



Sveriges lantbruksuniversitet
Swedish University of Agricultural Sciences

**Faculty of Veterinary Medicine
and Animal Science**

Pharmacodynamic effects of dexmedetomidine infusion in isoflurane anaesthetised horses

**Farmakodynamiska effekter vid infusion av
dexmedetomidin hos hästar sövda med isofluran**

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SUMMARY

The aim of the present study was to analyse pharmacodynamic effects of a dexmedetomidine constant rate infusion (CRI) during general anaesthesia. This experimental study included six isoflurane anaesthetised horses, which during anaesthesia received a $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ dexmedetomidine CRI. Physiological parameters were measured and blood samples (both samples for blood gas analysis and dexmedetomidine plasma concentration analysis) were collected continuously during the entire anaesthesia and for 60 minutes after the CRI was disconnected.

All horses quickly reached a significant dexmedetomidine plasma concentration after the dexmedetomidine CRI was commenced. Mean dexmedetomidine concentration in plasma stayed above $0.15 \text{ ng}\cdot\text{mL}^{-1}$ during the entire anaesthesia, including 60 minutes after the dexmedetomidine CRI was disconnected. A previous study reported a dexmedetomidine plasma concentration of $0.15 \text{ ng}\cdot\text{mL}^{-1}$ to correspond to the nociceptive threshold in conscious horses.

Heart rate decreased significantly during the first hour after the dexmedetomidine CRI was started and mean arterial blood pressure was significantly increased during the first 15 minutes. Cardiac index decreased in five of six horses after dexmedetomidine was administered but the mean value was not significantly different compared to baseline. The overall cardiovascular changes were expected and within clinically acceptable levels. The termination of dexmedetomidine CRI during ongoing anaesthesia caused significant tachycardia for at least 30 minutes in all horses, a finding not described in previous studies.

There was no significant reduction in end-tidal isoflurane concentration during the course of anaesthesia.

Treatment of expected complications during inhalation anaesthesia in horses, e.g. hypotension and hypoxemia, were successfully treated with dobutamine and pulsed inhaled nitrogen monoxide.

In summary, the dexmedetomidine CRI during inhalation anaesthesia in horses seems to be a promising clinical method to improve analgesia and sedation during anaesthesia and recovery. The unexpected circulatory change in the form of tachycardia after the CRI needs to be investigated further.

SAMMANFATTNING

Syftet med studien var att analysera farmakodynamiska effekter vid CRI (*constant rate infusion*) av dexmedetomidin under inhalationsanestesi. Denna experimentella studie inkluderade sex hästar sövda med isofluran, som under anestestesin erhöll ett CRI med dexmedetomidin på $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. Fysiologiska parametrar mättes och blodprover (både prover för blodgasanalys och analys av dexmedetomidinkoncentration i plasma) samlades in kontinuerligt under hela anestesi samt 60 minuter efter att infusionen med dexmedetomidin stängts av.

Samtliga hästar nådde snabbt en signifikant koncentration av dexmedetomidin i plasma efter att infusionen med dexmedetomidin påbörjats. Medelkoncentrationen dexmedetomidin i plasma var över $0.15 \text{ ng}\cdot\text{mL}^{-1}$ under hela anestesi, inklusive 60 minuter efter att infusionen med dexmedetomidin stängts av. En tidigare studie har visat att $0.15 \text{ ng}\cdot\text{mL}^{-1}$ motsvarar den nociceptiva tröskeln för dexmedetomidin hos vaken häst.

Efter att dexmedetomidin-infusionen startats sjönk hjärtfrekvensen signifikant under den första timmen medan medelartärtryck ökade signifikant under de första 15 minuterna. *Cardiac index* minskade hos fem av sex hästar under dexmedetomidininfusionen men förändringen i medelvärde var inte signifikant. Överlag var de kardiiovaskulära förändringarna förväntade och de höll sig inom en klinisk acceptabel nivå. Avslutningen av dexmedetomidininfusionen under pågående anestesi orsakade signifikant takykardi under minst 30 minuter hos samtliga hästar, ett fynd som inte finns beskrivet i tidigare studier.

Ingen signifikant reducering av den end-tidal isoflurankoncentration kunde genomföras med bibehållet narkosdjup i denna studie.

Behandling av förväntade komplikationer under inhalationsanestesi på häst, t.ex. hypotension och hypoxemi, kunde framgångsrikt behandlas med dobutamin respektive pulsat inhalerat kväveoxid.

Sammanfattningsvis kan CRI med dexmedetomidin vara en tänkbar klinisk metod för att förbättra analgesi och sedering under både anestesi- och uppvakningsperioden. De oväntade cirkulatoriska förändringarna i form av takykardi när behandlingen avbröts behöver studeras vidare.

CONTENT

INTRODUCTION	1
Aims and hypothesis	2
LITERATURE REVIEW	3
Anaesthesia in horses	3
Dexmedetomidine	4
Previous studies	5
Dexmedetomidine as an intravenous bolus dose in standing horses.....	5
Dexmedetomidine as a CRI in standing horses.....	5
Dexmedetomidine as a CRI during anaesthesia.....	6
MATERIALS AND METHODS	8
Study design	8
Horses	8
Instrumentation and anaesthesia	8
Collection of data and analysis	10
Calculation of data	11
Statistical analysis	11
RESULTS	12
Part 1) Dexmedetomidine plasma concentration	12
Part 2) Circulation	13
Relation between dexmedetomidine concentration and circulation.....	13
Circulation during dexmedetomidine and dobutamine CRI.....	15
Circulation during elimination phase of dexmedetomidine.....	17
Part 3) Isoflurane concentration	19
Part 4) Arterial oxygenation	20
Arterial oxygen saturation.....	21
Partial pressure of arterial oxygen.....	22
DISCUSSION	23
Dexmedetomidine plasma concentration	23
Circulation	24
Heart rate.....	25
Arterial blood pressure (MAP).....	26
Cardiac index.....	26
Isoflurane concentration	27
Arterial oxygenation	28
CONCLUSIONS	29
POPULÄRVETENSKAPLIG BESKRIVNING	30
REFERENCES	33

ABBREVIATIONS

ASA	American Society of Anaesthesiologists
CI	Cardiac index ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)
CO	Cardiac output ($\text{L} \cdot \text{min}^{-1}$)
CRI	Continuous rate infusion
CVP	Central venous pressure (mmHg)
DAP	Diastolic arterial pressure (mmHg)
EtCO ₂	End-tidal carbon dioxide concentration (%)
EtO ₂	End-tidal oxygen concentration (%)
EtISO	End-tidal isoflurane concentration (%)
FiO ₂	Fraction inspired oxygen (%)
HR	Heart rate (beats/min)
IPPV	Intermittent positive pressure ventilation
MAC	Minimal alveolar concentration
MAP	Mean arterial pressure (mmHg)
NO	Nitric oxide
RR	Respiratory rate ($\text{breaths} \cdot \text{min}^{-1}$)
SaO ₂	Oxygen saturation in blood (%)
SAP	Systolic arterial pressure (mmHg)
SV	Stroke volume ($\text{L} \cdot \text{beat}^{-1}$)
SVR	Systemic vascular resistance ($\text{mmHg} \cdot \text{min} \cdot \text{L}^{-1}$)
SVRI	Systemic vascular resistance index ($\text{mmHg} \cdot \text{min} \cdot \text{L}^{-1} \cdot \text{kg}^{-1}$)
PaO ₂	Partial pressure of oxygen in arterial blood (kPa)
PAPD	Pulmonary artery pressure diastolic (mmHg)
PAPM	Pulmonary artery pressure mean (mmHg)
PAPS	Pulmonary artery pressure systolic (mmHg)
PA wedge	Pulmonary arterial wedge pressure (mmHg)
PEEP	Peak end expiratory pressure (cmH_2O)
PiNO	Pulse-delivered inhaled nitric oxide
PIP	Peak inspiratory pressure (cmH_2O)
TV	Tidal volume (L)

INTRODUCTION

General anaesthesia in horses entails a higher risk for complications compared to anaesthesia in small animals or humans (Johnston *et al.*, 2002). Most of the mortalities are related to the anaesthesia (Gozalo-Marcilla *et al.*, 2010) and a total volatile anaesthesia is associated with a higher mortality risk than a total intravenous anaesthesia (Valverde, 2013). Different balanced anaesthetic protocols are often used in order to minimize the amount of inhalation anaesthetics, increase the anaesthetic depth and provide analgesia. By combining multiple anaesthetic and analgesic drugs the goal is to make them act synergistically considering the desired analgesic effects and minimize the side effects (Gozalo-Marcilla *et al.*, 2012). Several studies have shown that adding a CRI of an α_2 -agonist reduces the minimal alveolar concentration (MAC) of the inhalation gas significantly, most likely due to its sedative and analgesic effects (Gozalo-Marcilla *et al.*, 2015).

Until 2005 there had not been any reported studies in the subject of administering dexmedetomidine to horses. Since then several studies have been performed and dexmedetomidine is now starting to be a popular drug used as an intravenous infusion, both in standing procedures and partial/total intravenous anaesthesia (PIVA/TIVA) (Gozalo-Marcilla *et al.*, 2017). The minimal cardiopulmonary side effects reported with dexmedetomidine favour its use over other α_2 -agonists (Bettschart-Wolfensberger *et al.*, 2005). Dexmedetomidine given as a CRI during anaesthesia is showing a lot of promise and can come to play an important role in equine anaesthesia in the future. However, more studies are needed to further investigate the pharmacodynamic and pharmacokinetic effects of dexmedetomidine during anaesthesia (Rezende *et al.*, 2015).

In the present study a dexmedetomidine CRI with a concentration of $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ was used. A dexmedetomidine CRI during anaesthesia has been shown to reduce the needed concentration of inhalation anaesthetics (Gozalo-Marcilla *et al.*, 2013a; Gozalo-Marcilla *et al.*, 2013b; Gozalo-Marcilla *et al.*, 2014; Risberg *et al.*, 2016). A previous study has determined the nociceptive threshold to correspond to a dexmedetomidine plasma concentration of $0.15 \text{ ng}\cdot\text{mL}^{-1}$, in conscious horses (Risberg *et al.*, 2014), and that threshold was used in the present study. In the present study pulsed inhaled nitric oxide (PiNO) was also added during the anaesthesia, in order to treat hypoxemia, as described in previous studies (Grubb *et al.*, 2008; Grubb *et al.*, 2012b; Nyman *et al.*, 2012; Grubb *et al.*, 2013; Wiklund, 2014).

This was the first study to analyse physiological effects during the elimination phase of dexmedetomidine (after the CRI was disconnected) in anaesthetised horses. Nor has any previous study analysed the pharmacodynamic and pharmacokinetic effects of a dexmedetomidine CRI in anaesthetised horses without a prior loading dose (or premedication) of dexmedetomidine.

Aims and hypothesis

In this experimental study the physiological effects of an intravenous infusion of dexmedetomidine with the concentration $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ was investigated in six isoflurane anaesthetised horses. The aim was to study i) if the dexmedetomidine CRI resulted in a plasma concentration above the nociceptive threshold ($0.15 \text{ ng}\cdot\text{mL}^{-1}$); ii) the physiological effects during and after a dexmedetomidine CRI; iii) if the isoflurane concentration could be reduced during the CRI; iv) the effects on arterial oxygenation with PiNO during a dexmedetomidine CRI.

Our hypothesis was that a dexmedetomidine CRI would affect the circulation by a decrease in heart rate and cardiac index meanwhile arterial blood pressure increased. We also expected to be able to reduce the end-tidal isoflurane concentration by adding a dexmedetomidine CRI to the anaesthesia.

LITERATURE REVIEW

Anaesthesia in horses

Equine surgery is today a very important part in treating injuries and diseases in our horses. Surgeries are performed both under general anaesthesia and during standing procedures on conscious horses (HästSverige, 2016). It is well known that anaesthesia in horses is associated with a higher mortality and morbidity compared to anaesthesia in small animals and humans. The cardiovascular depression (hypotension, reduced blood flow and hypoventilation) is more explicit in horses than in dogs and cats (Lee, 2006). Studies have shown a mortality rate of 1% in healthy horses undergoing elective surgery (compared to a mortality rate of 0.01-0.001% in humans). In emergency cases and in horses with systemic disease the mortality rate is much higher (Dugdale & Taylor, 2016). Many of the mortalities are related to the cardiovascular depression seen with inhalation anaesthesia (Gozalo-Marcilla *et al.*, 2010).

Balanced anaesthesia means combining several anaesthetics/analgesics/sedatives in order to summate the advantage effects and avoid disadvantage effects. The horse is being sedated, the pain is minimized and the dose-dependent side effects seen with total volatile anaesthetics are reduced (Bettschart-Wolfensberger *et al.*, 2007). Many studies have been performed in order to produce a safer and more beneficial anaesthesia (Johnston *et al.*, 2002). Different intravenous drugs have long been used as supplements to inhalational anaesthesia (Gozalo-Marcilla *et al.*, 2015).

Isoflurane is a well-used inhalation anaesthetic in equine anaesthesia. It induces a peripheral vasodilation and hypotension. The cardiovascular depression is dose-dependent, as with other inhalation anaesthetics. Since isoflurane depresses the respiratory function, isoflurane is usually combined with intermittent positive pressure ventilation (IPPV), a controlled ventilation where lung inflation is produced by a positive pressure (Lee, 2006), improving alveolar ventilation (Kalchofner *et al.*, 2009).

Maintenance of a good blood flow is crucial in order to achieve sufficient oxygenation and prevent hypoxemia (Gozalo-Marcilla *et al.*, 2010). Under clinical circumstances the horse often receives dobutamine during anaesthesia in order to prevent hypotension and improve central and muscular blood flow. Dobutamine is a synthetic catecholamine and is an inotropic drug. It stimulates β_1 -adrenergic receptors and increases cardiac output by an increase in myocardial contractility (Ohta *et al.*, 2013).

The position of the horse during anaesthesia will likely induce cardiovascular and respiratory changes (Doherty *et al.*, 2006). When placed in dorsal recumbency the expansion of the lungs is reduced due to compression of the abdominal contents on the diaphragm (Lee, 2006). Horses easily develop hypoxemia (defined as PaO_2 of <8.0 kPa) during anaesthesia when blood is shunted through the lungs without gas exchange (Auckburally & Nyman, 2017). This occurs because most of the blood is distributed to the caudodorsal parts of the lungs, even though those parts become atelectatic when the horse is placed in dorsal recumbency. The well-ventilated cranioventral parts of the lungs come in contact with only a small proportion of the circulating blood (Wiklund 2014).

One way to redistribute the blood to ventilated lung regions is by administering nitric oxide (NO) during anaesthesia. Inhaling NO causes a selective, local pulmonary vasodilation (Wiklund, 2014) in contrast to administering NO systemically leading to a generalised vasodilation and through that causing a peripheral hypotension (Auckburally & Nyman, 2017). The shunt fraction is reduced which improves the gas exchange and the arterial oxygenation. This effect is seen both in spontaneously breathing horses and when they are mechanically ventilated. The improved shunt fraction is only seen when the NO is pulsed (PiNO) in the beginning of the breaths, not during the second half of the breaths (Auckburally & Nyman, 2017). In higher doses NO can be toxic and exhaled NO can interfere with the soda lime in the breathing circuit (Wiklund, 2014).

Dexmedetomidine

Dexmedetomidine is the most selective α_2 -agonist with high affinity (1620:1) for the α_2 -receptor. For over 15 years, dexmedetomidine has been used clinically in dogs and cats; however it is not indicated for use in horses yet (Gozalo-Marcilla *et al.*, 2017).

Dexmedetomidine is the active enantiomer of medetomidine (Savola & Virtanen, 1991). Medetomidine consists of equal parts of dexmedetomidine and levomedetomidine. Dexmedetomidine is responsible for the sedative and analgesic effects, while levomedetomidine potentiate bradycardia and reduce the sedative and analgesic effect (Kuusela *et al.*, 2001).

Dexmedetomidine, like other α_2 -agonists, decreases the concentration of epinephrine and norepinephrine in plasma. The lower concentration of catecholamines affects many physiological functions and causes sedation (Grimsrud *et al.*, 2015). Alpha-2 agonists depress cardiopulmonary function, induce bradycardia and decrease cardiac output (CO). The magnitude of the side effects depends on type of α_2 -agonist, its dose and route of administration (Hopster *et al.*, 2014). Alpha-2 agonists increase vascular resistance by receptor activation, followed by a reflex bradycardia. The bradycardia is additionally induced via central mechanisms (Maze & Tranquilli, 1991).

Dexmedetomidine causes the same side effects as other α_2 -agonists but of very short duration because of a rapid redistribution, large volume of distribution, and short half-life. This indicates that plasma concentration of dexmedetomidine rapidly can be adjusted during anaesthesia (Bettschart-Wolfensberger *et al.*, 2005).

There are three subtypes of the receptor; α_{2A} -receptors mediate sedation, analgesia (both visceral and somatic), bradycardia and hypotension; α_{2B} -receptors mediate vascular resistance and bradycardia; α_{2C} -receptors mediate hypothermia. Alpha-2 receptors are located extrasynaptically in vascular endothelium, in platelets and pre- and postsynaptically throughout the body (Tranquilli *et al.*, 2007).

Previous studies

Dexmedetomidine as an intravenous bolus dose in standing horses

Administration of dexmedetomidine to horses was first studied in a report published by Bettschart *et al.* (2005). Eight young ponies (group A) and six mature ponies (group B) both received a bolus dose of $3.5 \mu\text{g}\cdot\text{kg}^{-1}$. In group A pharmacodynamic parameters and blood gases were analysed continuously for 60 minutes after administration. In both groups kinetic blood samples were collected continuously for 240 minutes after administration. Within 60-90 minutes the plasma concentration of dexmedetomidine had drop below limit of detection ($0.05 \text{ ng}\cdot\text{mL}^{-1}$) in both groups. Half-life was longer in the older ponies (29 minutes) compared to the younger ponies (20 minutes). The horses in group A showed a significant decrease in cardiac index (CI), a significant increase in mean arterial blood pressure (MAP) and systemic vascular resistance index (SVRI), however the changes were only significant the first five to ten minutes after the bolus dose was administrated. No significant reduction in heart rate (HR) was observed.

Rezende *et al.* (2015) analysed pharmacodynamic and pharmacokinetic effects of dexmedetomidine in eight standing horses receiving a bolus dose of $5 \mu\text{g}\cdot\text{kg}^{-1}$. Blood samples were collected for pharmacokinetic calculations. Physiological parameters were analysed before and continuously for six hours after administration. Half-life was eight minutes and within 30-60 minutes the concentration of dexmedetomidine in plasma was below $0.1 \text{ ng}\cdot\text{mL}^{-1}$. Heart rate decreased significantly for the first ten minutes after administration.

Dexmedetomidine as a CRI in standing horses

Several studies have been performed regarding standing procedures in conscious horses receiving dexmedetomidine as a CRI. In a report by Risberg *et al.* (2014) ten horses were sedated with a dexmedetomidine CRI in three different concentrations (first $2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$, then $4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ and last $6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$). A $0.96 \mu\text{g}\cdot\text{kg}^{-1}$ bolus dose preceded each CRI. The horses were electrically stimulated in order to determine tolerance and nociceptive threshold by analysing behaviour and electromyography. A median plasma concentration of $0.15 \text{ ng}\cdot\text{mL}^{-1}$ dexmedetomidine was considered to provide nociceptive effects in all analysed parameters in the study. In all three CRI concentrations antinociceptive effects were seen, although the concentration of dexmedetomidine in plasma during the $2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ CRI was too low to be measured. There was a big individual variation in plasma concentration between the horses (Risberg *et al.*, 2014).

A study by Ranheim *et al.* (2015) showed a significant individual difference in plasma concentration of dexmedetomidine during a 150 minutes long $8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ CRI in seven horses. Kinetic blood samples were taken continuously during the CRI and for approximately one hour after the CRI ended. Mean plasma elimination half-life was 20.9 minutes. The sedation effect covaried with the plasma concentration level. No pharmacodynamic effects were observed in this study.

Dexmedetomidine as a CRI during anaesthesia

Several studies have been performed where different α_2 -agonists (xylazine, romifidine, detomidine and medetomidine) significantly have reduced MAC of isoflurane, sevoflurane or halotane (Gozalo-Marcilla *et al.*, 2013a). Both experimental and clinical studies have shown that a medetomidine CRI provides good recovery and analgesia during surgery and cardiopulmonary function remained stable. In humans and dogs studies have shown a significant reduction of MAC of isoflurane when given a dexmedetomidine CRI (Gozalo-Marcilla *et al.*, 2010).

The first documented study to administrate dexmedetomidine as a CRI during inhalation anaesthesia to horses, observed the cardiopulmonary effects in six ponies receiving two different dose rates of dexmedetomidine. Three ponies were administrated $1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ for 30 minutes and then $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ for 30 minutes (after a washout period of 30 minutes between the two infusions). The other three ponies received the infusions in the opposite order. A $3.5 \mu\text{g}\cdot\text{kg}^{-1}$ bolus dose of dexmedetomidine was administered as premedication in both groups before the first CRI. This experimental study showed that HR, CI and oxygen delivery decreased significantly while SVRI, SAP and right arterial pressure increased significantly. These effects were statistically significant but the cardiovascular function remained within a clinically acceptable level. No significant differences in the results were seen between the two different doses (Gozalo-Marcilla *et al.*, 2010).

Gozalo-Marcilla *et al.* (2012) did a rather comprehensive clinical study (blinded, placebo-controlled and randomized) including 40 horses undergoing elective surgery (ASA I-II). The horses were anaesthetised with isoflurane and premedicated with a $3.5 \mu\text{g}\cdot\text{kg}^{-1}$ bolus dose of dexmedetomidine. One group of horses (group D) received a CRI of $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ and the other group of horses (group S) received a saline CRI and functioned as a control group. In this study there was no significant difference between the two groups regarding the concentration of inhaled isoflurane. The horses in group D showed significantly better recovery scores (longer time until first attempt to stand and fewer attempts to stand needed) than the control group. The observed cardiopulmonary effects produced by the α_2 -agonists in this study confirmed the results seen in Gozalo-Marcilla *et al.* (2010).

Gozalo-Marcilla *et al.* (2013a) published an experimental study looking at how a dexmedetomidine CRI would affect the MAC of inhalation anaesthetic. The study included six ponies that were anaesthetised twice with a washout period of three weeks. Three ponies were, after induction, first administrated a $3.5 \mu\text{g}\cdot\text{kg}^{-1}$ bolus dose of dexmedetomidine followed by a CRI of $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ and the other time with a $3.5 \mu\text{g}\cdot\text{kg}^{-1}$ bolus dose of saline followed by a CRI of $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ of saline. The other ponies received the treatments in the opposite order. Anaesthesia was induced and maintained with sevoflurane and no premedication was administrated. During anaesthesia the ponies were electrically stimulated in order to evaluate if dexmedetomidine made it possible to reduce the concentration of inhalation anaesthetic. All six ponies showed a decreased MAC when given dexmedetomidine compared to saline. The decrease was significant with a reduction of sevoflurane by 53% (Gozalo-Marcilla *et al.*, 2013a).

Gozalo-Marcilla *et al.* (2013b) published yet another study (clinical, blinded and randomized), comparing the effects of a dexmedetomidine (group D) versus a morphine (group M) CRI in 20 isoflurane anaesthetised horses undergoing elective surgery (ASA I-II). The horses in group D were premedicated with a $3.5 \mu\text{g}\cdot\text{kg}^{-1}$ bolus dose of dexmedetomidine followed by a CRI of $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ during anaesthesia. The horses in group M were premedicated with a $3.5 \mu\text{g}\cdot\text{kg}^{-1}$ bolus dose of dexmedetomidine and morphine ($0.15 \text{mg}\cdot\text{kg}^{-1}$) followed by a CRI of morphine ($0.1 \text{mg}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$). The horses receiving only dexmedetomidine showed a significantly more stable anaesthetic depth (fewer alterations in the isoflurane concentration was needed), had a reduced MAC of isoflurane after 60 minutes of surgery and showed better recoveries. Group D also had a significantly higher MAP, significantly lower CI and SVI but the changes were within clinically acceptable levels (Gozalo-Marcilla *et al.*, 2013b).

Gozalo-Marcilla *et al.* (2014) compared horses receiving a CRI with only morphine (control group) versus horses receiving a CRI with both morphine and dexmedetomidine (group D) during anaesthesia. The study included five ponies and they were anaesthetised twice with a washout period of three weeks. One time they were administrated a $0.15 \text{mg}\cdot\text{kg}^{-1}$ bolus dose of morphine followed by a CRI of $0.1 \text{mg}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ during inhalation anaesthesia and the other time they were administrated a bolus dose of both morphine ($0.15 \text{mg}\cdot\text{kg}^{-1}$) and dexmedetomidine ($3.5 \mu\text{g}\cdot\text{kg}^{-1}$) followed by a CRI of both morphine ($0.1 \text{mg}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$) and dexmedetomidine ($1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$). This was an experimental study in which the horses were electrically stimulated during anaesthesia. The study showed that group D had a significant reduced MAC of sevoflurane (mean MAC 0.89%) compared to the control group (mean MAC 2.79%) with a mean reduction of 67% (Gozalo-Marcilla *et al.*, 2014).

Risberg *et al.* (2016) performed an experimental blinded study including eight anaesthetised horses. One group was administrated a $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ CRI of dexmedetomidine (group D) and the control group received a saline CRI of the same volume. Both groups were premedicated with an $8 \mu\text{g}\cdot\text{kg}^{-1}$ bolus of dexmedetomidine. The horses were subjected to electrical stimulus. At an equivalent depth of anaesthesia the horses in group D showed a 22% reduction in MAC of isoflurane compared to the control group. The horses receiving dexmedetomidine CRI showed a significantly decreased HR and CI, and increased arterial blood pressure. All horses in group D stood on the first attempt in recovery while the horses in the control group required a median of three attempts. This was the first study including the pharmacokinetics of a dexmedetomidine CRI during anaesthesia (Risberg *et al.*, 2016).

Sacks *et al.* (2017) included 60 horses undergoing elective surgery (ASA I-II) in a clinical, blinded study comparing the effects dexmedetomidine (a $3.5 \mu\text{g}\cdot\text{kg}^{-1}$ bolus followed by a CRI of $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$) versus medetomidine (a $7 \mu\text{g}\cdot\text{kg}^{-1}$ bolus followed by a CRI of $3.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$) during anaesthesia maintained with isoflurane. Significantly more horses receiving dexmedetomidine needed supplemental doses of dexmedetomidine in order to fulfil the sedation criteria prior to induction. The cardiopulmonary effects or end-tidal isoflurane concentration (EtISO) did not differ significantly between the groups. The horses in the dexmedetomidine group showed a significantly better recovery compared to the horses receiving medetomidine (Sacks *et al.*, 2017).

MATERIALS AND METHODS

Study design

This was a prospective, experimental study performed at the Swedish University of Agricultural Sciences under standardised conditions striving to mimic a clinical situation as far as possible. The study was conducted without a control group of horses. The six horses included in the study worked as their own control in the way that data was collected before the horses started receiving dexmedetomidine.

Horses

All horses included in the study were private owned and donated by their owners to be part of the present study. The horses were of different breed and size (Table 1). At the end of anaesthesia the horses were euthanized. The horses were fasted for 12 hours prior to anaesthesia. Water was not withheld.

Table 1. *Horses included in the study*

Horse	Breed	Age	Gender	Weight (kg)
1	Welsh pony	15	Gelding	275
2	Swedish warmblood	18	Mare	615
3	Swedish warmblood	18	Mare	676
4	Swedish riding pony	20	Mare	450
5	Quarter horse	18	Gelding	650
6	Swedish warmblood	21	Gelding	750

Instrumentation and anaesthesia

The horses were premedicated with 0.03 mg·kg⁻¹ acepromazine (Plegicil 10 mg·mL⁻¹; Pharmaxim, Sweden) intramuscularly, 45 minutes before anaesthesia was induced.

Before induction, the areas in which all catheters were placed were clipped and aseptically prepared. The skin was locally infiltrated with mepivacaine (Carbocain 2%; Aspen Nordic, Denmark). The venous catheter (Intranule, 14-gauge; Vygon, Sweden) was placed in the left jugular vein and only used for administration of drugs and Ringer Acetate infusion. Two catheter-introducers (One-piece Catheter Introducer, 8.5 Fr; ArgonMedical Devices Inc; USA) were placed in the right jugular vein (one introducer 15 cm more proximally than the other) using the Seldinger technique.

The anaesthesia was induced with guaifenesin (Myorelax 100 mg·mL⁻¹; Dechra, UK) and thiopental (Thiopental Ebb; Ebb Medical, Sweden). Guaifenesin was given intravenously symptomatically (approximately 100-150 mL/100 kg bodyweight) until the horses started to show ataxia.

Thiopental was resolved in sterile water and the solution (which was prepared in advance) was given intravenously (initially ½ gram/100 kg bodyweight, although some horses needed an extra bolus of 10% of the start dose).

The horses were intubated with a cuffed endotracheal tube and placed in dorsal recumbency. The tube was connected to a large animal circle breathing system (Tafonius T33; Vetronic Services Ltd, UK) and anaesthesia was maintained with isoflurane (Attane vet. 1000 mg/g; VM Pharma, Sweden) in oxygen. Intermittent positive pressure ventilation (IPPV) was applied. A tidal volume (TV) of $10 \text{ mL}\cdot\text{kg}^{-1}$, a respiratory rate (RR) of $7 \text{ breaths}\cdot\text{minute}^{-1}$ and a peak inspiratory pressure (PIP) of $25 \text{ cmH}_2\text{O}$ was set (PIP had to be adjusted in some of the horses).

During anaesthesia, Ringer's acetate solution (Ringer-Acetate; Fresenius Kabi, Sweden) was infused at a rate of approximately $5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$. A urinary catheter was placed.

After connection to the anaesthesia machine, a catheter (Criticath, 7 Fr, 110 cm; Argon Medical Devices Inc, USA) was passed through the distal introducer in the right jugular vein and placed in the pulmonary artery. The catheter was correctly positioned by observing the blood pressure waveforms displayed on a cardiovascular monitor (Datex Ohmeda; GE healthcare). This catheter was used to measure CO and pulmonary artery pressure (PAP) as well as for collection of central venous blood for the venous blood gases. A Pigtail catheter was passed through the proximal introducer, placed in the right atrium and connected to the same pressure transducer as the arterial catheter. This catheter was used to measure central venous pressure (CVP).

The arterial catheter (BD Venflon Pro, 20-gauge; BD, Switzerland) was placed in the facial artery and connected to a pressure transducer (Hemodynamic Monitoring System; BD, Switzerland) placed at the level of the right atrium and zeroed to atmospheric pressure. The arterial catheter was used for measurement of invasive arterial pressure and collection of blood samples (for analysis of blood gases and dexmedetomidine concentration).

Dexmedetomidine (Cepedex $0.5 \text{ mg}\cdot\text{mL}^{-1}$; VM Pharma, Sweden) was diluted in 500 mL saline (Sodium chloride 0.9%; Fresenius Kabi, Sweden), and the horses received a dexmedetomidine CRI of $1.75 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ using an infusion pump (Infusomat Space; Braun, Sweden). No bolus dose (or premedication) of dexmedetomidine was given.

Thirty minutes after the dexmedetomidine CRI was started, a dobutamine infusion was initiated (Dobutamin Carino 250 mg/50 mL; Carinopharm, Germany) using a syringe pump (IVAV P3000; Alaris). The horses started the dobutamine CRI at a rate of $0.5 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{minute}^{-1}$ and the rate was then adjusted as required in order to keep MAP at 70-75 mmHg during the entire anaesthesia.

During the anaesthesia the horses also received pulsed inhaled nitric oxide (PiNO) through a special built device (Datex-Ohmeda Research Unit, Finland) connected to the endotracheal tube. The nitric oxide was delivered as a pulse during the first part of every breath. The negative pressure that preceded the inhalation of gas stimulated the device.

Collection of data and analysis

Table 2. *Samples were collected and parameters recorded according to following schedule*

	Blood samples for dex conc.	Arterial & venous blood gases	HR, SAP/DAP, MAP, PAP, EtCO ₂ , FiO ₂ , EtO ₂ , EtISO, PIP	CVP, CO, PA wedge, temperature
Start IPPV Start of isoflurane	---	---	---	---
Baseline 60	✓	✓	✓	✓
Start dexmedetomidine	---	---	---	---
Dex 15 15 minutes after start of CRI	✓	✓	✓	---
Dex 30 30 minutes after start of CRI	✓	✓	✓	✓
Start dobutamine (dob)	---	---	---	---
Dex 45 + dob 15 minutes after start of dob.	---	✓	✓	---
Dex 60 + dob 30 minutes after start of dob.	✓	✓	✓	✓
Start PiNO	---	---	---	---
Dex 75 + dob + PiNO 15 minutes after start of PiNO	---	✓	✓	---
Dex 90 + dob + PiNO 30 minutes after start of PiNO	✓	✓	✓	✓
Stop PiNO	---	---	---	---
Dex 105 + dob 15 minutes after stopping PiNO	---	✓	✓	---
Dex 120+ dob 30 minutes after stopping PiNO	✓	✓	✓	✓
Stop dexmedetomidine	---	---	---	---
Elimination 5 5 minutes after stopping dex	✓	---	✓	---
Elimination 10	✓	---	✓	---
Elimination 15	✓	✓	✓	✓
Elimination 20	✓	---	✓	---
Elimination 30	✓	✓	✓	✓
Elimination 40	✓	---	✓	---
Elimination 50	✓	---	✓	---
Elimination 60	✓	✓	✓	✓
Stop anaesthesia Euthanasiation	---	---	---	---

✓ = measured/collected

--- = not measured/collected

After induction the horses were maintained on isoflurane anaesthesia for 60 minutes in order for a steady state to be achieved before the dexmedetomidine CRI was initiated.

Both the arterial and venous samples were collected in syringes with 0.1 mL added heparin/tube (Heparin LEO 5000 IE·mL⁻¹; LEO Pharma, Denmark). The blood samples were collected over three breaths and the venous and arterial blood were collected at the exact same time. Blood gases were immediately analysed using an ABL 90 FLEX PLUS; Radiometer, Denmark. Before sampling, 3 mL blood was withdrawn and wasted.

The blood samples used to analyse the dexmedetomidine concentration were collected from the fascial artery. Before sampling, 3 mL blood was withdrawn and wasted. The blood was transferred into heparinized tubes (BD Vacutainer Lithium Heparin; BD, Switzerland). The tubes were stored on ice and after the sampling kept on ice until centrifugation. The plasma was harvested and stored in a freezer until analysis (AdmeScope; Finland). Lowest concentration level of detection (LoD) was defined as 0.02 ng·mL⁻¹.

Cardiorespiratory parameters were recorded on the anaesthesia monitor and the cardiovascular monitor (Table 2). An ECG recorded HR and heart rhythm. Cardiac output was measured by bolus thermodilution. Iced saline (30 mL) was injected into the right atrium during the expiratory phase of the respiratory cycle. The change in blood temperature was measured in the pulmonary artery and CO calculated. Three injections were made at every measurement and the average value was used for the analysis. The saline had to be injected rather quickly and the quality of the waveform on the monitor confirmed the injection was fast enough.

The anaesthetic depth was evaluated every five minutes (cardiovascular parameters and reflexes) and the inspired isoflurane concentration was adjusted according to the clinical parameters in order to keep the horse in sufficient anaesthetic depth. The total length of the anaesthesia was approximately four hour.

Calculation of data

$$\text{Cardiac index (CI)} = \frac{CO}{\text{body weight}}$$

$$\text{Systemic vascular resistance index (SVRI)} = \frac{MAP}{CI}$$

Statistical analysis

All collected data was compiled in Microsoft Excel 2011. The statistical analysis was made with GraphPad Prism 7.0. The graphs were designed in Excel. The dots in the graphs indicate the time of sampling.

A Wilcoxon matched-pairs signed rank test was used to calculate statistical significance. Regarding evaluation of heart rate during the elimination phase, a Friedman ANOVA with Dunn's multiple comparison test was used. A confidence interval of 95% was applied and $p < 0.05$ indicated statistical significance.

RESULTS

Part 1) Dexmedetomidine plasma concentration

Within the first measurement after the start of the CRI, the nociceptive threshold ($0.15 \text{ ng}\cdot\text{mL}^{-1}$) was reached with a marginal in all of the horses (Figure 1). In one horse, the plasma concentration was below the nociceptive threshold 30 minutes after the disconnection of the CRI, while four horses still were above the threshold 60 minutes after the disconnection (Table 3).

Table 3. Concentration (ng/mL) of dexmedetomidine in arterial blood during anaesthesia. $\text{LoD} < 0.02 \text{ ng}\cdot\text{mL}^{-1}$

	Horse 1	Horse 2	Horse 3	Horse 4	Horse 5	Horse 6
Start dex	<LoD	<LoD	<LoD	<LoD	<LoD	<LoD
Dex 15	1.02	1.03	0.81	0.74	0.75	0.78
Dex 30	1.20	1.34	1.13	1.02	0.89	1.01
Dex 45 + dob	1.13	1.41	1.12	1.08	0.80	1.15
Dex 60 + dob + PiNO	0.96	1.37	0.93	0.99	0.69	1.03
Dex 120 +dob	0.79	1.25	1.03	0.92	0.68	0.91
Elimination 5	0.30	0.82	1.04	0.54	0.35	0.53
Elimination 10	0.42	0.65	0.60	0.45	0.27	0.43
Elimination 15	0.35	0.50	0.51	0.34	0.22	0.37
Elimination 20	0.30	0.44	0.44	0.33	0.18	0.32
Elimination 30	0.14	0.29	0.36	0.28	0.15	0.26
Elimination 40	0.12	0.21	0.27	0.25	0.13	0.21
Elimination 50	0.11	0.18	0.24	0.21	0.11	0.19
Elimination 60	0.10	0.16	0.18	0.18	0.10	0.18

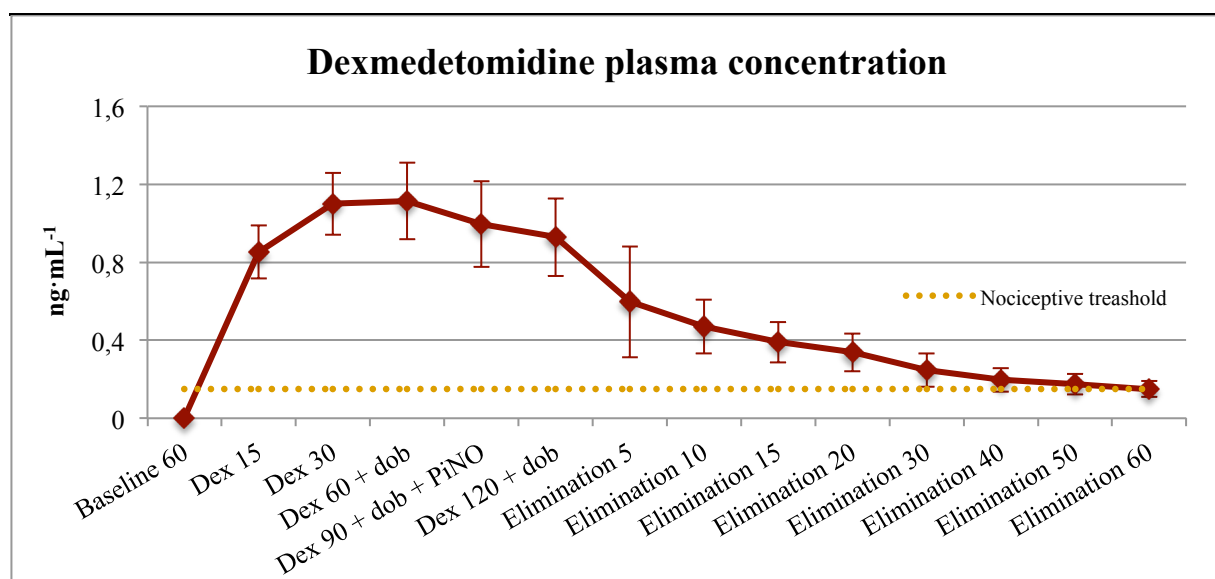


Figure 1. Mean \pm SD of dexmedetomidine plasma concentration during and after the CRI in six horses.

Part 2) Circulation

Heart rate was significantly decreased during a dexmedetomidine CRI of $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$. Heart rate increased rapidly after the disconnection of the dexmedetomidine CRI (Figure 2).

Mean arterial blood pressure was significantly increased by the dexmedetomidine CRI (Figure 2). The dobutamine infusion rapidly and significantly increased MAP in all of the horses (Figure 3). The concentration of dobutamine was then adjusted during anaesthesia in order to keep MAP at 70-75 mmHg.

Mean cardiac index was not significantly changed by the dexmedetomidine CRI. Cardiac index decreased in five of the six horses after the start of dexmedetomidine CRI; however horse 3 differed and instead CI increased (Figure 3). The dobutamine infusion rapidly and significantly increased CI in all of the horses.

Relation between dexmedetomidine concentration and circulation

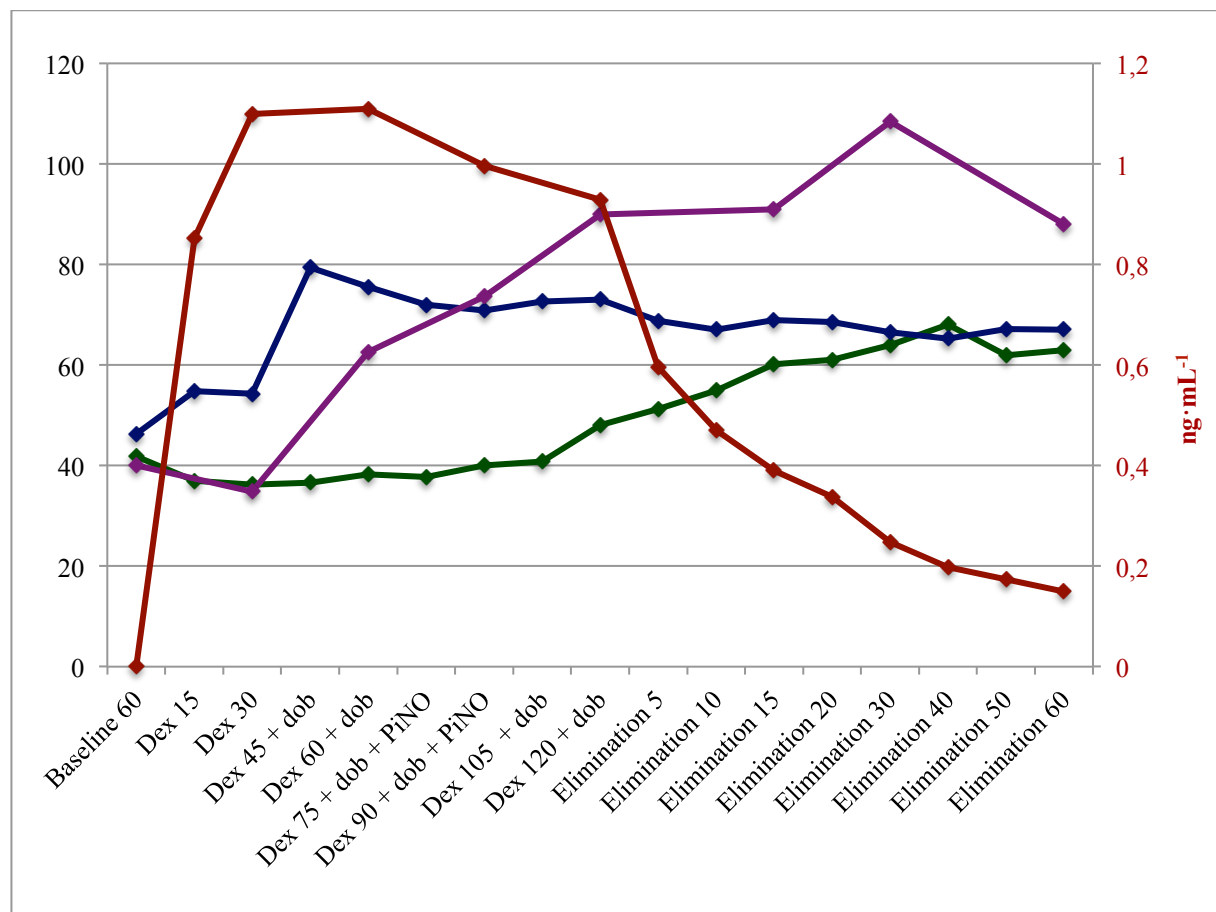


Figure 2. Mean values of HR, MAP, CI (left axis) and dexmedetomidine concentration in arterial blood (right axis).

◆ HR (beats·min⁻¹)
 ◆ MAP (mmHg)
 ◆ CI (mL·kg⁻¹·min⁻¹)
 ◆ Conc (ng·mL⁻¹)

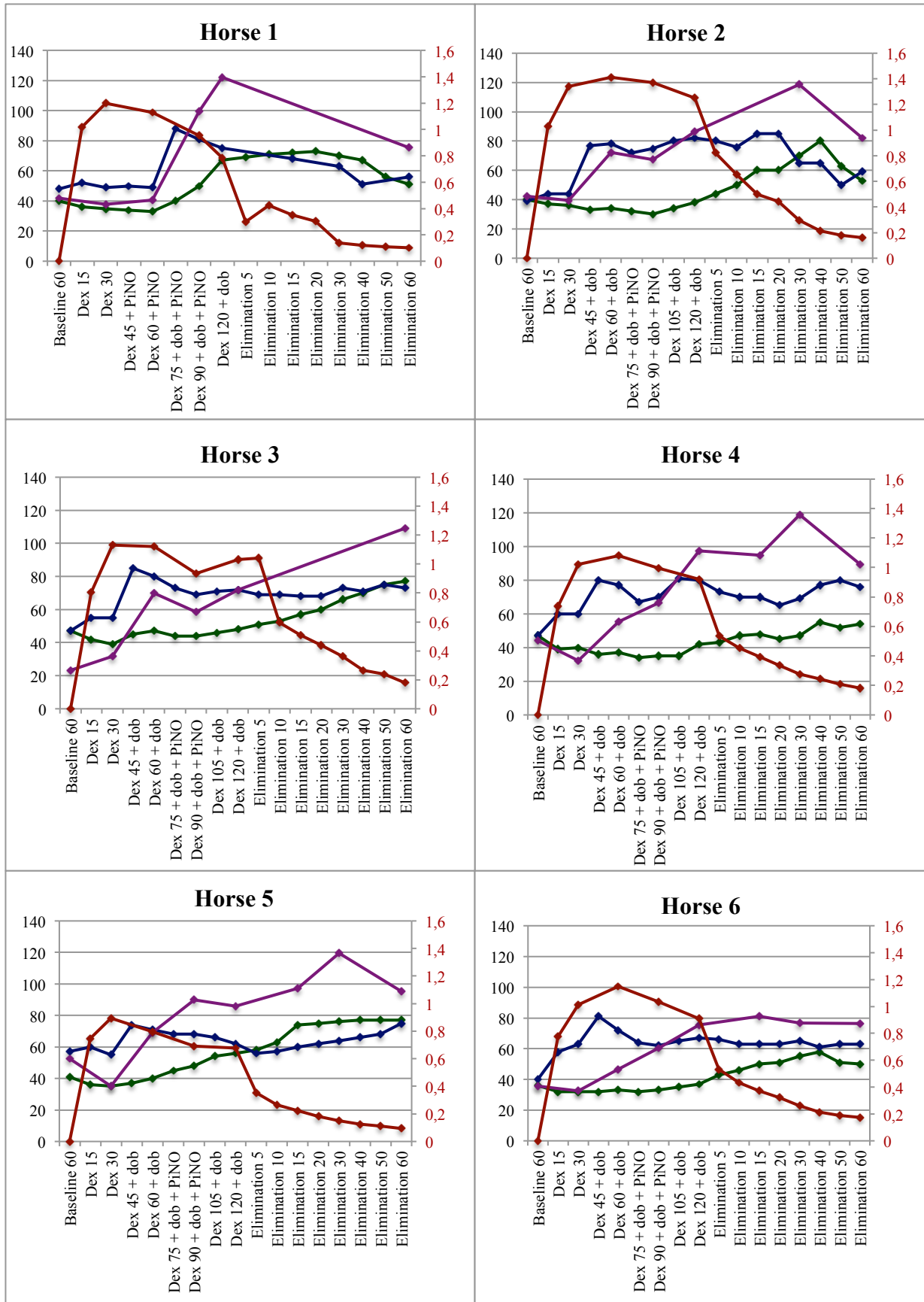


Figure 3. HR, MAP, CI (left axis) and dexmedetomidine concentration in ng·mL⁻¹ (right axis).

◆ HR (beats·min⁻¹)
 ◆ MAP (mmHg)
 ◆ CI (mL·kg⁻¹·min⁻¹)
 ◆ Conc (ng·mL⁻¹)

Circulation during dexmedetomidine and dobutamine CRI

Heart rate

Heart rate decreased significantly during the dexmedetomidine CRI (Figure 4a) and was significantly lower at *dex 15*, *dex 30*, *dex 45+dob* and *dex 60+dob* ($p < 0.05$) compared to *baseline 60*. After that heart rate was no longer significantly different compared to *baseline 60* (Table 4).

MAP

Mean arterial blood pressure increased significantly during the dexmedetomidine CRI and was significantly higher at *dex 15* $p < 0.05$ compared to *baseline 60*. At *dex 30* MAP was still higher in five of six horses compared to *baseline 60* but the average MAP for the group was not significantly different from *baseline 60* ($p = 0.09$).

During the dobutamine infusion MAP increased significantly (Figure 4b) compared to both *baseline 60* and *dex 30*; *dex 45+dob* and *dex 60+dob* ($p < 0.05$) (Table 4).

Cardiac index

Cardiac index did not change significantly during the dexmedetomidine CRI (Figure 4c) compared to *baseline 60* ($p = 0.2$ at *dex 30*) (Table 4).

During dobutamine infusion CI increased significantly ($p < 0.05$ at *dex 60+dob*) compared to before dobutamine was given (*dex 30*). Horse 1 was not included since no cardiac index was obtained from this horse at *dex 60+dob*.

Table 4. Mean \pm SD of cardiovascular parameters during anaesthesia

	HR (beats·min ⁻¹)	MAP (mmHg)	CI (mL·kg ⁻¹ ·min ⁻¹)	SVRI (mmHg·kg ⁻¹ ·min ⁻¹)
Baseline 60	42 \pm 5 n = 6	46 \pm 7 n = 6	39 \pm 11 n = 6	1.2 \pm 0.4 n = 6
Dex 15	37 \pm 4 ↓ n = 6	55 \pm 6 ↑ n = 6		
Dex 30	36 \pm 3 ↓ n = 6	54 \pm 7 ↔ n = 6	34 \pm 3 ↔ n = 6	1.6 \pm 0.3 ↔ n = 6
Dex 45 + dob	37 \pm 5 ↓ n = 5	79 \pm 4 ↑ n = 5		
Dex 60 + dob	38 \pm 6 ↓ n = 6	76 \pm 4 ↑ n = 5	63 \pm 11 ↑ n = 5	1.2 \pm 0.2 ↔ n = 6

↓ = Significant decrease compared to baseline 60.

↑ = Significant increase compared to baseline 60.

↔ = No significant increase/decrease compared to baseline 60.

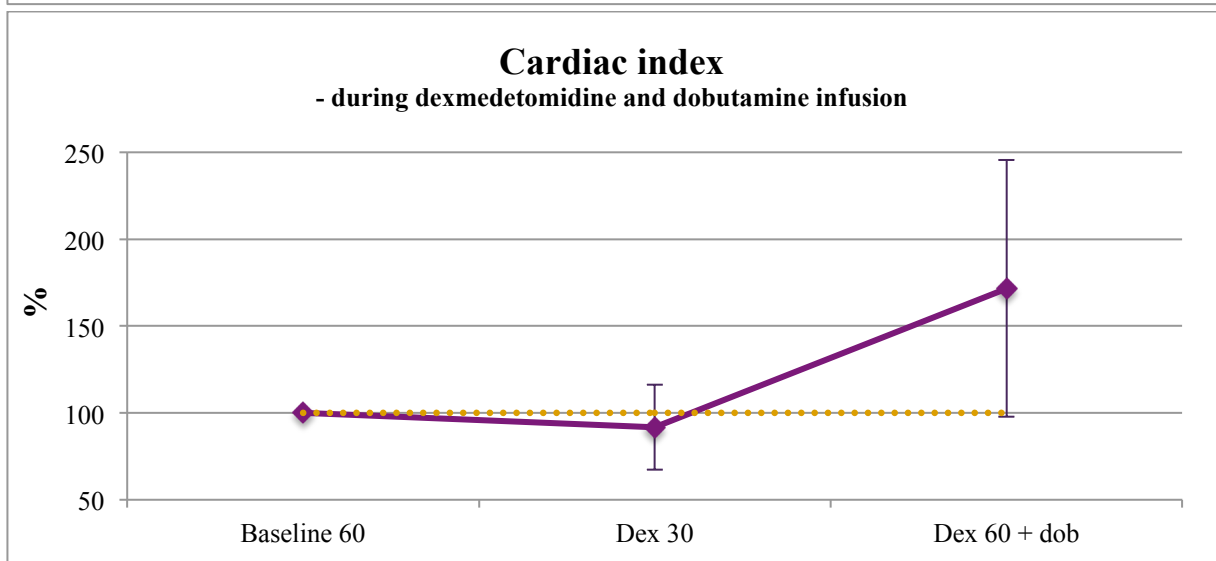
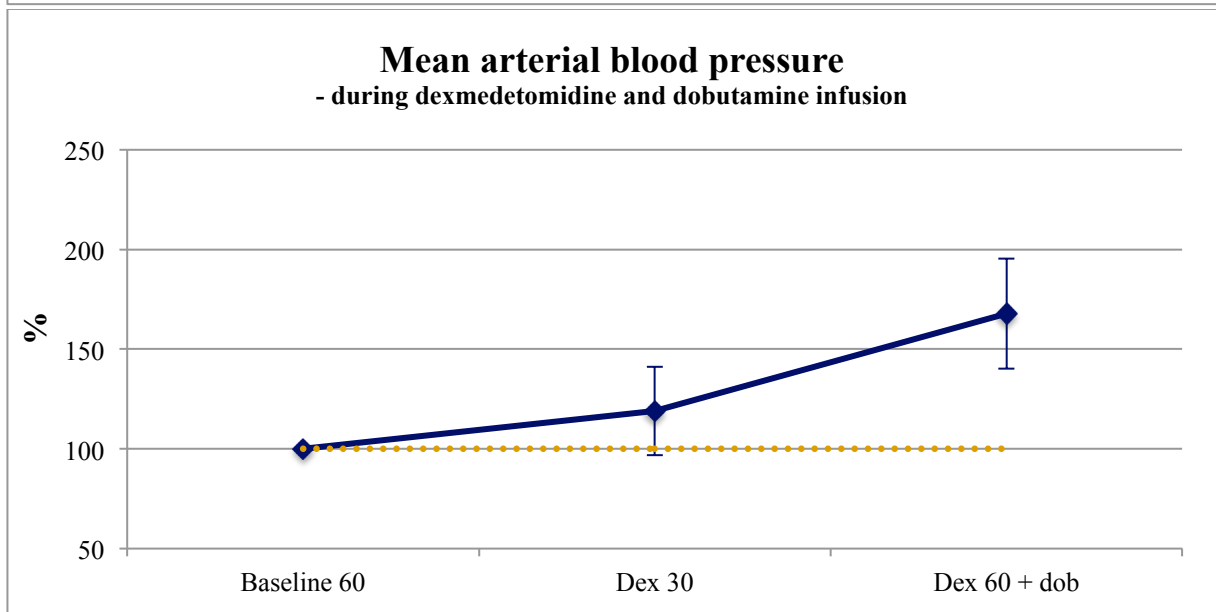
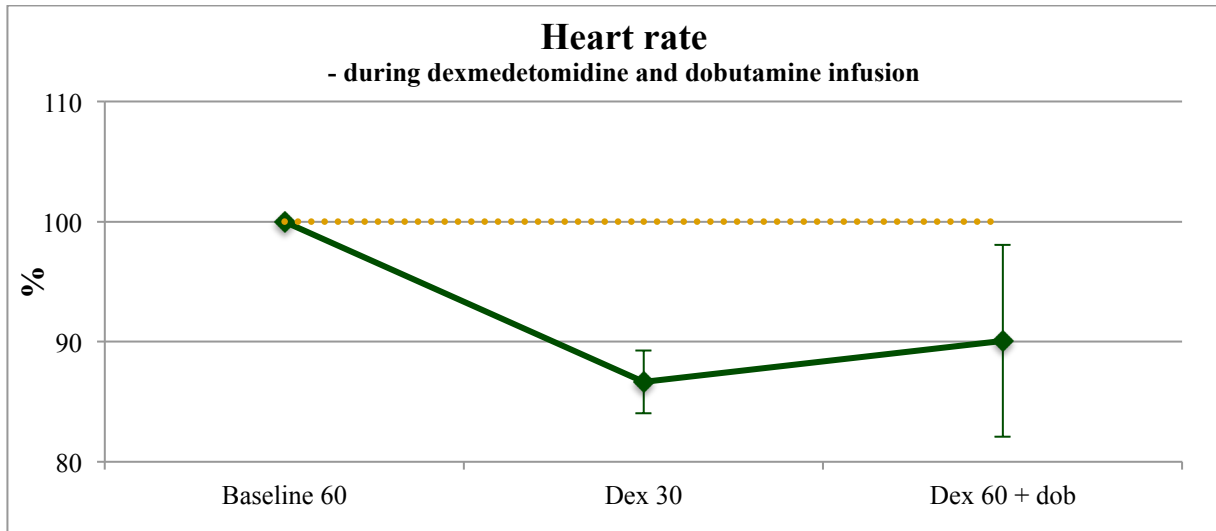


Figure 4a, 4b and 4c. Mean \pm SD of HR, MAP and CI during the dexmedetomidine and dobutamine CRI, calculated in relative change with 100% at baseline 60.

Circulation during elimination phase of dexmedetomidine

Heart rate

The heart rate was significantly increased (Figure 5a) 30 to 60 minutes after the disconnection of the dexmedetomidine CRI ($p < 0.05$ from *elimination 30* to *elimination 60*) compared to the final recording before the dexmedetomidine CRI was disconnected (*dex 120+dob*) (Table 5).

MAP

No significant change in MAP occurred after the dexmedetomidine CRI was disconnected (Figure 5b and Table 5).

Cardiac index

No significant change in CI occurred after the dexmedetomidine CRI was disconnected (Figure 5c and Table 5).

Table 5. Mean \pm SD of cardiovascular parameters during the elimination phase

	HR (beats·min ⁻¹)	MAP (mmHg)	CI (mL·kg ⁻¹ ·min ⁻¹)	SVRI (mmHg·kg ⁻¹ ·min ⁻¹)
Dex 120 + dob	44 \pm 8 n = 6	73 \pm 9 n = 6	83 \pm 10 n = 6	0.8 \pm 0.1 n = 6
Elimination 5	51 \pm 11 \leftrightarrow n = 6	69 \pm 9 \downarrow n = 5		
Elimination 10	55 \pm 10 \leftrightarrow n = 6	67 \pm 7 \downarrow n = 5		
Elimination 15	60 \pm 11 \leftrightarrow n = 6	69 \pm 10 \leftrightarrow n = 6	91 \pm 9 \leftrightarrow n = 3	0.7 \pm 0.1 \leftrightarrow n = 3
Elimination 20	61 \pm 12 \leftrightarrow n = 6	69 \pm 9 \leftrightarrow n = 5		
Elimination 30	64 \pm 11 \uparrow n = 6	67 \pm 4 \leftrightarrow n = 6	108 \pm 21 \leftrightarrow n = 4	0.6 \pm 0.1 \leftrightarrow n = 4
Elimination 40	68 \pm 10 \uparrow n = 6	68 \pm 6 \leftrightarrow n = 6		
Elimination 50	62 \pm 11 \uparrow n = 6	67 \pm 12 \leftrightarrow n = 5		
Elimination 60	60 \pm 13 \uparrow n = 6	69 \pm 8 \leftrightarrow n = 6	90 \pm 13 \leftrightarrow n = 6	0.8 \pm 0.1 \leftrightarrow n = 6

\downarrow = Significant decrease compared to dex 120+dob.

\uparrow = Significant increase compared to dex 120+dob.

\leftrightarrow = No significant increase/decrease compared to dex 120+dob.

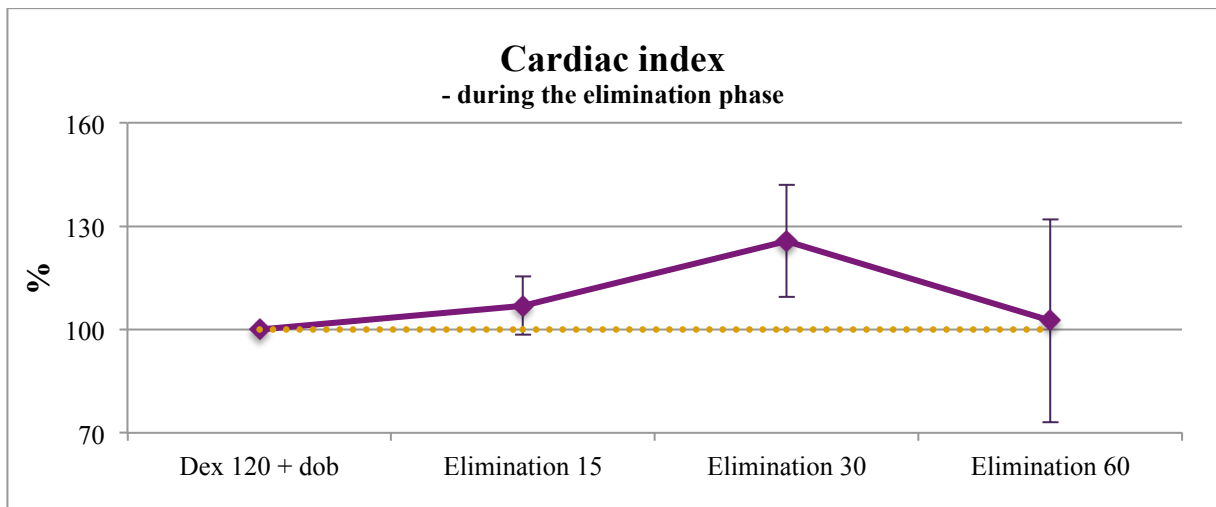
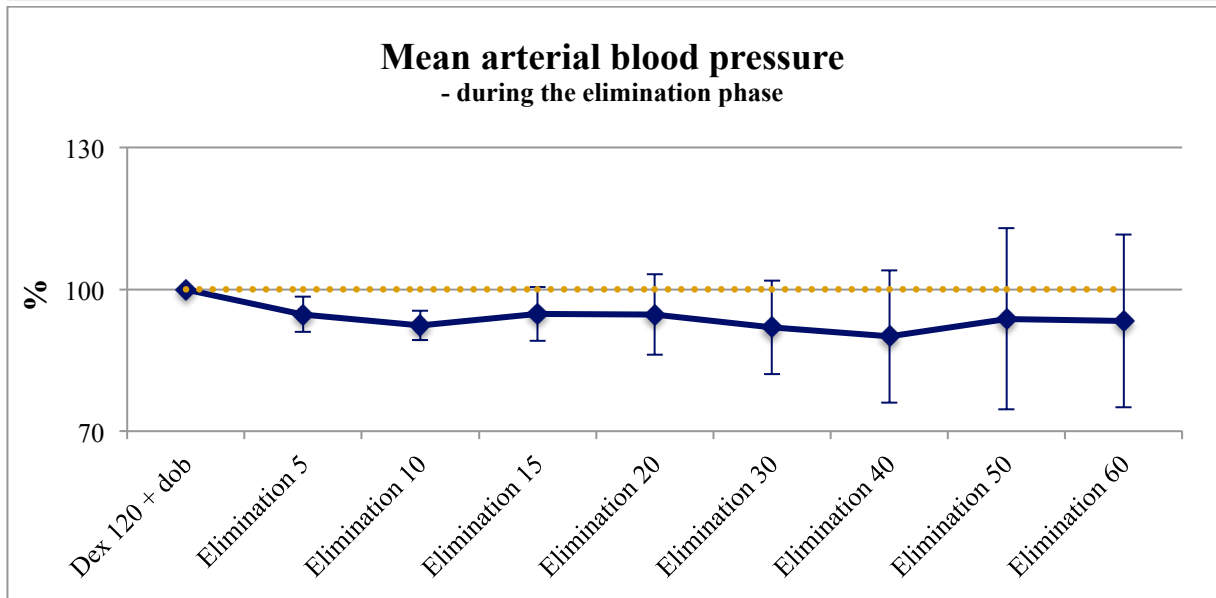
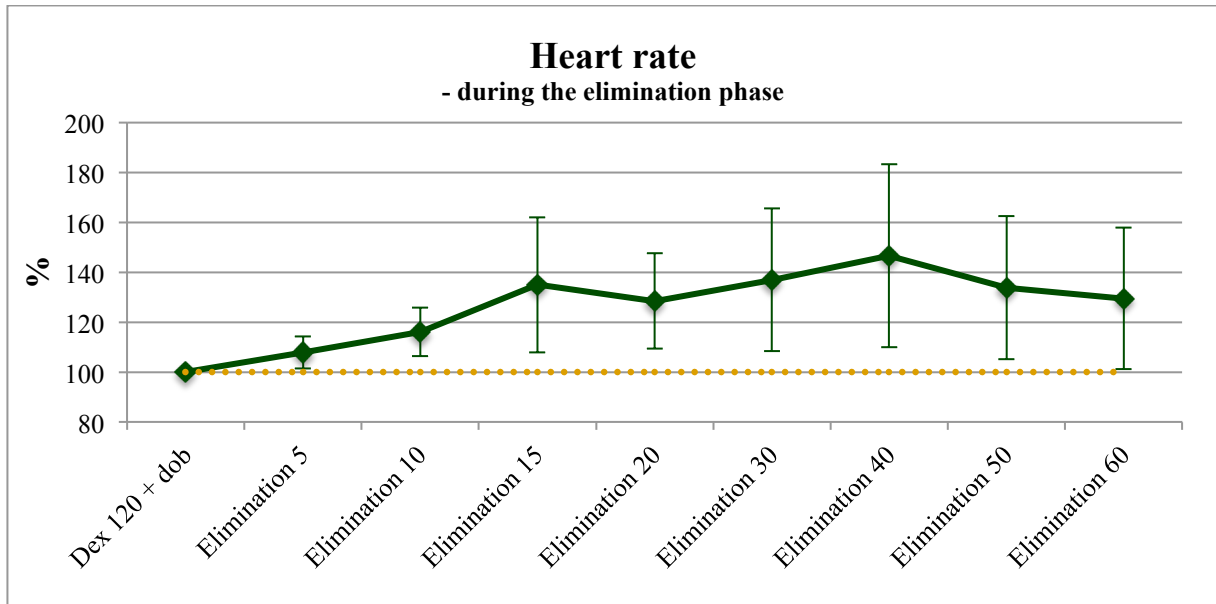


Figure 5a, 5b and 5c. Mean \pm SD of HR, MAP and CI after the dexmedetomidine CRI was disconnected, calculated in relative change with 100% at dex 120+dob.

Part 3) Isoflurane concentration

A dexmedetomidine CRI of $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ did not significantly decrease end-tidal isoflurane concentration (compared to *baseline 60*) during the anaesthesia.

The horses showed an individual difference regarding the amount of isoflurane they needed in order to stay at an equivalent and ideal depth of anaesthesia (Figure 6b). A decrease in mean end-tidal isoflurane concentration over time was seen (Figure 6a) although the change was not significant.

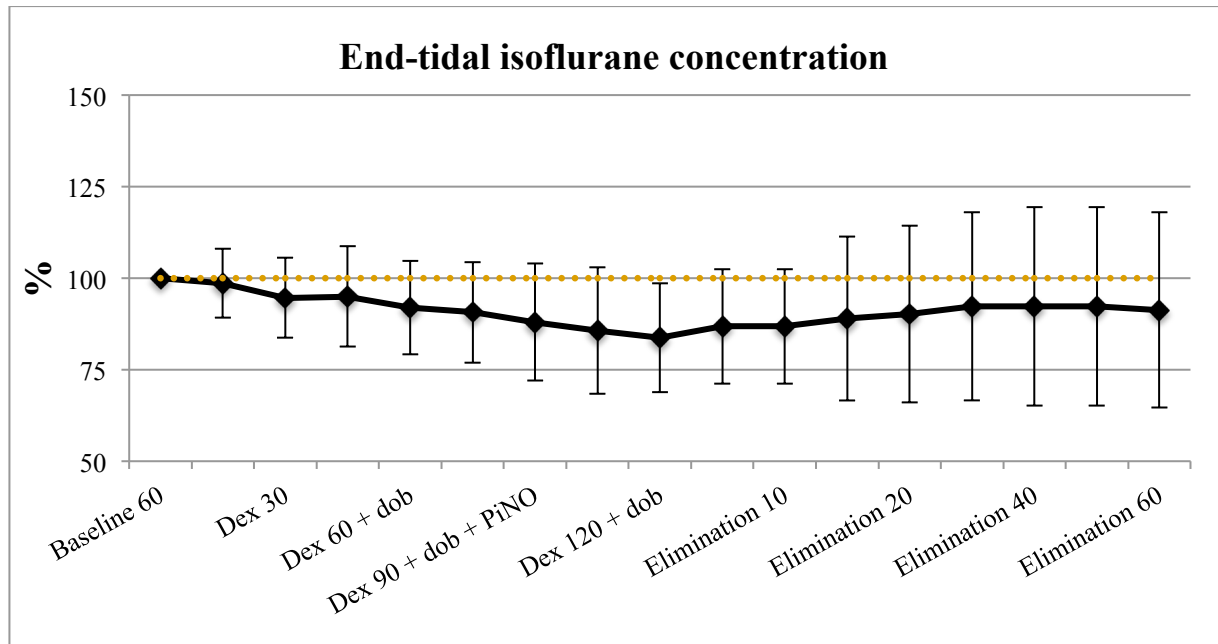


Figure 6a. Mean \pm SD values of end-tidal concentration of isoflurane during anaesthesia, calculated in relative change with a 100% at baseline 60.

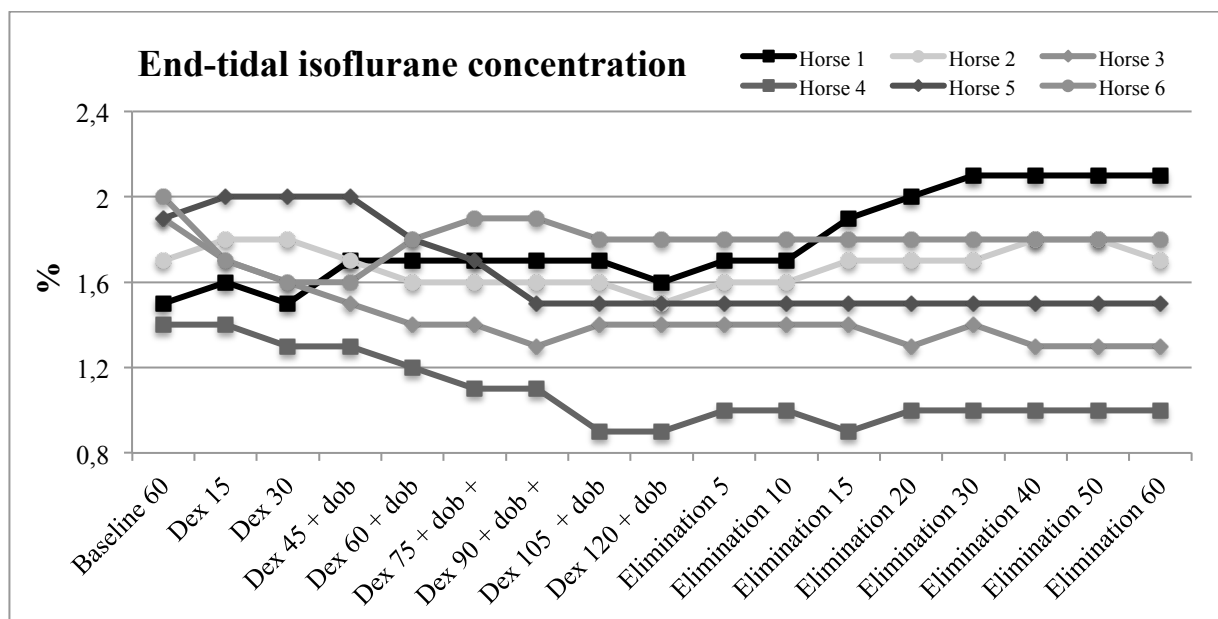


Figure 6b. Individual end-tidal isoflurane concentration during anaesthesia.

Part 4) Arterial oxygenation

Horse 1 received PiNO for 30 minutes before dobutamine was administered during the dexmedetomidine CRI. The following horses received PiNO for 30 minutes during the combined dexmedetomidine and dobutamine CRI.

The reason for the change in order was to optimise blood flow and increase the blood pressure before PiNO was administered in order for the nitric oxide to have full effect.

Table 6. Mean \pm SD of oxygenation parameters during anaesthesia

	PaO₂ (kPa)	SaO₂ (%)	PAPM (mmHg)
Baseline 60	8.6 \pm 3.1 n = 6	88 \pm 8 n = 6	16 \pm 4 n = 6
Dex 30	6.3 \pm 1.2 \downarrow n = 6	80 \pm 9 \downarrow n = 6	16 \pm 3 \leftrightarrow n = 6
Dex 60 + dob	8.0 \pm 1.7 \leftrightarrow n = 5	85 \pm 7 \leftrightarrow n = 5	19 \pm 4 \uparrow n = 5
Dex 75 + dob + PiNO	15.4 \pm 7.2 \uparrow n = 6	94 \pm 2 \uparrow n = 6	19 \pm 4 \leftrightarrow n = 6
Dex 90 + dob + PiNO	20.0 \pm 8.2 \uparrow n = 6	96 \pm 1 \uparrow n = 6	19 \pm 7 \leftrightarrow n = 6
Dex 120 + dob	14.5 \pm 6.3 \uparrow n = 6	94 \pm 2 \uparrow n = 6	24 \pm 5 \uparrow n = 6
Elimination 60	13.6 \pm 6.3 \leftrightarrow n = 6	94 \pm 2 \leftrightarrow n = 6	21 \pm 6 \leftrightarrow n = 6

\downarrow = Significant decrease compared to baseline 60.

\uparrow = Significant increase compared to baseline 60.

\leftrightarrow = No significant increase/decrease compared to baseline 60.

Partial pressure of arterial oxygen and oxygen saturation in arterial blood slowly decreased after the horses were anaesthetised (Figure 7a and 8a). There was no change in the arterial oxygen parameters during the dobutamine infusion.

A pronounced increase in PaO₂ and SaO₂ was measured when PiNO was administered in all six horses (Figure 7b and 8b). Even though PiNO was only administered for 30 minutes during the anaesthesia the partial pressure and oxygen saturation in arterial blood remained high during the entire anaesthesia (Table 6).

Arterial oxygen saturation

There was a significant decrease in oxygen saturation (SaO_2) in arterial blood during the dexmedetomidine CRI ($p < 0.05$ at *dex 30* compared to *baseline 60*). At *dex 60+dob* there was no significant change. The oxygen saturation increased significantly during PiNO ($p < 0.05$ at *dex 75+dob+PiNO*, *dex 90+dob+PiNO* and *dex 120+dob* compared to *baseline 60*).

Also, oxygen saturation increased significantly during PiNO compared to the measurement before PiNO was commenced ($p < 0.05$ at *dex 75+dob+PiNO* and *dex 90+dob+PiNO* compared to *dex 60+dob*).

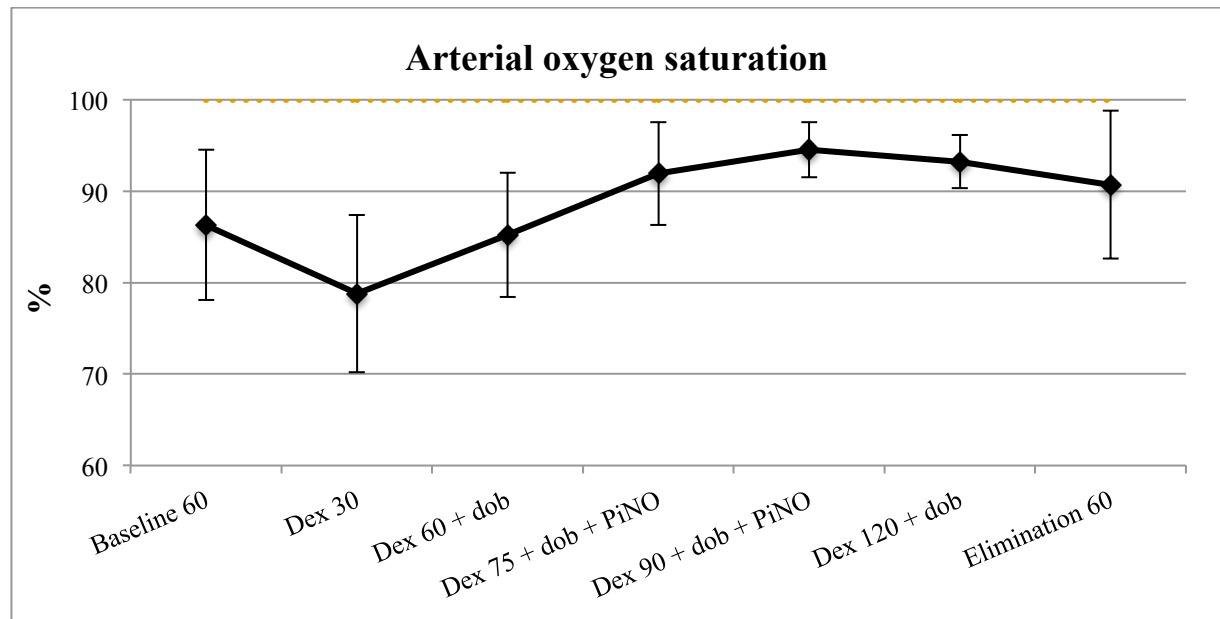


Figure 7a. Mean \pm SD of oxygen saturation in arterial blood during anaesthesia.

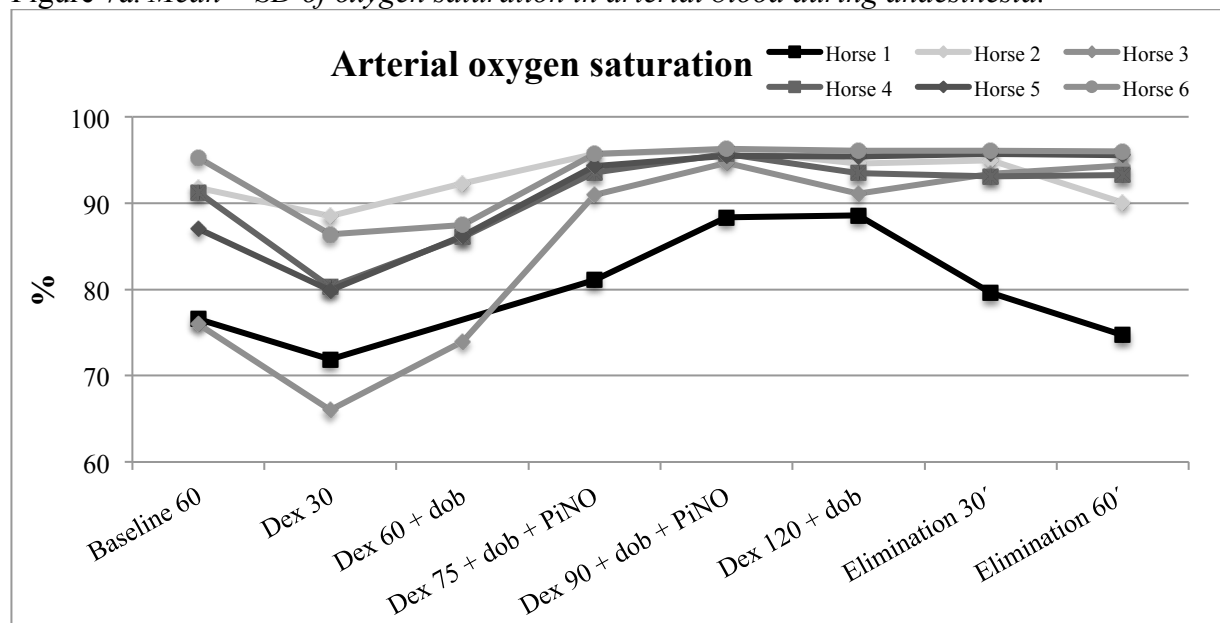


Figure 7b. Individual oxygen saturation in arterial blood during anaesthesia.

Partial pressure of arterial oxygen

There was a significant decrease in partial pressure of arterial oxygen (PaO_2) during the dexmedetomidine CRI ($p < 0.05$ at *dex 30* compared to *baseline 60*). At *dex 60+dob* there was no significant change. The partial pressure increased significantly during PiNO ($p < 0.05$ at *dex 75+dob+PiNO*, *dex 90+dob+PiNO* and *dex 120+dob* compared to *baseline 60*).

Also, PaO_2 increased significantly during PiNO compared to the measurement before PiNO was commenced ($p < 0.05$ at *dex 75+dob+PiNO* and *dex 90+dob+PiNO* compared to *dex 60+dob*).

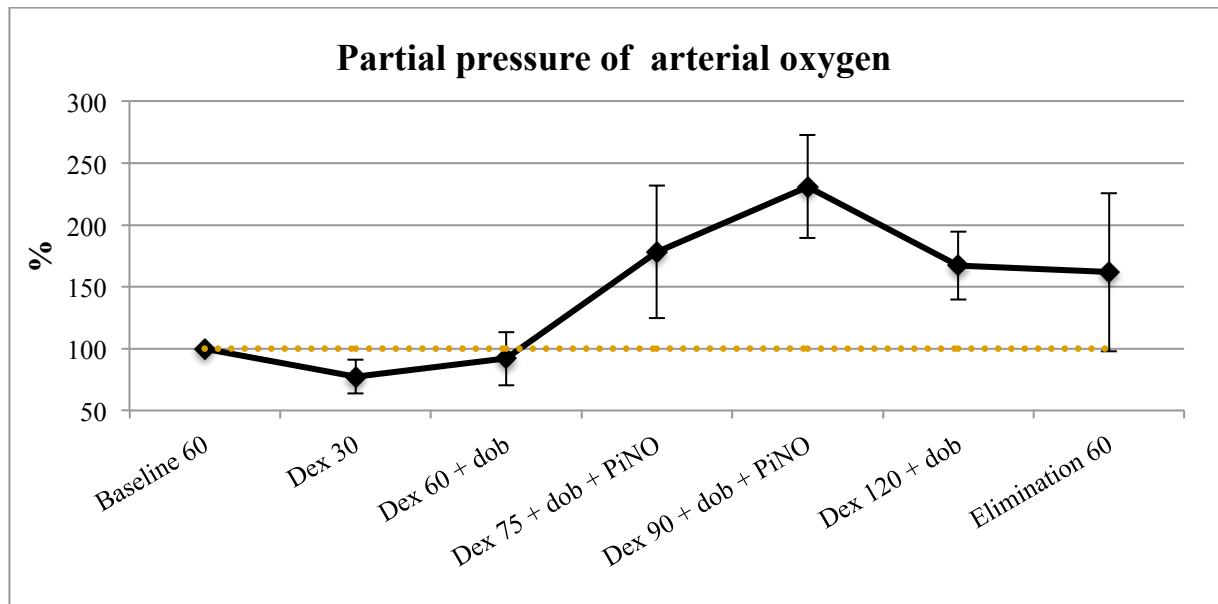


Figure 8a. Mean \pm SD of partial pressure of oxygen in arterial blood during anaesthesia, calculated in relative change with a 100% at baseline 60.

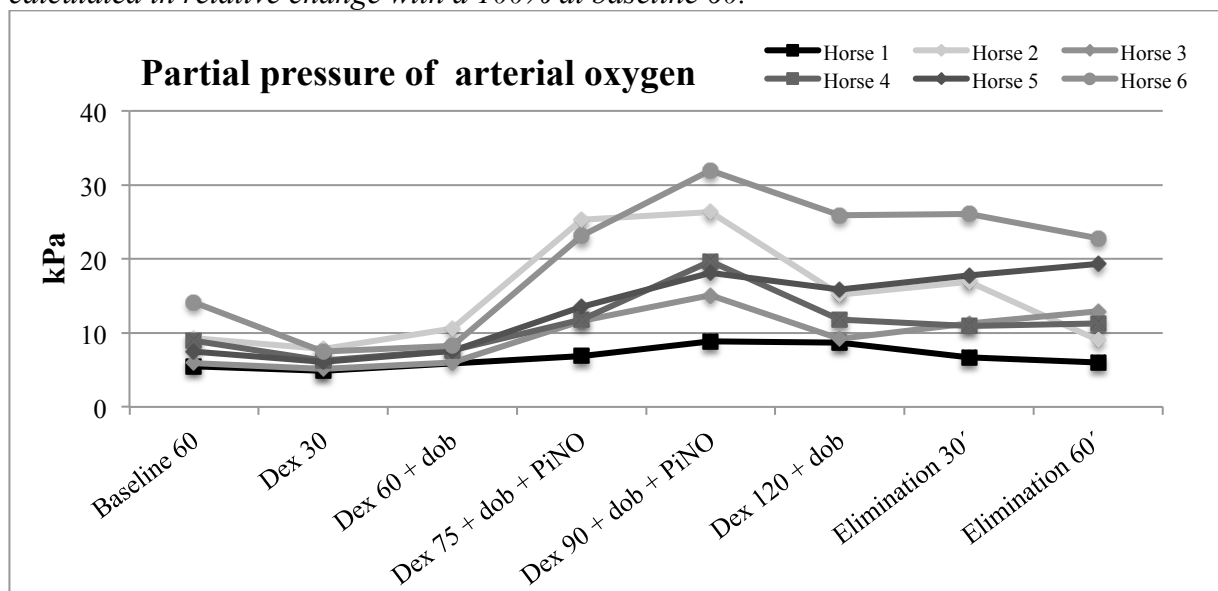


Figure 8b. Individual partial pressure of oxygen in arterial blood during anaesthesia.

DISCUSSION

The major findings in the present study were that an intravenous infusion of $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ dexmedetomidine during inhalation anaesthesia resulted in plasma concentration above the previously described threshold of $0.15 \text{ ng}\cdot\text{mL}^{-1}$ determined in conscious horses. Including dexmedetomidine CRI during inhalation anaesthesia resulted in decreased heart rate, cardiac index and arterial oxygenation while arterial blood pressure increased. Adding a dobutamine CRI during the dexmedetomidine CRI improved cardiac index and mean arterial blood pressure. The end-tidal isoflurane concentration could not be reduced during the dexmedetomidine CRI however no surgery was performed in this experimental study. Finally, introducing PiNO during on-going dexmedetomidine and dobutamine CRI improved arterial oxygenation and oxygen delivery.

No reported previous study has analysed pharmacodynamic effects of a dexmedetomidine CRI after disconnecting the CRI during ongoing inhalation anaesthesia. In the present study physiological parameters and dexmedetomidine concentration in plasma were analysed during 60 minutes after the disconnection of the dexmedetomidine CRI.

The major limitation of the study was that a blinded study with a control group of horses would have been preferable but that was not feasible with the limited number of horses available in the present study.

Another limitation in the present study was the non-objective method of evaluating the anaesthetic depth in the horses. Looking at ocular parameters is a rather rough method of assessing anaesthetic depth and small differences in isoflurane requirements may easily go undetected. Introduction of a flow-chart in order to more correctly assess the anaesthetic depth probably needs to be introduced if dexmedetomidine was to be included in the anaesthesia protocol.

Dexmedetomidine plasma concentration

The dose $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ has been used in several studies and one reason to choose this dose was to be able to compare the results in the present study with the results reported in previous studies (Gozalo-Marcilla *et al.*, 2010; Gozalo-Marcilla *et al.*, 2012; Gozalo-Marcilla *et al.*, 2012a; Gozalo-Marcilla *et al.*, 2013b; Gozalo-Marcilla *et al.*, 2014; Risberg *et al.*, 2016; Sacks *et al.*, 2017).

In the present study we assumed the nociceptive threshold to be $0.15 \text{ ng}\cdot\text{mL}^{-1}$, a concentration Risberg *et al.*, (2014) reported to fulfill all of the nociceptive parameters analysed in their study, although some nociceptive qualities were evident even at plasma concentrations $<0.02 \text{ ng}\cdot\text{mL}^{-1}$ (the lowest detectable limit of dexmedetomidine in plasma). Their study was not blinded, which would have been preferable. Also, their study was performed on conscious horses, and the nociceptive threshold could differ between conscious and anaesthetised horses. However, there is no equivalent study on nociception during dexmedetomidine CRI on anaesthetised horses yet.

A significant individual difference in plasma concentration after administration of dexmedetomidine (both after a CRI and after a single bolus dose) has been reported in conscious horses (Risberg *et al.*, 2014; Ranheim *et al.*, 2015). During general anaesthesia, dexmedetomidine plasma concentrations are much less variable between the individual horses (Risberg *et al.*, 2016; Hopster *et al.*, 2014). In the present study, the individual variation of the dexmedetomidine plasma concentration was relatively small.

In the present study, the plasma dexmedetomidine concentration seen in all horses 30 minutes after the start of the $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ dexmedetomidine CRI, was higher than the concentration in standing horses receiving a $8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ dexmedetomidine CRI 30 minutes after the start of the CRI (Ranheim *et al.*, 2015). The difference is striking, demonstrating possible differences in distribution and elimination in conscious versus anaesthetised horses. In standing horses administered a dexmedetomidine CRI at a rate of $2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ (Risberg *et al.*, 2014), the mean plasma concentration of dexmedetomidine was ten times lower than in anaesthetised horses receiving $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$. This indicates that the pharmacokinetic profile differs in awake and anaesthetised horses, most likely due to reduced CO caused by co-administration of other anaesthetics and sedatives, probably interfering with the dexmedetomidine elimination (Ranheim *et al.*, 2015).

It has been discussed in other studies (Gozalo-Marcilla *et al.*, 2010) that a loading dose of dexmedetomidine should be included in the protocol before the CRI is started in order to rapidly achieve an adequate plasma concentration, however in the present study we could show that no bolus dose was required under anaesthesia circumstances. Dexmedetomidine quickly reached a significant plasma concentration after the start of the chosen CRI, despite a relatively slow distribution of dexmedetomidine. The concentration rapidly reached the nociceptive threshold (with a mean concentration of 0.85 ng/mL 15 minutes after the start of the CRI). In two horses the plasma concentration was $<0.15 \text{ ng}\cdot\text{mL}^{-1}$ 30-40 minutes after disconnection of the CRI, but the remaining four horses had concentration $>0.15 \text{ ng}\cdot\text{mL}^{-1}$ still after 60 minutes.

Circulation

It cannot be ruled out that other drugs used during premedication, induction and anaesthesia may have influenced the physiological effects seen in the present study. Acepromazine decreases the vascular tone, produces hypotension but might enhance blood flow. Acepromazine is used routinely as a premedication before equine anaesthesia and has shown to reduce the mortality rate in horses when being used as premedication before anaesthesia (Doherty *et al.*, 2006). Dobutamine is regularly administered during anaesthesia in order to control blood pressure. Most likely did this influence our results as dobutamine improves cardiac performance (Kalchofner *et al.*, 2009). Since thiopental is reported to cause an increased heart rate, decreased contractility and vasodilatation, thus leading to hypotension and decreased pre-load, its administration could also have affected the results. Guaifenesin has minimal cardiovascular effects and should probably not influence the results in the present study. Neither acepromazine, thiopental, guaifenesin nor isoflurane provide any analgesic properties (Doherty *et al.*, 2006).

In many of the previous studies, our study included, the cardiovascular changes seen with dexmedetomidine were short-lived and mainly occurred in the initial phase at the start of the dexmedetomidine CRI, even though dexmedetomidine potentially had not reached steady state in plasma concentration at that time point.

One study (Gozalo-Marcilla *et al.*, 2010), showed no significant difference between administrations of a 1 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ CRI versus 1.75 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$, indicating that there probably is a ceiling effect regarding the side effects of dexmedetomidine. The analgesic and sedative effects caused by dexmedetomidine have an upper limit, meaning that increasing the dose will not provide more sedation or analgesia, only extend the duration of the effects (and side effects). The results from this study indicates that the expected cardiovascular changes occur even at a low dexmedetomidine concentration and it is possible that increasing the CRI will not worsen the cardiovascular changes (Gozalo-Marcilla *et al.*, 2010).

The cardiovascular changes seen in the present study were consistent with results seen in previous studies. (Bettschart-Wolfensberger *et al.*, 2005; Rezende *et al.*, 2015). The cardiovascular changes remained within clinically acceptable levels but one has to bear in mind that cardiac index and arterial blood pressure was supported with dobutamine infusion and fluid therapy.

Heart rate

In the present study, the heart rate decreased in all six horses after the start of dexmedetomidine CRI with a mean reduction of 12% and 15% at 15 and 30 minutes respectively after the start of the dexmedetomidine CRI. The result was expected and consisting with the results from similar studies (Gozalo-Marcilla *et al.*, 2010; Gozalo-Marcilla *et al.*, 2012; Gozalo-Marcilla *et al.*, 2013a; Gozalo-Marcilla *et al.*, 2014; Risberg *et al.*, 2016; Hopster *et al.*, 2014). The decrease in heart rate was significantly lower during the first 60 minutes after the start of the dexmedetomidine CRI, compared to baseline. Dexmedetomidine has been reported to induce bradycardia both by central mechanisms and as a reflex secondary to the initial vasoconstriction caused by the activation of α_{2B} -adrenoceptors (Maze & Tranquilli, 1991).

An interesting and surprising finding in the present study was the rapid increase in heart rate during the elimination phase of dexmedetomidine. Heart rate increased dramatically in all horses after the disconnection of the dexmedetomidine CRI and reached the highest value 40 minutes after disconnection of the CRI. This finding is not described in the literature before, probably because no previous study as analysed physiological parameters after disconnection of the dexmedetomidine CRI during ongoing anaesthesia. The increased heart rate could be due to a compensatory mechanism induced by vasodilatation, once the vasoconstrictor effect of dexmedetomidine wears off. Another possibility could be a release of the inhibition of the sympathetic nervous system caused by a rapid clearance of the already low plasma dexmedetomidine level resulting in a rapid norepinephrine release (Gozalo-Marcilla *et al.*, 2010).

Arterial blood pressure (MAP)

Arterial blood pressure increased immediately after the start of the dexmedetomidine CRI. The increase was, undoubtedly, caused by vasoconstriction. A vasoconstriction on endothelial smooth muscle leads to an increase in SVR and hence an increased arterial blood pressure (Maze & Tranquilli, 1991). In line with previous studies, the increase was short-lived; in the present study the increase was only significant during the first 15 minutes after the start of the CRI.

A dexmedetomidine CRI during isoflurane anaesthesia may be used to improve the arterial blood pressure by vasoconstriction. However, since isoflurane has the opposite effect on the peripheral vascular tone, by inducing vasodilatation, dose dependent impairment in blood pressure and hypotension are common complications during equine anaesthesia (Lee, 2006).

As expected, MAP increased rapidly when the horses received dobutamine and after that point it is difficult to analyse what effect dexmedetomidine may or may not have had on MAP. Nevertheless, studies have showed that horses receiving a medetomidine CRI need significantly less dobutamine during anaesthesia in order to support MAP (Kempshen *et al.*, 2012).

Interestingly, no change in MAP was measured during the elimination phase, although the heart rate significantly increased. Even though no significant change was found MAP could be regulated by a slight decrease in stroke volume or SVR, or in both at the same time.

Cardiac index

In line with most previous studies, a significant reduction in cardiac index when administrating dexmedetomidine was expected. However, no significant change in cardiac index was seen in the present study, which is in line with the findings by Gozalo-Marcilla *et al.* (2012). The result could have been caused by a deviating value from one of the horses. All horses but one showed a decrease in cardiac index after the dexmedetomidine CRI was started but cardiac index increased in one horse in this study.

The decrease in CI described in the literature is probably a result of the low HR. The reduced CI is most likely the reason to the impaired oxygen delivery described during the dexmedetomidine CRI. However, the decreased CI will probably not cause any issues in a clinical situation because the blood pressure can be preserved with infusion of dobutamine.

In several of the previous studies the difference in CI between horses receiving dexmedetomidine and horses compared to a control groups was not significant. At the time when those studies were performed, the pharmacokinetics of dexmedetomidine in horses was not known. The pharmacokinetic results from the study by Risberg *et al.* 2016 indicate that the comparison of CI with a control group in numerous of the studies (Gozalo-Marcilla *et al.*, 2010, 2012; Gozalo-Marcilla *et al.*, 2013a) probably was influenced by the premedication since the control groups also received dexmedetomidine as premedication.

Isoflurane concentration

As seen in previous studies there was a considerable individual difference in isoflurane concentration between the horses. In the present study no significant change in end-tidal isoflurane concentration (EtISO) during or after the $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ dexmedetomidine CRI could be shown. It is possible that no reduction was seen because the horses were not subjected to any stimuli.

It is fair to assume that one reason to why dexmedetomidine (and other potent α_2 -agonists) have been shown to decrease the concentration of required inhalation anaesthetics is due to its analgesic properties. Isoflurane and other inhalation anaesthetics have none (or very poor) analgesic effects. During surgeries, it is therefore, normally, not possible to reduce the anaesthetic depth without administering analgesics (Gozalo-Marcilla, 2013c). It is possible that a reduction of isoflurane concentration in the present study would have been possible if the included horses were subjected to painful stimuli, or rather more likely, we would have seen an increased need for higher isoflurane concentration in a control group of horses.

The results regarding the concentration of inhalation anaesthetics during a dexmedetomidine CRI and whether it is possible or not to lower the concentration under the influence of dexmedetomidine are contradictive. One experimental study showed lower isoflurane concentration needed during anaesthesia with a dexmedetomidine CRI compared to a control group (Risberg *et al.*, 2016). Gozalo-Marcilla *et al.* (2013b) could not show an overall difference in EtISO in horses receiving morphine versus dexmedetomidine during the first 60 minutes of surgery, although the horses receiving dexmedetomidine gradually required lower concentration of isoflurane and the difference became significant after 60 minutes. The horses receiving dexmedetomidine in that study also spent a longer time in the "ideal" depth of anaesthesia with fewer alterations in the isoflurane concentration compared to the horses receiving morphine.

In the study from 2012 by Gozalo-Marcilla *et al.*, where dexmedetomidine CRI failed to reduce the dose of isoflurane, one could argue that it could be because it was difficult to correctly assess the anaesthetic depth. One study showed that horses anaesthetised with a medetomidine CRI appeared more lightly in the anaesthetic depth (spontaneous blinking, tearing and other ocular parameters are often seen) even though they are in an "ideal surgical anaesthetic depth" (HR and blood pressure are stable and no movements occur) (Kalchofner *et al.*, 2006). Therefore, horses receiving a dexmedetomidine CRI may falsely be assessed as being in a light anaesthetic depth by the anaesthetist (Gozalo-Marcilla *et al.*, 2012). Gozalo-Marcilla *et al.* (2013b) used a flow-chart in their study in order to more correctly assess the anaesthetic depth. It has been suggested that arterial blood pressure and other physiological parameters could be more widely used, in addition to ocular parameters, to prevent horses receiving α_2 -agonists to be too deeply anaesthetised during surgery. It is also worth mentioning that in both of the above described clinical studies (Gozalo-Marcilla *et al.*, 2012; Gozalo-Marcilla *et al.*, 2013b), the horses in the control group also received dexmedetomidine as premedication, which could have affected the results.

Arterial oxygenation

The positive effect of PiNO on the arterial oxygenation is well described in previous studies, both under experimental and clinical circumstances (Grubb *et al.*, 2008; Grubb *et al.*, 2012b; Nyman *et al.*, 2012; Grubb *et al.*, 2013; Wiklund, 2014). In the present study the aim was to analyse whether PiNO would work well together with a dexmedetomidine CRI.

Both isoflurane and dexmedetomidine have an inhibitory effect on cardiac index. Also intermittent positive pressure ventilation (IPPV) results in a decreased cardiac index compared to spontaneously breathing horses. This because IPPV produces high intrathoracic pressure, which leads to a decreased venous blood return to the heart (Kalchofner *et al.*, 2009), by compression of the vena cava (Auckburally & Nyman, 2017). Impaired cardiac index can lead to secondary hypoxemia since a smaller amount of the blood flow will be oxygenated (Grubb, 2012a).

As expected, the arterial oxygenation (both partial pressure of arterial oxygen and arterial oxygen saturation) was low initially during anaesthesia, probably due to the factors described above. Gozalo-Marcilla *et al.* (2012) showed that horses receiving a dexmedetomidine CRI during general anaesthesia had significantly lower PaO₂ compared to the horses receiving a saline CRI. All of the six horses in the present study developed hypoxemia (PaO₂ < 8.0 kPa) 30 minutes after the dexmedetomidine CRI was started (two of the horses showed hypoxemia already at baseline). As seen in previous studies (Grubb *et al.*, 2008; Grubb *et al.*, 2012b; Nyman *et al.*, 2012; Grubb *et al.*, 2013; Wiklund, 2014) PiNO had a remarkable effect on PaO₂ and SaO₂. In the present study, PaO₂ increased more than 200% and SaO₂ was well above 90% during the treatment.

Another finding was that horse 1 did not show the same degree of improvement after administration of PiNO as the other horses did (when receiving PiNO horse 1 increased PaO₂ with 60 % compared to baseline, in comparison with the rest of the horses that showed a mean increase of 140 %). This is most likely due to the fact that horse 1 did not receive dobutamine prior to PiNO, and therefore it is possible that cardiac index was too low to improve the perfusion distribution of well aerated lung regions. Thirty minutes later when also dobutamine was added, a more distinct increase in PaO₂ was seen in this horse.

In line with previous studies the effects of PiNO continued for approximately 30 minutes after termination of PiNO.

CONCLUSIONS

In conclusion, the present study showed that a $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ dexmedetomidine CRI during inhalation anaesthesia resulted in a plasma concentration well over the previously described nociceptive threshold ($0.15 \text{ ng}\cdot\text{mL}^{-1}$). The significant cardiovascular effects caused by the dexmedetomidine CRI included a decrease in heart rate and an increase in mean arterial blood pressure. These effects were short-lived and within clinically acceptable levels.

It was not possible to reduce the isoflurane concentration in the current experimental study possibly because it was carried out without painful stimuli. Most likely is the expected analgesic effect of dexmedetomidine CRI difficult to assess without any surgical stimuli.

The study also shows that it was possible to treat both hypotension and hypoxemia with dobutamine and PiNO, respectively.

Future studies are encouraged to evaluate the effect of dexmedetomidine during equine surgery and the following recovery period.

POPULÄRVETENSKAPLIG BESKRIVNING

Detta var en experimentell studie som utfördes på universitetsdjursjukhusets hästklinik i Uppsala. Studien inkluderade sex hästar av varierande ras, ålder och kön. Hästarna sövdes på kliniken och vidhölls i narkos med narkosgasen isofluran. Målet med studien var att utvärdera hur hästarna påverkades av att lägga till dexmedetomidin, en substans med både lugnande och smärtstillande egenskaper, under narkosen.

Narkos på häst är ett riskfyllt moment. Hästar drabbas lätt av blodtrycksfall och dålig syresättning när de är under narkos, mycket beroende på att de är placerade antingen på sidan eller på rygg vilket skapar ett högt tryck på lungorna. Den vanligaste metoden är att hästar sövs med narkosgas som dock oftast ger negativa effekter på cirkulation och andning. Det är därför eftersträvansvärt att hålla koncentrationen av inandad narkosgas så låg som möjligt men utan att riskera att hästen hamnar för ytligt i narkosen. För att undvika detta utförs flera studier för att hitta alternativ för att göra narkosen mer säker och minska risken för komplikationer.

Den grupp av sederande (lugnande) läkemedel som används inom veterinärmedicinen är huvudsakligen så kallade alfa2-agonister, vilka också har smärtstillande egenskaper. Till den gruppen räknas även dexmedetomidin. Det är den mest potenta alfa2-agonisten och har i tidigare studier visat sig vara den alfa2-agonist som finns kvar kortast tid i kroppen efter en injektion. Det är en eftertraktansvärd egenskap, dels genom att det i teorin snabbt går att ändra graden av sedering genom att justera dosen, dels blir biverkningsprofilen mindre uttalad. Dexmedetomidin har visat sig ge samma biverkningar som andra alfa2-agonister men effekterna blir mer kortlivade.

Läkemedlet kan dels ges som engångsdos intravenöst (i blodet) eller som ett kontinuerligt dropp/infusion (ett så kallat CRI) intravenöst. Dexmedetomidin har under en längre tid använts till hund och katt men substansen är relativt ny inom hästmedicinen. Den första studien där dexmedetomidin gavs till hästar genom ett CRI var 2005 och sedan dess har ett antal studier gjorts inom området, både där dexmedetomidin getts som ett komplement under narkos och vid stående ingrepp på vakna hästar. Dessa studier har visat att genom att administrera dexmedetomidin under narkos kan koncentrationen narkosgas sänkas, troligtvis genom dexmedetomidins smärtstillande egenskaper.

Målet med denna studie var att studera huruvida koncentrationen isofluran kunde minskas under narkosen och hur dexmedetomidin påverkade hästarnas cirkulation. Ytterligare ett mål var att studera hur koncentrationen dexmedetomidin i blodet tedde sig samt hur syresättningen påverkades då hästarna samtidigt erhöll dexmedetomidin och pulsat inhalerat kväveoxid (PiNO).

Hästarna sövdes och kopplades upp på narkosgas i operationsrummet. I en timme låg de enbart på narkosgas för att stabilisera sig och uppnå ett så kallat baseline. Efter 60 minuter startades ett CRI med dexmedetomidin med en koncentration på $1.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ (en koncentration som använts i flera tidigare studier).

Efter 30 minuter adderades en infusion med ett blodtryckshöjande läkemedel (dobutamin), vilket är en substans som används rutinmässigt under kliniska omständigheter för att hålla hästens blodtryck på en bra nivå under narkos. Ytterligare 30 minuter in i narkosen fick hästarna kväveoxid under en halvtimme, en substans som stimulerar respirationen och förbättrar syresättningen. När kväveoxiden stängdes av, låg hästarna kvar på infusion med dexmedetomidin och dobutamin i ytterligare en halvtimme innan infusionen med dexmedetomidin stängdes av. En timme senare avlivades hästarna på operationsbordet.

Under hela experimentet togs blodprover efter ett förbestämt schema, dels för att analysera blodgaser och dels för att kunna analysera koncentrationen dexmedetomidin i blodet. Kontinuerligt utlästes och analyserades även olika cirkulatoriska och respiratoriska parametrar (bland annat hjärtfrekvens, artärblodtryck och hjärtminutvolym) samt koncentration isofluran.

Resultaten sammanställdes och statistiska analyser genomfördes. De sex hästarna inkluderade i vår studie utgör enbart ett stickprov av den sanna hästpopulationen. I denna studie har statistisk signifikans räknats vid $p < 0.05$ – det vill säga att sannolikheten att ett resultat (av signifikant värde) i vår studie med 95 % sannolikhet kommer överensstämma med övriga hästpopulationen.

Isoflurankoncentrationen var inte signifikant lägre efter att hästarna gavs dexmedetomidin jämfört med baseline (innan infusionen med dexmedetomidin startades). Däremot minskade medelvärdet av isoflurankoncentration men skillnaden var inte tillräckligt stor för att vara signifikant.

Hjärtfrekvensen minskade och denna förändring var signifikant den första timmen efter att dexmedetomidin började ges. Medelblodtrycket ökade signifikant de första 15 minuterna efter att dexmedetomidin börjades ges. Ingen signifikant skillnad kunde ses i hjärtminutvolym. Minskad hjärtfrekvens och ökat blodtryck är kända cirkulatoriska effekter som ses vid administrering av en alfa2-agonist. Förändringarna var dock kortlivade (liknande som setts i andra studier) och de cirkulatoriska värdena höll sig hela tiden inom en kliniskt acceptabel nivå.

I andra studier har hästarna innan infusionen med dexmedetomidin erhållit en startdos dexmedetomidin, antingen som lugnande substans innan kastningen eller precis innan infusionen med dexmedetomidin startats under narkosen (en stötdos för att snabbt nå en hög koncentration i blodet). Denna studie var den första studien där hästarna inte erhållit dexmedetomidin innan infusionen påbörjades. Detta för att vi ville utvärdera huruvida en stötdos verkligen var nödvändig för att nå över den så kallade nociceptiva tröskeln (den koncentration dexmedetomidin i blodet som krävs för full smärtlindring vid smärtsamma stimuli) och dels för att vi inte ville att en tidigare given stötdos av dexmedetomidin skulle påverka resultaten. Vi kunde i vår studie visa att en loading dose inte krävs, trots den låga koncentrationen dexmedetomidin i infusionen i denna studie steg koncentrationen i blodet snabbt. Efter att infusionen med dexmedetomidin stängdes av sjönk koncentrationen på ett förväntat sätt. Sextio minuter efter avslutandet av infusionen låg koncentrationen dexmedetomidin i blodet i medeltal på 0,15 ng/mL (den koncentration som i en tidigare studie visat sig motsvara den nociceptiva tröskeln).

Slutsatsen var att de cirkulatoriska förändringarna orsakade av dexmedetomidin under narkosen var milda och kortvariga. Tyvärr sågs ingen reduktion i isoflurankoncentrationen under de rådande omständigheterna men det kan förklaras genom att hästarna inte utsattes för något stimuli (som de gör under operationer). I denna experimentella studie kom inte dexmedetomidins smärtstillande egenskaper till uttryck. Vi kunde också se att de vanligaste narkos-komplikationerna (blodtrycksfall och försämrad syresättning) framgångsrikt kunde behandlas med dobutamin och PiNO.

Mer forskning krävs för att utvärdera hur dexmedetomidin skulle fungera under kliniska omständigheter.

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