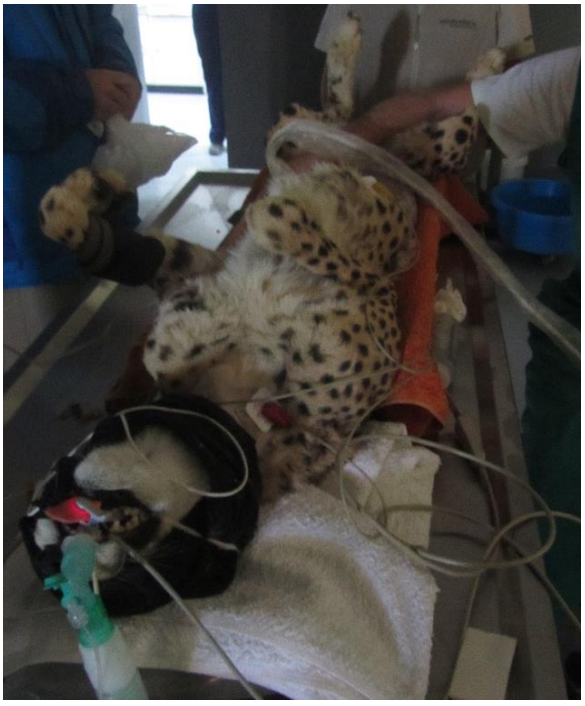


Photo 2 Cheetah undergoing abdominal ultrasonography as part of health evaluation. Note ECG electrode placement and pulse oximeter on tongue.

Monitoring

Cardiopulmonary parameters were monitored continuously throughout anaesthetic maintenance using a multiparameter monitor (Cardiocap 5; Datex-Ohmeda; Finland). All parameters, including the Et-Iso, vaporiser setting and propofol infusion rate were recorded at five minute intervals. Pulse rate and peripheral oxygen haemoglobin saturation (SpO_2) were measured with a transmittance pulse oximeter probe placed on the tongue. An electrocardiogram was monitored with electrodes placed in a base-apex configuration (RA electrode on right jugular groove; LA electrode left thorax at point of maximum intensity; Ground electrode left scapular). A strain gauge transducer (DXT Plus Disposable Transducer; BD Medical; South Africa), zeroed to atmospheric air pressure at the level of the right atrium, was coupled to the multiparameter monitor to measure direct arterial pressure from the dorsal

pedal artery. The transducer calibrated automatically whenever the probe was activated and the calibration was verified daily by using a hand held manometer at static pressures of 50, 75, 100, 150 and 200 mmHg. Tolerance was accepted within a 2 mmHg range.

End-tidal carbon dioxide and fractional inspired oxygen tensions ($P_E'CO_2$ and FiO_2, respectively) were determined using a side-stream gas sampler (sampling rate 200 mL $minute^{-1}$) attached to the machine end of the ET-tube. Respiratory rate was taken from the capnograph and correlated with visual assessment.

Body temperature was measured using an oesophageal probe, with the cheetah being maintained normothermic (37.0 to 38.5 °C) by encapsulating the cheetah in blankets, when required. Animals presenting hyperthermic following darting (body temperature above 40.5 ^oC) were actively cooled to 39.0 °C with cold water and fans, following which efforts were made to maintain normothermia.

Three arterial blood samples were taken for blood gas determination from each cheetah using the indwelling catheter in the dorsal pedal artery. An initial sample (T_0) was taken from the immobilised cheetah prior to starting anaesthetic maintenance (the infusion or inhalation agent) or initiating oxygen support. The second sample (T_{30}) was taken at 30 minutes of maintenance and the third (T_E) immediately prior to stopping the maintenance. Samples were collected anaerobically in pre-heparinised syringes (lithium heparin) and analysed immediately on-site with a portable patient-side self-calibrating blood gas analyser (EPOC BGEM and smart cards; Epocal; Canada). The blood gas analyser provided many values, yet values of particular interest to this study included the measured arterial tension of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), arterial pH and lactate (enzymatic amperometry) and also the calculated bicarbonate

ion concentration (HCO_3^-) and base excess (blood and extracellular fluid). The arterial blood samples were interpreted using alpha-stat algorithms (temperature 37.0 °C), and were therefore not corrected to body temperature.

Recovery

At the end of the health check procedures, or after at least 60 minutes of anaesthetic maintenance, the vaporiser was turned off or the propofol infusion stopped. Maintenance time was recorded as the time from the start of the propofol infusion or isoflurane maintenance until the stopping of maintenance agents. The vascular catheters were removed, the cheetah was disconnected from all anaesthetic and monitoring equipment and was placed into a wooden transport crate in lateral recumbency for recovery.

Photo 3 Positioning of cheetah in a wooden transport crate for recovery.

The medetomidine was antagonised with a single intramuscular injection of atipamezole (200 µg kg^{-1} Antisedan; Zoetis; South Africa). The ET-tube was removed at the return of the ear twitch reflex. Recovery was observed and timed. Recovery time was defined as the time from administration of atipamezole until the cheetah could hold up its own head. Recovery times and drug dosages were recorded. Once able to stand, the cheetah was released from the crate into the camp. All cheetahs were observed for 24 hours following recovery from general anaesthesia for untoward effects.

Due to apparent delayed recoveries observed during the first four Group-P animals in the trial, it was decided to antagonise the zolazepam with flumazenil. As such, any animal not able to hold its head up after 30 minutes was administered flumazenil (0.005 mg kg^{-1} Anexate; Roche Products Ltd; Namibia) IM.

Rescue interventions

For the duration of the trial, cheetah health and safety was a priority. The following potential concerns and rescue interventions were identified to create a protocol for emergency assistance when required.

Potential concerns:

1. Apnoea defined as no breathing attempt for longer than 40 seconds (a shorter and more cautious time compared to the conventional 60 seconds based on clinical experience and welfare grounds).
2. Hypotension defined as a mean arterial blood pressure (MAP) of less than 60 mmHg for 120 seconds.
3. Cardiovascular collapse defined by asystole or pulseless electrical activity.
4. Respiratory compromise ($P_E'CO_2$ > 60 mmHg or SpO_2 < 90%)
5. Capture-induced hyperthermia (temperature > 40 ^oC following darting)

Rescue intervention for each of these concerns:

1. Tracheal intubation followed by intermittent positive pressure ventilation with an adult ambu bag attached to the ET-tube or using the reservoir bag on the anaesthetic machine once in the procedure room (Bain's breathing system: close exhalation valve - squeeze reservoir bag until chest rise - open exhalation valve).

2. Administer a balanced isotonic crystalloid fluid bolus at 30 mL kg^{-1} over 10 minutes until MAP increases and/or lighten the plane of anaesthesia by decreasing the maintenance agent by 20% increments every ten minutes.
3. Stop anaesthesia; administer reversal agents; begin standard cardiopulmonary resuscitation (Fletcher et al. 2012).
4. Start intermittent positive pressure ventilation at 4 to 6 breaths per minute, as described in point 1.
5. Active cooling by wetting and fan application. If temperature does not decrease, administration of atipamezole to antagonise the vasoconstriction induced by the medetomidine and assist in heat dissipation.

Statistics

Data was assessed for normality by calculating descriptive statistics, plotting of histograms and performing the Anderson-Darling test for normality. Data were described using the mean and standard deviation (mean ±SD). Changes over time for variables of interest (MAP, $P_E'CO_2$, heart rate, respiratory rate) were compared using a general linear mixed model (fixed factors: time and group; random factors: cheetah; interactions: time and time x group). Significant findings underwent post-hoc pairwise comparisons with Bonferroni correction. Age, weight, handling time, time to initiation of maintenance (time period between darting and starting the maintenance agent), duration of maintenance and recovery times were compared between groups using a t-test. Data were analysed using commercially available software (MiniTab 17.1; MiniTab Ltd; United Kingdom) and results interpreted at the 5% level of significance.

Results

The study was conducted at an altitude of 1532 meters above sea level. Barometric pressure ranged from 624-638 mmHg (83.2-85.1 kPa).

The age of the cheetahs was 6.8 ±2.9 years for Group-I and 7.1 ±3.1 years for Group-P (p = 0.841). The weight of the cheetahs was 39.1 ±5.0 and 40.0 ±5.1 kg for Group-I and Group-P, respectively (p = 0.663). There were 8 male and 4 female cheetahs in each group. All animals were healthy based on post-immobilisation clinical examination, haematology and serum biochemistry evaluation (values not reported). All twenty four cheetahs successfully completed the trial.

Immobilisation phase

The standardised tiletamine-zolazepam-medetomidine immobilisation combination handling time took 12.2 ±3.9 and 11.5 ±6.1 minutes for Group-I and Group-P, respectively (p = 0.748). Six cheetahs in Group-I and 4 cheetahs in Group-P required a single ketamine bolus prior to tracheal intubation. The time to initiation of maintenance was 45.3 ±10.0 minutes for Group-I and 42.3 ±9.1 minutes for Group-P (p = 0.449).

Table 1 Immobilisation and recovery drug dosages reported as mean ±standard deviation for 24 cheetah (*Acinonyx jubatus*) undergoing immobilisation and then isoflurane inhalation (Group-I; n = 12) or propofol infusion (Group-P; n = 12) maintenance of anaesthesia.

Drug	Unit	Mean (±SD)	
		Group-I	Group-P
		Immobilisation	
Zoletil	mg kg^{-1}	1.2 ±0.15	1.1 ±0.12
Medetomidine	µg kg^{-1}	38.6 ±4.2	36.8 ±3.6
		Recovery	
Atipamezole	mg kg^{-1}	3.71 ±0.33	3.67 ±0.44
Flumazenil	mg kg^{-1}	N/A	0.24 ±0.13*

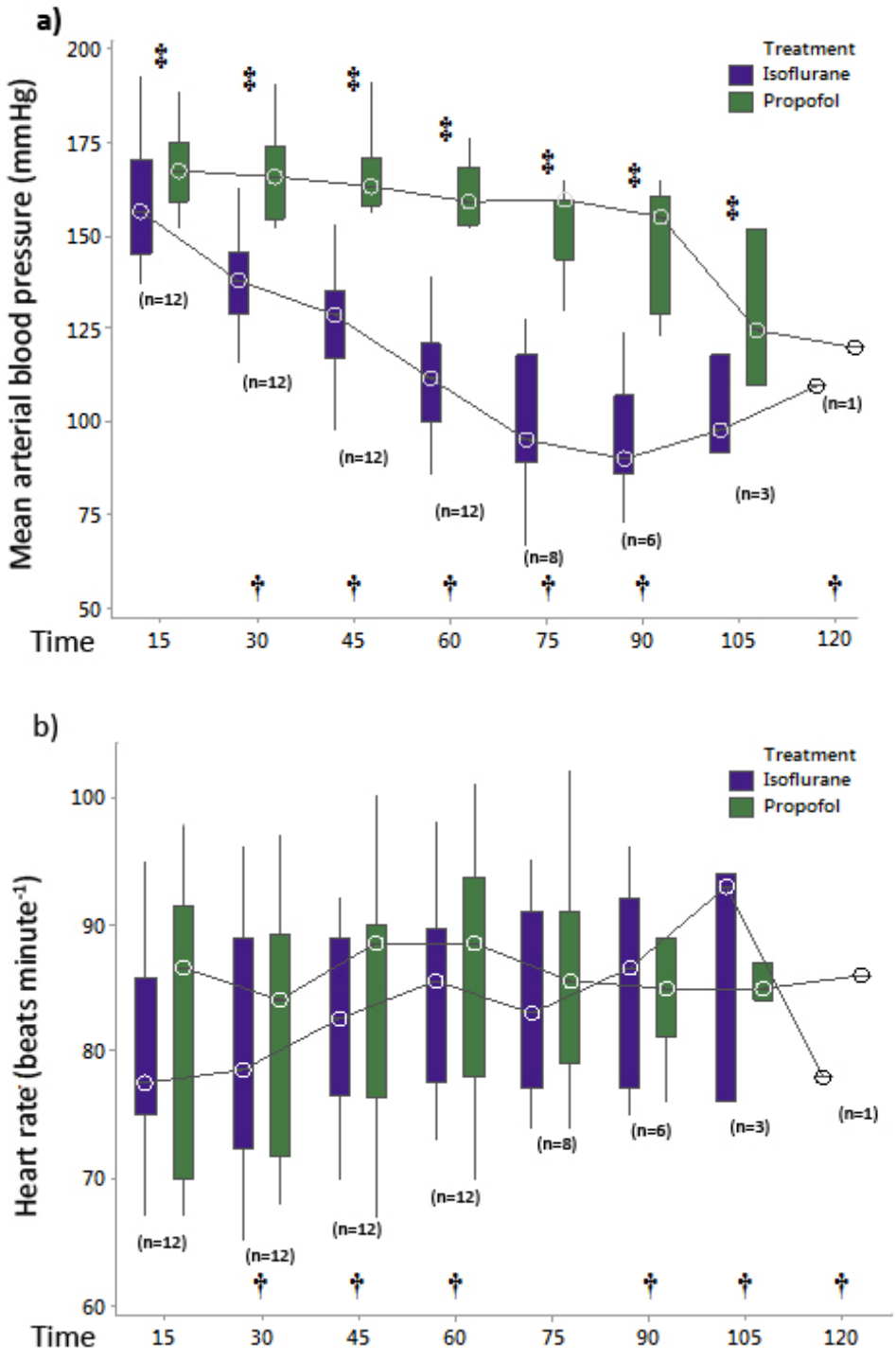
*6 of 12 cheetahs received flumazenil due to not being awake 30 minutes post-administration of atipamezole. Only these cheetah are included in the calculation.

Maintenance phase

The maintenance time was 92 ±17 minutes for Group-I and 86 ±21 minutes for Group-P (p = 0.500). Recumbency, with a lack of responsiveness to external manipulations was maintained for the entire maintenance period in all cases. End-tidal isoflurane concentration was 1.1 ±0.1%. No ketamine boluses were required. Propofol infusion rate was maintained at 0.1 mg kg^{-1} $minute^{-1}$ for all animals in Group-P and no additional propofol boluses were required. No conscious movements occurred in any animal in either group (p = 1.00) at any point during maintenance. The cheetah's muscles were relaxed and no evidence of muscle hypertonia were evident at any point in all cases. No withdrawal reflexes were present at any time in any cheetah. Lateral palpebral reflexes were absent in all cheetahs at all times. Medial palpebral reflexes remained sluggish-to-absent in all cheetah across all time points.

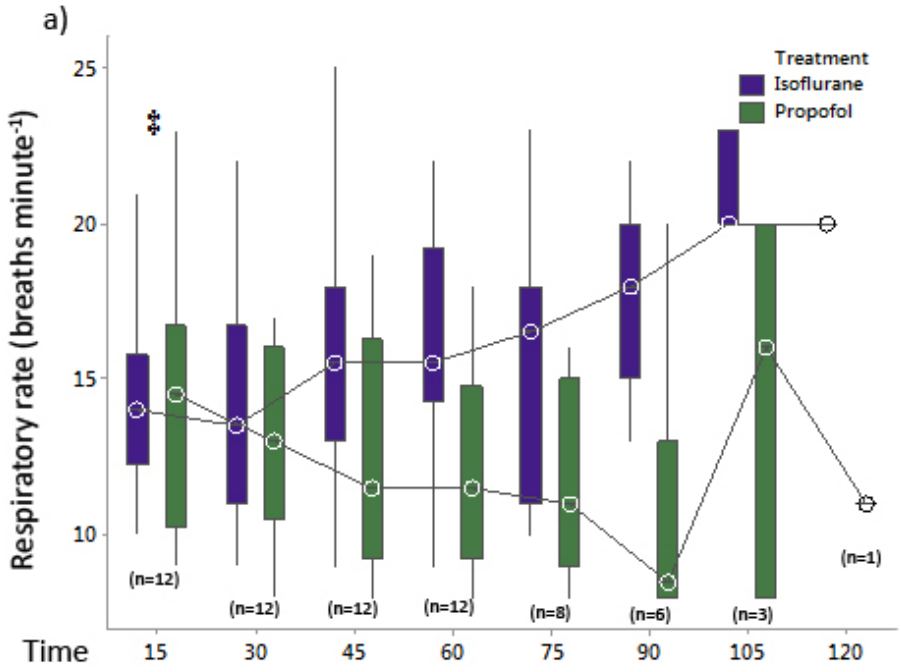
All the cheetahs were initially (15 minutes) hypertensive with systolic, mean and diastolic arterial blood pressures of 202 ±32, 163 ±18, and 143 ±11 mmHg for Group-I; no different to 209 ±27 (p = 0.678), 168 ±16 (p = 0.914) and 145 ±18 (p = 0.858) mmHg for Group-P. However, the initial hypertensive state progressively normalised over time in Group-I, unlike Group-P which tended to remain elevated (Figure 1a). The heart rates of 78 ±8 and 87 ±11 beats $minute^{-1}$ (at 15 minutes maintenance) remained comparatively constant throughout the maintenance overall for Group-I and Group-P, respectively (Figure 1b).

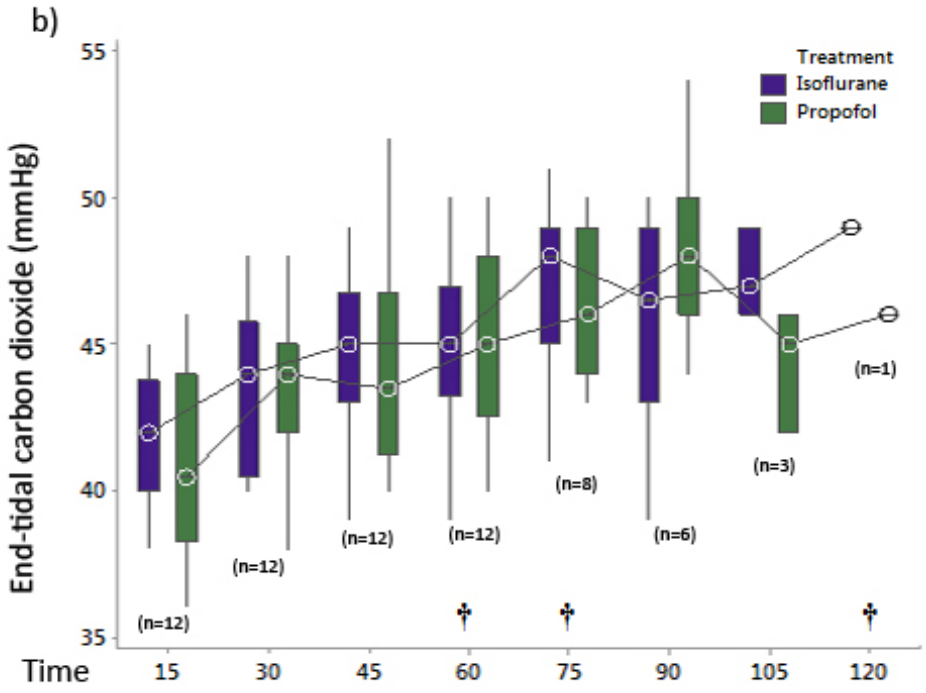
Figure 1 Boxplot and whiskers of **a)** mean arterial blood pressure and **b)** heart rate against maintenance time (minutes) for cheetah (*Acinonyx jubatus*) receiving either isoflurane inhalation (n = 12) or propofol continuous infusion (n = 12). Number (n = x) of cheetah per maintenance treatment group indicated in brackets. All cheetah underwent a minimum maintenance time of 60 minutes. † indicates a significant difference in the variable of interest over time (post hoc pairwise comparisons with Bonferroni correction; interaction: time). ‡ indicates a significant difference in the variable of interest taking both treatment and time into consideration (post-hoc pairwise comparisons with Bonferroni correction; interaction: treatment x time).



The initial respiratory rate (15 minutes) of 15 ±4 and 13 ±4 breaths minute^{-1} tended to increase for Group-I and decrease for Group-P, respectively, over time (Figure 2a). End-tidal carbon dioxide tension ($P_E'CO_2$) was initially (15 minutes) 42 ±2.2 and 41 ±3.2 mmHg for Group-I and Group-P, respectively. $P_E'CO_2$ increased slowly for both groups during anaesthetic maintenance, but remained within acceptable clinical limits (Figure 2b).

Figure 2 Boxplot and whiskers of **a)** respiratory rate and **b)** end-tidal carbon dioxide tension against maintenance time (minutes) for cheetah (*Acinonyx jubatus*) receiving either isoflurane inhalation (n = 12) or propofol continuous infusion (n = 12). Number (n = x) of cheetah per maintenance treatment group indicated in brackets. All cheetah underwent a minimum maintenance time of 60 minutes (n = 12). † indicates a significant difference in the variable of interest over time (post hoc pairwise comparisons with Bonferroni correction; interaction: time). ‡ indicates a significant difference in the variable of interest taking both treatment and time into consideration (post-hoc pairwise comparisons with Bonferroni correction; interaction: treatment x time).





Arterial blood gas parameters were no different between groups over time, yet within groups the parameters were statistically and clinically significant in their changes over time (Table 2). The calculated arterial oxygen saturation (SaO_2) showed weak positive correlation (correlation coefficient = 0.336) with the measured SpO_2 ($p = 0.006$). Arterial pH indicated an initial acidaemia which worsened progressively over time for both groups (Table 2).

Table 2 Physiological and calculated parameters of 24 cheetahs (*Acinonyx jubatus*) undergoing anaesthetic maintenance of either isoflurane inhalation (n = 12) or propofol infusion (n = 12). Parameters are reported as mean ±standard deviation prior to initiation of maintenance (T_0), after 30 minutes of maintenance (T_{30}) and immediately prior to the end of maintenance (T_E).

			Time			Significance	
Parameter	Unit	Group	T_0	T_{30}	T_E	Time	Group x Time
FiO_2	%	I	0.21 ±0.0	0.96 ±0.09	0.95 ±0.19	p < 0.001	p = 0.066
		P	0.21 ±0.0	0.97 ±0.09	0.97 ±0.09		
SpO_2	%	I	97.8 ±2.6	98.4 ±2.1	98.3 ±2.9	p = 0.112	p = 0.664
		P	98.3 ±2.9	99.4 ±0.8	99.8 ±0.4		
SaO_2	%	I	89.5 ±9.3	99.9 ±0.06	99.7 ±0.03	p < 0.001	p = 0.407
		P	92.0 ±1.6	99.9 ±0.10	99.8 ±0.09		
PaO_2	mmHg	I	66.4 ±6.7	367.8 ±51.4	321.9 ±96.9	p < 0.001	p = 0.987
		P	64.9 ±4.1	349.3 ±63.8	309.4 ±49.6		
	kPa	I	8.9 ±0.9	49.0 ±6.9	42.9 ±12.9		
		P	8.7 ±0.5	46.6 ±8.5	41.2 ±6.6		
P:F ratio	mmHg	I	316.2 ±31.9	381.2 ±51.4	335.9 ±98.7	p = 0.016	p = 0.836
		P	308.9 ±19.6	363.1 ±81.6	320.9 ±60.2		
$P_E'CO_2$	mmHg	I	38.5 ±3.0	43.4 ±2.7	47.6 ±3.6	p < 0.001	p = 0.169
		P	35.8 ±4.5	43.8 ±3.1	47.3 ±4.3		
	kPa	I	5.1 ±0.4	5.8 ±0.4	6.3 ±0.5		
		P	4.8 ±0.6	5.8 ±0.4	6.3 ±0.6		
$PaCO_2$	mmHg	I	30.7 ±6.1	50.9 ±7.8	65.6 ±4.7	p < 0.001	p = 0.080
		P	30.7 ±5.2	55.3 ±5.4	62.7 ±5.4		
	kPa	I	4.1 ±0.8	6.8 ±1.0	8.7 ±0.6		
		P	4.1 ±0.7	7.4 ±0.7	8.4 ±0.7		
$PaCO_2$ - $P_E'CO_2$	mmHg	I	-9.7 ±4.6	7.2 ±6.6	17.4 ±6.7	p < 0.001	p = 0.200
		P	-5.1 ±4.7	11.9 ±5.7	15.6 ±5.5		
pH		I	7.37 ±0.05	7.24 ±0.04	7.16 ±0.02	p < 0.001	p = 0.305
		P	7.35 ±0.08	7.21 ±0.03	7.17 ±0.04		
HCO_3^-	mmol L^{-1}	I	17.5 ±2.5	21.9 ±2.3	22.5 ±4.4	p < 0.001	p = 0.992
		P	17.7 ±2.3	22.1 ±1.1	22.5 ±3.0		
BE	mmol L^{-1}	I	-7.85 ±2.28	-5.48 ±2.24	-6.15 ±4.43	p = 0.041	p = 0.915
		P	-7.53 ±2.13	-5.83 ±1.15	-6.00 ±3.32		
Temp	°C	I	38.6 ±0.7	38.0 ±0.98	37.2 ±0.66	p < 0.001	p = 0.733
		P	38.4 ±0.96	38.1 ±1.0	37.1 ±1.3		

FiO_2 fractional inspired oxygen tension; SpO_2 peripheral arterial haemoglobin saturation; SaO_2 calculated oxygen saturation; PaO_2 arterial oxygen tension; P:F PaO_2:FiO_2 ratio (normal 450-530 mmHg, Dugdale 2010); $P_E'CO_2$ end tidal carbon dioxide tension; $PaCO_2$ arterial carbon dioxide tension; $PaCO_2$ - $P_E'CO_2$ gradient expected 3-8 mmHg; HCO_3^- arterial bicarbonate ion concentration; BE base excess; Temp oesophageal temperature.

Recovery phase

Dosages of recovery drugs are shown in Table 1. The recovery time was 10.8 ±5.0 and 51.9 ±23.5 minutes for Group-I and Group-P, respectively ($p < 0.001$). Recovery of cheetahs in Group-I was characterised as rapid but many cheetah demonstrated excitement with frequent emergence delirium. Recovery in Group-P was calm, but prolonged and characterised as "drowsy" whereby cheetah responded to noise by only focusing their pinna towards the origin of the sound and on occasion lifting their head (often with notable "head bobbing"). Furthermore, the cheetah calmly moved into sternal recovery with better coordination compared to the cheetahs recovering from isoflurane. Six of the cheetah in Group-P required flumazenil. Following flumazenil administration, cheetah recovered fully (20 ±15.8 minutes after flumazenil administration). Cheetah were observed for 24 hours following recovery from anaesthesia, with no ill effects observed.

In summary, no conscious movement to procedural manipulations was seen with either protocol during anaesthetic maintenance, thus there is insufficient evidence to reject the anaesthetic depth null hypothesis. Despite both protocols maintaining adequate blood pressure for clinical purposes and producing similar mild respiratory depression, the large differences in blood pressure observed between the two protocols was sufficient to reject the cardiopulmonary null hypothesis of the study. Recovery from propofol anaesthesia was significantly longer than from isoflurane, thus rejecting the recovery null hypothesis. Using post-hoc power analysis to detect a difference of 1 conscious movement during procedural manipulations between the two treatment groups at a power of 80% ($\beta = 0.8$) we required at least 17 cheetahs per group, which was not possible. However, all aspects of the study considered, determining the cardiopulmonary effects were the main focus of the study.

Discussion

To the authors' knowledge, this is the first study comparing the cardiopulmonary effects of isoflurane and propofol for maintenance of anaesthesia in cheetahs. Both the isoflurane and propofol provided adequate anaesthesia with lack of response to procedural manipulations during the health evaluation procedures. Both agents maintained clinically acceptable cardiopulmonary function, although there were differences in MAP, whereby isoflurane tended to normalise the initial post-immobilisation hypertension unlike propofol. Slowly increasing hypercapnia indicated progressive respiratory depression with both the isoflurane and propofol, although this remained permissive throughout maintenance for both drugs. Recovery was rapid in Group-I but prolonged in Group-P.

Drug doses for the study were chosen based on authors' previous experience with cheetahs. There is a paucity in literature on maintenance of anaesthesia in wild large felids. Woc Colburn et al. (2009) reported similar doses of propofol infusion in three cheetahs and Epstein et al. (2002) also used 0.1 mg kg^{-1} $minute^{-1}$ propofol to maintain anaesthesia in immobilised lions. The isoflurane dose was similar to that used previously for isolated surgical cases in cheetah (0.5-1% for femur fracture repair with epidural lidocaine and medetomidine-ketamine immobilisation) (Mwangi et al. 2016).

The doses of both maintenance drugs were, however, considerably lower than those required for anaesthetic maintenance as sole agents in domestic dogs and cats. The minimum alveolar concentration (MAC) for isoflurane to prevent purposeful movement in response to a standardised noxious stimulus in 50% of patients in dogs is approximately 1.39 ±0.25% (Kazama & Ikeda 1988). A review of isoflurane MAC studies in cats, postulated an end-tidal concentration of 1.71 +/- 0.07% based on an average across thirty studies (Shaughnessy & Hofmeister 2014).

Hall and Chambers (1987) suggested that 0.4 mg kg^{-1} $minute^{-1}$ propofol provided surgical anaesthesia in dogs premedicated with acepromazine and Ilkiw et al. (2003) showed that a propofol dose of 0.21 mg kg^{-1} $minute^{-1}$ prevented a response to a toe pinch (haemostat on phalanx), tetanic stimulus to ulnar nerve and tail clamp (haemostat over base of tail) in 50% of cats. However, it should be noted that the end point of our study was a light plane of anaesthesia; the depth of anaesthetic targeted was that which allowed for minimally invasive procedures such as gastroscopy, abdominal ultrasound and dental examination. Further, to facilitate working with wild animals, and to mimic field conditions, the cheetah were immobilised with the tiletamine-zolazopam-medetomidine combination. These drugs would both profoundly decrease the anaesthetic requirements, especially for the first 60-80 minutes following darting (Nam et al. 2013).

MAC_{-awake} describes the minimum alveolar concentration at which consciousness is regained in 50% of animals. Application of this principle allows for titration of inhalant anaesthetics to ensure unconsciousness, which is assumed to be achieved when the Et-Iso is greater than MAC_{-awake}. Estimates of MAC_{-awake} vary according to the species, study end-point and study design. Hofmeister et al. (2008) suggested MAC_{-awake} for dogs to be 1.0 ±0.1% (end point head lifting or chewing ET-tube) while Lopez et al. (2009) suggested 0.4 ±0.1% (end point of extubation). Thus, with the addition of immobilisation drugs, the choice of isoflurane dose in this study (Et-Iso 1.0%) seemed an appropriate starting point.

Campoy et al. (2012) performed procedural sedation with propofol in dogs. In their study, infusion rates of 0.07-0.15 mg kg^{-1} $minute^{-1}$ propofol did not result in unconsciousness. However, the addition of heavy premedication by way of the immobilisation drugs would have a significant

anaesthetic sparing effect, therefore the choice of the initial propofol infusion dose in this study (0.1 mg kg^{-1} $minute^{-1}$) seemed appropriate.

It is important to note that the doses of the two maintenance agents used are not necessarily equipotent. Previous studies in domestic dogs have suggested that a propofol infusion rate of 18 mg kg^{-1} $hour^{-1}$ (0.3 mg kg^{-1} $minute^{-1}$) is equivalent to an end-tidal isoflurane concentration of 1.4% (Deryck et al. 1996). This is not easily extrapolated to alternate doses or across species. In addition, our study is complicated by the effects of the immobilisation drugs. We can postulate, however, that the drugs provided comparable effect in terms of anaesthetic depth, and can thereby suggest that while not necessarily equipotent, the doses were equi-effective. Thus the cardiopulmonary effects of the two agents can be compared at the proposed doses for field anaesthesia for minimally invasive procedures.

The blood pressure of conscious cheetahs is not known, and this complicates interpretation of blood pressures obtained under general anaesthesia. Hypertension in domestic dogs and cats has been defined as a systolic blood pressure above 150 mmHg (Brown et al. 2007). By this definition all cheetah presented with a marked hypertension initially. This is, however, consistent with previous studies in cheetahs and is thought to be characteristic of the darting combination used (Deem et al. 1998; Stegmann & Jago 2006). Arterial blood pressure is the product of cardiac output and systemic vascular resistance, and thus an increase in either will precipitate an increase in blood pressure (Clarke et al. 2014). Medetomidine, as an $alpha_2$-adrenergic agonist, is a potent vasoconstrictor, as reviewed by Murrell and Hellebreakers (2005). Although this effect is usually transient, tiletamine also maintains blood pressure, and may even contribute to the hypertension through its indirect mechanism of stimulating catecholamine release that increases sympathetic tone (Hellyer et al. 1989).

Interestingly, the blood pressure normalised to commonly accepted mammalian pressures (systolic, mean and diastolic pressures 125-160 mmHg, 90-110 mmHg and 75-95 mmHg, respectively, Clarke et al. 2014) for cheetah in Group-I but remained high for cheetah in Group-P. Both isoflurane and propofol are known to reduce blood pressure in a dose-dependent manner, and again the doses of each drug used become relevant. At an end-tidal concentration of 1.2%, isoflurane has been shown to decrease systemic vascular resistance, myocardial contractility and arterial blood pressure in dogs (Mutoh et al. 1997). In contrast, Goodchild and Serrao (1989) showed that at low doses of less than 20 mg kg^{-1} $hour^{-1}$ (0.33 mg kg^{-1} $minute^{-1}$), propofol did not alter systemic vascular resistance in dogs and although it did increase venous capacitance, arterial blood pressure was not affected. Similarly, in domestic cats, an isoflurane-fentanyl combination, where the isoflurane concentration was very similar to our study (Et-Iso 1.16 ±0.18%), produced consistently lower blood pressures than a propofol-fentanyl infusion, with the propofol twice the dose of our study (propofol 11.9 ±0.6 mg kg^{-1} $hour^{-1}$ or 0.2 mg kg^{-1} $minute^{-1}$) (Liehmann et al. 2006). In light of this evidence, the greater decrease in arterial blood pressure in Group-I is not unexpected at the doses used in this trial. However, when starting with hypertension, the greater vasodilatory effect of isoflurane may be beneficial as sustained systemic hypertension can result in end-organ damage which may include renal, ocular or neurologic lesions (Brown et al. 2007).

The initial PaO_2 values, before oxygen supplementation, indicated borderline hypoxaemia (PaO_2 < 60 mmHg; altitude 1532 meter above sea level). This is consistent with other studies using the same immobilisation combination (Deem et al. 1998, Stegmann & Jago 2006) and PaO_2 improved to acceptable levels following oxygen supplementation. While the PaO_2:FiO_2 remained

acceptable (> 300 mmHg), it was less than desirable, indicating some hypoventilation or shunting throughout the anaesthesia (Dugdale 2010).

Both maintenance agents used in this trial caused mild respiratory depression, as indicated by the gradual increases in $P_E'CO_2$ and $PaCO_2$ and progressively worsening acidaemia. Both agents are known to cause dose-dependent respiratory depression (Clarke et al. 2014), however, all respiratory parameters were clinically acceptable for cheetah supplemented with oxygen and breathing spontaneously throughout maintenance. The arterial to end-tidal carbon dioxide tension ($PaCO_2$-$P_E'CO_2$) gradient was initially negative. This is seen in conditions of high cardiac output in combination with low minute volume (Shankar et al. 1991). This is possibly a result of activity following darting, or an effect of the anaesthetic agents. However, it should be noted that although blood gas samples were drawn within 5 minutes of recording $P_E'CO_2$, there may not be exact time matching.

The gradient became positive for cheetah in both groups and progressively increased during maintenance, suggesting a degree of ventilation-perfusion mismatching was present (Dugdale 2010). Pulmonary hypertension can also cause shunting, leading to a low $P_E'CO_2$ and thus increasing the $PaCO_2$-$P_E'CO_2$ gradient (Sun et al. 2002). It has been suggested that medetomidine can cause pulmonary hypertension, or at least rapid blood flow through the lungs, and this may have played a role (Kästner 2006). Another aspect to consider is the effect of FiO_2 on the $PaCO_2$-$P_E'CO_2$ gradient as increasing FiO_2 does increase the alveolar dead space and thus will increase the $PaCO_2$-$P_E'CO_2$ gradient (Yamauchi et al. 2011). This is thought to occur through preferential vasodilation of well-perfused alveoli causing a redistribution in blood flow to these alveoli from poorly-perfused alveoli (Yamauchi et al. 2011). Thus, the supplementation of oxygen may have contributed to the increasing $PaCO_2$-$P_E'CO_2$ gradient.

Cheetahs in both groups became progressively acidaemic throughout the maintenance period. This is likely the result of hypoventilation increasing the $PaCO_2$. The rudimentary analysis of the metabolic acid-base status reveals similar findings to domesticated cats. Both the bicarbonate ion (mean [range] of 18 [14.4 – 21.6] mEq L^{-1}) and base excess (mean ±SD of -6 ±4.8 mEq L^{-1}) are within similar published ranges for cats (Hopper et al. 2008). This similarity between our findings and domestic cats suggests that the worsening academia is most likely due to the rising carbon dioxide load. Unfortunately serum proteins, electrolytes and other organic acid loads (such as lactic acid) that are known to alter the plasma pH were not measured in this study, but could have contributed to the acidemia (Hopper & Haskins 2008). The bicarbonate was initially low, but increased during maintenance, suggesting that a compensation for the respiratory component was present. Regardless of the cause, acidosis can lead to decreased cardiac output and arterial blood pressure, respiratory muscle fatigue and increased metabolic demands, all of which could be detrimental if not treated (Adrogué and Madias 1998). In addition, acidaemia attenuates the effects of catecholamines on the heart and vasculature, this could have presented a problem in recovery following drug reversal.

Recovery time was taken from administration of atipamezole until “head up” and not standing due to the managemental need to recover animals in crates. It was feared that some cheetah would be unlikely to stand in the crate and thus recovery time was standardised to head up. Recovery from isoflurane was rapid, and similar to that reported for domestic dogs and cats. In dogs, a sternal time of 5.2 ±5.7 minutes (Tsai et al. 2007) has been reported and in cats a head up time of 6.0 ±3.0 minutes (Hikasa et al. 1996) has been documented following isoflurane maintenance. However, the recovery from propofol was prolonged. Generally propofol is associated with rapid recovery, even following prolonged infusion and in a wide range of species,

as reviewed in Clarke et al. (2014). In dogs, sternal recumbency at 12.8 ±15.4 minutes has been documented following propofol TIVA in acepromazine or diazepam premedicated dogs (Tsai et al. 2007) and in unpremedicated cats maintained with a 90 minute propofol CRI (0.2 mg kg^{-1} $minute^{-1}$), head lifting occurred at 10.8 ±4.3 minutes (Mendes & Selmi 2003).

Our study had a longer time to recovery with propofol. Delayed recovery from propofol infusions are occasionally documented in the literature. An unexpectedly long recovery following propofol infusion (90 minutes to head lift) compared to isoflurane inhalation maintenance (less than 40 minutes) was seen in dogs premedicated with dexmedetomidine (Kuusela et al. 2003). Despite the dexmedetomidine premedication not being reversed in that study, recovery from isoflurane maintenance was still markedly shorter than that from propofol TIVA. Similarly, in cats premedicated with medetomidine undergoing a 60 minute propofol CRI of 12.4 ±0.5 mg kg^{-1} $hour^{-1}$ (0.21 mg kg^{-1} $minute^{-1}$), head lifting occurred at 49.0 ±15.0 minutes post termination of propofol, a time similar to our study (Campagna et al. 2015). Again the medetomidine was not reversed in their study, but it does show a profound difference in recovery time than that documented by Mendes and Selmi (2003). It has been suggested that propofol may interfere with hepatic metabolism of other drugs (Mouton Perry et al. 1991), thus causing delayed recovery. In our study, tiletamine, zolazepam and medetomidine were all administered to the cheetah, and there may be interference between the drug metabolisms. As the medetomidine was antagonised as part of the protocol, antagonism of the zolazepam was used as a rescue intervention in cheetah recovering slowly. The cheetahs in Group-P were responsive (blinking in response to noise or light touch), but appeared “drowsy” and unwilling to lift their heads. This resembled arousal from benzodiazepine sedation. Since there may have been interference with the zolazepam metabolism, it was decided to administer flumazenil to antagonise any possible residual benzodiazepine effects. Recovery in antagonised animals was marginally quicker than

those not receiving the flumazenil. However, given the time that had elapsed between the end of maintenance and flumazenil administration, it is difficult to interpret whether there was any true benefit in its administration. Further investigation into the effect of zolazepam on propofol recovery and the role of flumazenil in cases of delayed recovery may be warranted.

Delayed recovery from propofol infusion is encountered more frequently in domestic cats than domestic dogs. The elimination half-life of propofol in cats is longer than in dogs (Court 2013). This is thought to be because cats are deficient glucuronidation pathways, and subsequently metabolism is assumed to occur through oxidation and sulfonidation (Court 2013). However, this explanation is unlikely to be the only one because interestingly in dogs, propofol is almost entirely eliminated through oxidation, with only 2% of a given dose being eliminated by glucuronidation (Simons et al. 1991). The metabolism of propofol by cheetahs has not been investigated, and it may resemble either dogs, cats or an amalgam of the two.

Length of propofol infusion may also play a role in delayed recovery due to drug accumulation. Pascoe et al. (2006) demonstrated slower recovery with longer propofol infusion duration in domestic cats. Although there was no significant difference in time to head up between cats receiving a propofol infusion for 30 minutes versus 150 minutes, the cats in the latter group took significantly longer to walk without ataxia (148 ±40 versus 18 ±15 minutes). Woc Colburn et al. (2009) reported delayed recovery in 3 cheetahs undergoing propofol anaesthesia of longer than 20 minutes.

Cheetahs in Group-P did, however, recover in a much calmer manner than those in Group-I. This is similar to studies in domestic dogs, which documented significantly calmer recovery from propofol TIVA than isoflurane inhalation maintenance in dogs (Tsai et al. 2007). Granone et al.

(2012) highlighted the importance of functional recovery in contrast to simply being awake when they looked at time to ability to track following recovery from inhalation anaesthesia in red-tailed hawks. Although cheetahs anaesthetised with propofol took longer to move to “head up”, they were more coordinated when they did move to “head up” than the cheetahs recovering from isoflurane. In the Granone et al. (2012) study, sevoflurane and desflurane yielded significantly shorter times to return of ability to track than isoflurane. A similar situation might be expected in other animals, with faster return to function with the other inhalation agents, and these may be better choices for wild animals.

The major limitation of this study is that the doses of propofol and isoflurane were not titrated down to find a nadir dose. The study design targeted a lack of response to stimuli as adequate depth of anaesthesia, however, we did not decrease the maintenance agents to test for an effective dose. This leaves the question as to whether the doses were actually higher than required. Future studies could investigate the lowest dose of propofol or isoflurane required to maintain anaesthesia, however, the question remains as to the sensibility of finding minimum infusion rates (MIR) and MAC in wild animals. Although determining the lowest effective dose of a drug is useful to prevent unnecessary drug usage and burden on organ systems, allowing a wild animal to return to consciousness and respond carries great risk. Physical restraint of wild animals causes great stress, and possibly harm (stress-induced hyperthermia, myopathies), to the animal and carries significant risk of injury to personnel (Chinnadurai et al. 2016). Thus the very real risks of wrestling stressed wild animals may outweigh the need to determine a MIR or MAC.

Due to their various effects on anaesthesia, the inclusion of immobilisation agents in the protocol could be considered a further limitation when interpreting the cardiopulmonary data.

However, large wild animals cannot practically be anaesthetised using inhalant or intravenous drugs without prior chemical capture. The immobilisation drugs were included in the protocol to mimic field anaesthesia practices and thus allow assessment of the maintenance protocols for feasibility when used in real-life simulations.

Conclusion

The results of this study indicate that either propofol total intravenous anaesthesia or isoflurane inhalation may be appropriate choices for maintenance of anaesthesia in cheetah in a field setting as both agents prevented movement during procedural manipulations. Cardiopulmonary function was well maintained by both agents, although isoflurane was seen to have greater effect in decreasing blood pressure than propofol. Both agents caused mild respiratory depression and oxygen supplementation should be considered essential with either agent. The prolonged recovery time associated with propofol infusion may make it an undesirable agent for wild animal anaesthesia, where fast recovery for quick release is essential, however, it may still be an acceptable alternative to isoflurane when animals are crated for recovery to provide environmental protection until recovery is deemed sufficient for release.

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Addendum

Contents

I Data collection form

Animal Identification

Number: _____ Sex: _____

Age: _____ Body mass: _____

Date: _____

Trial Number: _____

Immobilisation

Dart Preparation

Zoletil			**mL**
Medetomidine			**mL**
			Total dart volume **mL**

Capture

Dart Time	
Number of dart attempts	
Recumbency Time	

Intubation: Ketamine

Calculated dose	2 mg/kg	mg	**mL**
Bolus dose	0.5 mg/kg	mg	**mL**
Boluses administered		Total administered	**mL**
Induction Time			
ET-tube size			

Additional Notes and Comments

Initial Monitoring

Time	**HR**	**RR**	**Temp**	**SpO_2**

Animal ID: _____
Trial ID: _____

Maintenance

Initial Anaesthetic Preparation

Circle appropriate

Propofol		**mL/min**
Isoflurane		

Fluid Rate

Ringers Lactate	5 mL/kg/hr	**mL/hr**
Total fluids given		**mL**

Times

Anaesthetic start time	
Anaesthetic stop time	
Total maintenance time	

Additional Notes and Comments

Barometric Pressure

Time	

Animal ID: _____
Trial ID: _____

Recovery

Reversal Drugs

Atimpamezole (IM)	mg/kg	mg	**mL**	**Time from end of maintenance**	
Flumazenil (IV)	mg/kg	mg	**mL**		

Recovery

Extubation time	
Sternal time	
Standing time	

Additional Notes and Comments

Cheetah ID: _____ Trial Number: _____ Date: _____

Monitoring

Anaes (min)	Actual Time	Propofol (ml/h)	Et-Iso (%)	Pulse (bpm)	Syst BP (mmHg)	Diast BP (mmHg)	Mean BP (mmHg)	Resp Rate (bpm)	$EtCO_2$	SPO_2	Temp (°C)	FiO_2	Palpeb Reflex
0													
5													
10													
15													
20													
25													
30													
35													
40													
45													
50													
55													
60													
65													
70													
75													
80													
85													
90													
95													
100													
105													
110													
115													
120													

II Presentations and publications arising from this study

The following presentations and publications have resulted from this study:

Presentations

Event	Venue	Date	Title	Type
AVA Autumn Meeting 2016	Prague, Czech Republic	21 September 2016	Cardiopulmonary effects of propofol versus isoflurane in cheetah (*Acinonyx jubatus*)	Abstract presentation

Publications

Buck RK, Tordiffe ASW, Zeiler GE. Cardiopulmonary effects of anaesthesia maintained by propofol infusion versus isoflurane inhalation in cheetahs (*Acinonyx jubatus*). *Veterinary Anaesthesia and Analgesia* (In Press).

III Animal ethics approval certificate

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Animal Ethics Committee

PROJECT TITLE	**Laparoscopic sterilisation of the Cheetah *(Acinonyx jubatus)***
PROJECT NUMBER	**V014-14**
RESEARCHER/PRINCIPAL INVESTIGATOR	**Dr. MJ Hartman**

STUDENT NUMBER (where applicable)	**87 01 4239**
DISSERTATION/THESIS SUBMITTED FOR	**PhD**

ANIMAL SPECIES	**Cheetah *(Acinonyx jubatus)***	
NUMBER OF ANIMALS	**19**	
Approval period to use animals for research/testing purposes		**29 June-9 July 2014**
SUPERVISOR	**Prof. JP Schoeman**	

KINDLY NOTE:

Should there be a change in the species or number of animal/s required, or the experimental procedure/s - please submit an amendment form to the UP Animal Ethics Committee for approval before commencing with the experiment

APPROVED	Date	24 February 2014
CHAIRMAN: UP Animal Ethics Committee	Signature	

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Animal Ethics Committee

PROJECT TITLE	**Comparison of zoletil-medetomidine and ketamine-medetomidine immobilization for propofol continuous infusion anaesthesia in cheetah (Acinonyx jubatus)**
PROJECT NUMBER	**V052-16**
RESEARCHER/PRINCIPAL INVESTIGATOR	**Dr. R Buck**

STUDENT NUMBER (where applicable)	———
DISSERTATION/THESIS SUBMITTED FOR	**Academic**

ANIMAL SPECIES	**Cheetah**	
NUMBER OF ANIMALS	**To be reported**	
Approval period to use animals for research/testing purposes		**May 2016 – May 2017**
SUPERVISOR	**Dr. G Zeiler**	

Conditions: The AEC has noted that this project will be completed in a facility outside of South Africa. Since the AEC has not inspected the facility, please note that we cannot comment on the quality of the facility other than what was provided in the study questionnaire

KINDLY NOTE:

Should there be a change in the species or number of animal/s required, or the experimental procedure/s - please submit an amendment form to the UP Animal Ethics Committee for approval before commencing with the experiment

APPROVED	Date 30 May 2016
CHAIRMAN: UP Animal Ethics Committee	Signature

S4285-15