



FACULTEIT DIERGENEESKUNDE  
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# **Diagnosis and treatment of cardiovascular depression in anaesthetized horses: new perspectives**

**Stijn Schauvliege**

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# LIST OF ABBREVIATIONS

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ABE	Actual base excess
AF	Atrial fibrillation
ARF	Acute renal failure
ATP	Adenosine triphosphate
AV	Atrioventricular
AVP	Arginine vasopressin
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CaO <sub>2</sub>	Arterial oxygen content
CEPEF	Confidential Enquiry into Perioperative Equine Fatalities
CHF	Congestive heart failure
CI	Cardiac index
CcO <sub>2</sub>	End-capillary pulmonary oxygen content
CRI	Constant rate infusion
CvO <sub>2</sub>	Venous oxygen content
Cv̄O <sub>2</sub>	Mixed venous oxygen content
CVP	Central venous pressure
DA <sub>1</sub> receptor	Dopamine 1 receptor
DA <sub>2</sub> receptor	Dopamine 2 receptor
DAG	Diacylglycerol
DAP	Diastolic arterial pressure
DO <sub>2</sub>	Oxygen delivery
DO <sub>2</sub> I	Oxygen delivery index
dP/dT	Rate of increase in left ventricular pressure
dP/dT <sub>max</sub>	Maximal rate of increase in left ventricular pressure
E	Enoximone
EC	Enoximone and calcium chloride
ED	Enoximone and dobutamine
ECG	Electrocardiogram
FE <sub>T</sub> Iso	End-tidal isoflurane concentration
FIO <sub>2</sub>	Inspiratory oxygen fraction
GTP	Guanosine triphosphate
Hb	Haemoglobin
HPV	Hypoxic pulmonary vasoconstriction
HR	Heart rate
IP <sub>3</sub>	Inositol triphosphate
IV	Intravenous(ly)
LAR	Large intestines
LiDCO	Lithium dilution cardiac output
MAP	Mean arterial pressure
N <sub>2</sub> O	Nitrous oxide
PaO <sub>2</sub>	Arterial oxygen tension
PAO <sub>2</sub>	Alveolar oxygen tension
P(A-a)O <sub>2</sub>	Alveolar to arterial oxygen tension gradient
PaCO <sub>2</sub>	Arterial carbon dioxide tension
PAP	Pulmonary artery pressure
PcO <sub>2</sub>	End-capillary pulmonary oxygen tension
PIO <sub>2</sub>	Oxygen tension in inspired air
PvO <sub>2</sub>	Venous oxygen tension
Pv̄O <sub>2</sub>	Mixed venous oxygen tension

PCV	Packed cell volume
PCWP	Pulmonary capillary wedge pressure
PDE	Phosphodiesterase
PE'CO <sub>2</sub>	End-tidal carbon dioxide partial pressure
PIP	Peak inspiratory pressure
PIP <sub>2</sub>	Phosphatidylinositol 4,5-biphosphate
Pmsf	Mean systemic filling pressure
PulseCO	Pulse contour analysis
PVR	Pulmonary vascular resistance
Q <sub>s</sub> /Q <sub>t</sub>	Degree of venous admixture
Q <sub>t</sub>	Cardiac output
Q <sub>tLiDCO</sub>	Cardiac output measured using the lithium dilution technique
Q <sub>tPulseCO</sub>	Cardiac output estimated using the pulse contour analysis technique
RAP	Right atrial pressure
RR	Respiratory rate
S	Saline
SAP	Systolic arterial pressure
SBC	Standard bicarbonate
SBE	Standard base excess
SA	Sinoatrial
SaO <sub>2</sub>	Arterial haemoglobin saturation with oxygen
S $\bar{c}$ O <sub>2</sub>	End-capillary pulmonary haemoglobin saturation with oxygen
SI	Stroke index
SMA	Small intestines
SO <sub>2</sub>	Haemoglobin saturation with oxygen
SR	Sarcoplasmic reticulum
SV	Stroke volume
SvO <sub>2</sub>	Venous haemoglobin saturation with oxygen
S $\bar{v}$ O <sub>2</sub>	Mixed venous haemoglobin saturation with oxygen
SVR	Systemic vascular resistance
SVR <sub>LiDCO</sub>	Systemic vascular resistance calculated from MAP, RAP and Q <sub>tLiDCO</sub>
SVR <sub>PulseCO</sub>	Systemic vascular resistance calculated from MAP, RAP and Q <sub>tPulseCO</sub>
tCO <sub>2</sub>	Total carbon dioxide content
TnI	Troponin-I
V <sub>D</sub> /V <sub>T</sub>	Alveolar dead space-to-tidal volume ratio
VO <sub>2</sub>	Oxygen consumption







"It is good to have an end to journey toward,  
but it is the journey that matters, in the end."

(U. Le Guin)



In horses, perioperative mortality rates are higher than in many other species. Reasons for this include their character, high body weight, and the frequent occurrence of severe ventilation-perfusion mismatching and cardiovascular depression during anaesthesia. Several of these factors cannot be altered substantially or are difficult to treat, but different approaches to treat cardiovascular depression are available. The first step is to confirm its presence. Clinical evaluation of the cardiovascular status and routine monitoring of heart rate and arterial blood pressure provide useful information, but do not allow assessment of cardiac output and vascular tone. An easily applicable and reliable method of measuring cardiac output would allow better evaluation of the cardiovascular status of each patient. Therefore, the first aim of this PhD thesis was to identify and evaluate possible alternative techniques to measure cardiac output in horses.

Once low cardiac output has been detected, inotropic drugs are often needed to normalize oxygen delivery in anaesthetized horses. The second major aim of this PhD thesis was to evaluate alternative drugs with inotropic properties that could be used in horses under clinical conditions. The human and equine literature was reviewed to identify an inotropic drug which had received little attention but appeared promising for use during equine anaesthesia. Subsequently, the effectiveness and safety of this drug were evaluated, both under experimental conditions and in clinical cases, alone or combined with other commonly used drugs.



# CHAPTER 1

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## **Inadequate oxygen delivery in anaesthetized horses: consequences, aetiology, diagnosis and treatment**





## **Cardiovascular depression as a cause of inadequate tissue oxygen supply during equine anaesthesia: diagnostic aids and principles of treatment**



### **SUMMARY**

**Anaesthesia-related mortality is higher in horses compared to other species and is often attributable to inadequate tissue oxygenation, resulting from the effects of anaesthetic drugs, recumbency and other predisposing factors. More specifically, arterial oxygen content, arterial blood pressure and cardiac output are often low during equine anaesthesia. Diagnostic techniques routinely available to the equine anaesthetist for detecting cardiovascular depression include subjective clinical assessment and measurement of arterial blood pressure. An easily applicable, continuous, reliable and cheap method for measuring cardiac output would allow a better estimation of oxygen delivery. Pulse contour analysis appears promising in this respect. Once cardiovascular depression has been diagnosed, an appropriate treatment should be initiated, including reduction of anaesthetic depth, fluid therapy and use of cardiovascular stimulant drugs.**

# Diagnosis & treatment of cardiovascular depression

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## Introduction

The mortality rate associated with general anaesthesia and/or surgery in horses was assessed by different groups of researchers, but results from these studies are variable and usually difficult to compare. Although death should be a clear-cut outcome that can be assessed objectively, it is more difficult to determine whether death is related to or induced by anaesthesia, or rather the result of underlying diseases or surgical complications. Perioperative mortality was reported to be 0.8 % in horses undergoing different types of surgery (Tevik 1983), 0.63 % in horses undergoing elective surgery, with only 0.08 % directly attributable to anaesthesia (Mee et al. 1998a), 0.68 % in horses undergoing orthopaedic surgery, radiography or minor soft tissue surgery (Young & Taylor 1993) and 31.4 % in horses undergoing emergency procedures (Mee et al. 1998b). More recently, Bidwell et al. (2007) reported a comparatively low mortality rate in horses undergoing surgery in a private referral practice, with a prevalence of fatalities directly related to anaesthesia of 0.12 %, which rose to 0.24 % with the inclusion of horses killed or dying within 7 days after general anaesthesia. The majority of these horses were healthy and underwent procedures lasting less than 1 hour, which may have contributed to the low mortality rates. Other reasons may include differences in the criteria used to define anaesthesia related death, the reasons for surgery, familiarity of the anaesthetists with the relatively fixed anaesthetic protocols used in this practice, etc.

Undoubtedly, the largest epidemiological study investigating equine peri-anaesthetic mortality was the “Confidential Enquiry into Perioperative Equine Fatalities” (CEPEF). In this report, Johnston et al. (2002) described the risk of death during anaesthesia or within 7 days following anaesthesia in 41,824 horses, anaesthetized in 129 different clinics over a period of 6 years. At the end of the 7 day period, an overall death rate of 1.9 % was found. These horses were classified as ‘dead’ because they died unexpectedly or were euthanized because of perioperative complications unrelated to pre-existing disease. Another 4.8 % of the horses died or were euthanized because of an inoperable lesion found at surgery or as a result of pre-existing disease, but these horses were classified as ‘put to sleep’.

When cause of death was further analyzed in noncolic horses in the CEPEF study, it was demonstrated that 33 % of deaths were due to cardiac arrest (including postoperative cardiovascular collapse), 32 % of horses were euthanized because of fractures or myopathies observed during the recovery period, while the remaining 35 % of deaths were from a range of causes (Johnston et al. 2002). The study therefore confirmed the well accepted concept that

most causes of perianaesthetic death in horses are linked with cardiovascular depression and/or inadequate tissue oxygen supply. Indisputably, cardiac arrest is a form of cardiovascular depression and is often caused by inadequate myocardial oxygen supply. Also, the association between hypotension during anaesthesia and postoperative myopathy has been well established in horses (Grandy et al. 1987, Serteyn 1988, Lindsay et al. 1989, Richey et al. 1990). Even in the muscles of healthy anaesthetized horses, an anaerobic metabolic response has been demonstrated using the microdialysis technique (Edner et al. 2005). Although myopathies are not necessarily lethal, the prognosis is often very poor when larger muscle groups are involved or when a more generalized myopathy occurs. The horses are unable to stand, leading to excitation and prolonged recumbency, thus causing further muscle damage. In some cases, this vicious circle necessitates euthanasia. Additionally, myoglobin from affected muscles can cause nephropathy and acute renal failure. Fractures may also occur during unsuccessful attempts to stand due to muscle weakness (Lindsay et al. 1989). It therefore seems likely that at least some of the fractures in the CEPEF study were associated with muscle dysfunction/myopathy caused by inadequate oxygen delivery during anaesthesia. Young & Taylor (1993) obtained comparable results in 1,314 ASA (American Society of Anaesthesiologists) class I and II horses. The main cause of death in that study was myopathy (4 out of 9 horses), while another 2 horses re-fractured a leg after osteosynthesis, most likely as a result of myopathy. In conclusion, it can be stated that perioperative death in horses is closely linked with inadequate tissue oxygen delivery.

The death rate for noncolic horses was calculated to be 0.9 %, while this number increased to 11.7 % in colic horses (Johnston et al. 2002). In most studies investigating the prognosis of equine colic cases, variables which assess cardiovascular status were found to be good prognostic guides. Examples include heart rate (HR), packed cell volume (PCV), capillary refill time, mucous membrane colour and/or blood pressure (Parry et al. 1983, Pascoe et al. 1983, Puotunen-Reinert 1986, French et al. 2002, Stephen et al. 2004, Mair & Smith 2005, Proudman et al. 2005, Proudman et al. 2006). Once again, this confirms the importance of maintaining cardiovascular function during anaesthesia, especially in high risk patients such as the colic horse. Appropriate monitoring of anaesthetized horses should enable the clinician to detect cardiovascular depression in a timely fashion. However, before appropriate measures can be taken to prevent or treat inadequate tissue oxygen supply, a clear understanding of the underlying mechanisms is necessary to allow a logical approach to treatment.

## Diagnosis & treatment of cardiovascular depression

### Cardiovascular depression as a cause of inadequate tissue oxygen supply

Oxygen delivery ( $DO_2$ ) is calculated as the product of arterial oxygen content ( $CaO_2$ ) and cardiac output ( $\dot{Q}t$ ) (Lumb 2005) (Table 1). However, oxygen supply to individual tissues is not only determined by total oxygen delivery, but also by the degree of perfusion of individual tissues. The latter depends on  $\dot{Q}t$ , smooth muscle tone in precapillary arterioles (which also determines systemic vascular resistance) and transmural pressure in the blood vessels of a certain tissue, which is important for maintaining the patency of these vessels. Since transmural pressure is the difference between intravascular and extravascular pressures, it is highly influenced by blood pressure. Inadequate tissue oxygen supply can therefore result from decreases in arterial oxygen content,  $\dot{Q}t$ , systemic vascular resistance (SVR) or blood

**Table 1: Formulas to calculate some valuable cardiovascular/respiratory parameters**

Variable	Formula
Oxygen delivery ( $DO_2$ ) (L/min)	$DO_2 = \frac{CaO_2 \text{ (mL/L)} * \dot{Q}t \text{ (L/min)}}{1000}$
Arterial oxygen content ( $CaO_2$ ) (mL/L)	$CaO_2 = [Hb \text{ concentration (g/L)} * 1.39 * SaO_2] + [PaO_2 \text{ (kPa)} * 0.225]$
Mixed venous oxygen content ( $C\bar{v}O_2$ )	$C\bar{v}O_2 = [Hb \text{ concentration (g/L)} * 1.39 * S\bar{v}O_2] + [P\bar{v}O_2 \text{ (kPa)} * 0.225]$
End-capillary pulmonary oxygen content ( $C\acute{c}O_2$ )	$C\acute{c}O_2 = [Hb \text{ concentration (g/L)} * 1.39 * S\acute{c}O_2] + [P\acute{c}O_2 \text{ (kPa)} * 0.225]$ (For practical reasons, $P\acute{c}O_2$ is usually assumed to be equal to $PAO_2$ )
Alveolar oxygen partial pressure ( $PAO_2$ ) (kPa)	$PAO_2 = PIO_2 \text{ (kPa)} - 1.2 PaCO_2 \text{ (kPa)}$ (where $PaCO_2$ = arterial carbon dioxide tension and $PIO_2$ = partial pressure of inspired oxygen = $FIO_2(P_B \text{ (kPa)} - 6.3 \text{ kPa})$ (with $FIO_2$ = oxygen fraction in inspired dry air)
Degree of venous admixture ( $\dot{Q}s/\dot{Q}t$ ) (%)	$\frac{\dot{Q}s}{\dot{Q}t} = \frac{C\acute{c}O_2 - CaO_2}{C\acute{c}O_2 - C\bar{v}O_2} * 100\%$
Alveolar-to-arterial oxygen tension gradient ( $P(A-a)O_2$ ) (kPa)	$P(A-a)O_2 = PAO_2 \text{ (kPa)} - PaO_2 \text{ (kPa)}$
Systemic Vascular Resistance (SVR) (dyne.sec/cm <sup>5</sup> )	$SVR = \frac{80 * [MAP \text{ (mm Hg)} - RAP \text{ (mm Hg)}]}{\dot{Q}t \text{ (L/min)}}$ (where MAP = mean arterial pressure and RAP = right atrial pressure)

## Chapter 1.1: Inadequate tissue oxygen supply

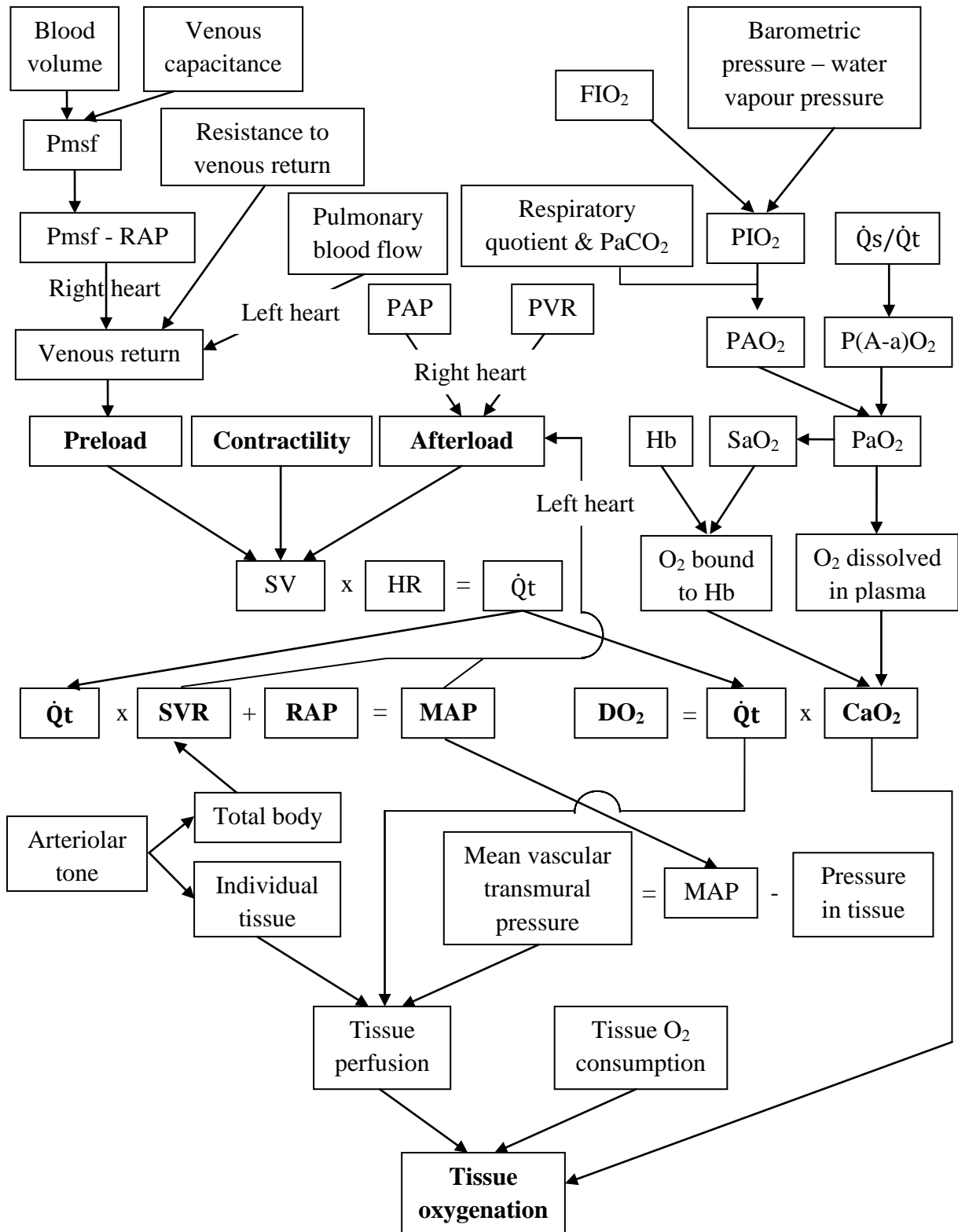
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pressure, especially in tissues with high extravascular pressures (e.g. muscles) or high oxygen consumption (e.g. brain). Due to a complicated interplay between all these factors (Fig. 1), a delicate balance must be maintained by the body and interference with the normal homeostatic mechanisms by administration of anaesthetic drugs can result in pronounced changes in oxygen supply to individual tissues.

Arterial oxygen content is the sum of the amount of oxygen bound to haemoglobin and the amount of oxygen dissolved in plasma (Table 1). The former is measured as the saturation of haemoglobin with oxygen in arterial blood ( $SaO_2$ ), the latter as the arterial partial pressure of oxygen ( $PaO_2$ ). In anaesthetized horses, respiratory function is often compromised due to mismatching between ventilation and perfusion of the lungs (Nyman & Hedenstierna 1989), leading to dead-space or 'wasted' ventilation and right to left pulmonary shunts. These respiratory problems seem to occur due to the combined effects of recumbency and general anaesthesia, since in laterally recumbent conscious ponies, mean  $PaO_2$  and  $PaCO_2$  were reported to range between 85 and 97 mm Hg and between 39 and 43 mm Hg respectively. These values were not significantly different from those in standing ponies (Rugh et al. 1984). Pulmonary shunt fractions ( $\dot{Q}_s/\dot{Q}_t$ ) (Table 1) of 20 to 25 % were reported in healthy, spontaneously breathing, laterally recumbent, halothane anaesthetized horses (Hall et al. 1968). In another study, the shunt fraction increased from a mean of 1 % in conscious horses to a mean of 34 % in dorsally recumbent anaesthetized horses (Nyman & Hedenstierna 1989). It was suggested that this was mainly due to atelectasis (Nyman et al. 1990). These shunt flows induce an increased alveolar-to-arterial oxygen tension gradient ( $P(A-a)O_2$ ) (Table 1), leading to a lower than expected value for  $PaO_2$ . Although  $PaO_2$  is important because it represents unbound oxygen immediately available for diffusion into the tissues, the amount of oxygen bound to haemoglobin ( $SaO_2$ ) is quantitatively of greater importance as it forms a much larger part of the total  $CaO_2$ . Fortunately, the sigmoid shape of the oxyhaemoglobin dissociation curve allows a large reduction in  $PaO_2$  before  $SaO_2$  starts to decline (Bohr et al. 1904), thus avoiding large changes in  $CaO_2$  until respiratory function is severely compromised.

The second determinant of tissue oxygen supply is  $\dot{Q}_t$ , which is usually lower during anaesthesia than in conscious animals. Many anaesthetic drugs commonly used in horses, including acepromazine (Stepien et al. 1995),  $\alpha_2$  agonists (Wagner et al. 1991), barbiturates (Patschke et al. 1975) and volatile agents (Steffey & Howland 1980), reduce  $\dot{Q}_t$ , either

# Diagnosis & treatment of cardiovascular depression



**Fig. 1: Schematic overview of the different factors which play a role in determining tissue oxygenation**  
**For abbreviations: see general list of abbreviations**

through a direct negative inotropic and/or negative chronotropic effect, a central depressant effect (reduced sympathetic and/or increased vagal outflow) or any combination of these. The exact mechanisms through which the agents exert these effects differ from drug to drug, but



## Chapter 1.1: Inadequate tissue oxygen supply

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as volatile anaesthetics are an essential component of most clinical protocols used for prolonged anaesthetic procedures in horses, the mechanism of their cardiovascular depressant action deserves further attention.

Volatile anaesthetics depress myocardial contractility by influencing calcium homeostasis in the cardiac cell (Pagel et al. 1993, Wheeler et al. 1994), with a decrease in intracellular calcium transients (Bosnjak & Kampine 1986, Bosnjak et al. 1992). Most agents inhibit the influx of calcium through slow channels (Rusy and Komai 1987) and depress the maximal uptake of calcium by the sarcoplasmic reticulum (Casella et al. 1987). Halothane was also reported to evoke a net loss of calcium from the sarcoplasmic reticulum of rat heart cells (Wheeler et al. 1988). In addition, inhalants decrease the myofibrillar responsiveness to calcium and/or the calcium sensitivity of the contractile proteins (Housmans & Murat 1988, Bosnjak et al. 1992). Finally, small but significant decreases in serum ionized and total calcium concentrations were reported in horses anaesthetized with halothane and isoflurane (Gasthuys et al. 1985, Grubb et al. 1999).

Besides their effects on  $\dot{Q}_t$ , many anaesthetic drugs, including acepromazine (Steffey et al. 1985),  $\alpha_2$  agonists (McCashin & Gabel 1975), propofol (Oku et al. 2006), isoflurane (Raisis et al. 2000) and sevoflurane (Aida et al. 1996), also affect vascular smooth muscle tone in horses. The net result of constriction or dilation of vessels depends on the type and number of vessels involved and their localization. As an example, large veins normally contain about 60 % of the blood volume, but their capacitance can be greatly altered by autonomic nervous system activity (Power & Kam 2001). Together with the effective circulating blood volume, venous capacitance determines the mean systemic filling pressure ( $P_{msf}$ ), which represents the theoretical pressure throughout the systemic blood vessels when blood flow would stop. The difference between  $P_{msf}$  and RAP determines venous return to the right heart (Fig. 1). Venous vasodilation may reduce  $P_{msf}$  and therefore venous return, although this effect is somewhat attenuated because of a simultaneous decrease in venous resistance (Fig. 1). The arteriolar smooth muscle tone determines the distribution of  $\dot{Q}_t$  towards the different organs, SVR (and thus arterial pressure) and intravascular pressure in the capillaries (Power & Kam 2001). When all other factors remain constant, arteriolar vasodilation will increase the perfusion in a tissue, but if this occurs on a larger scale throughout the body, eg. due to the administration of larger doses of acepromazine (Steffey et al. 1985), systemic vascular resistance may decline markedly, leading to hypotension and possibly collapse of the vessels

## Diagnosis & treatment of cardiovascular depression

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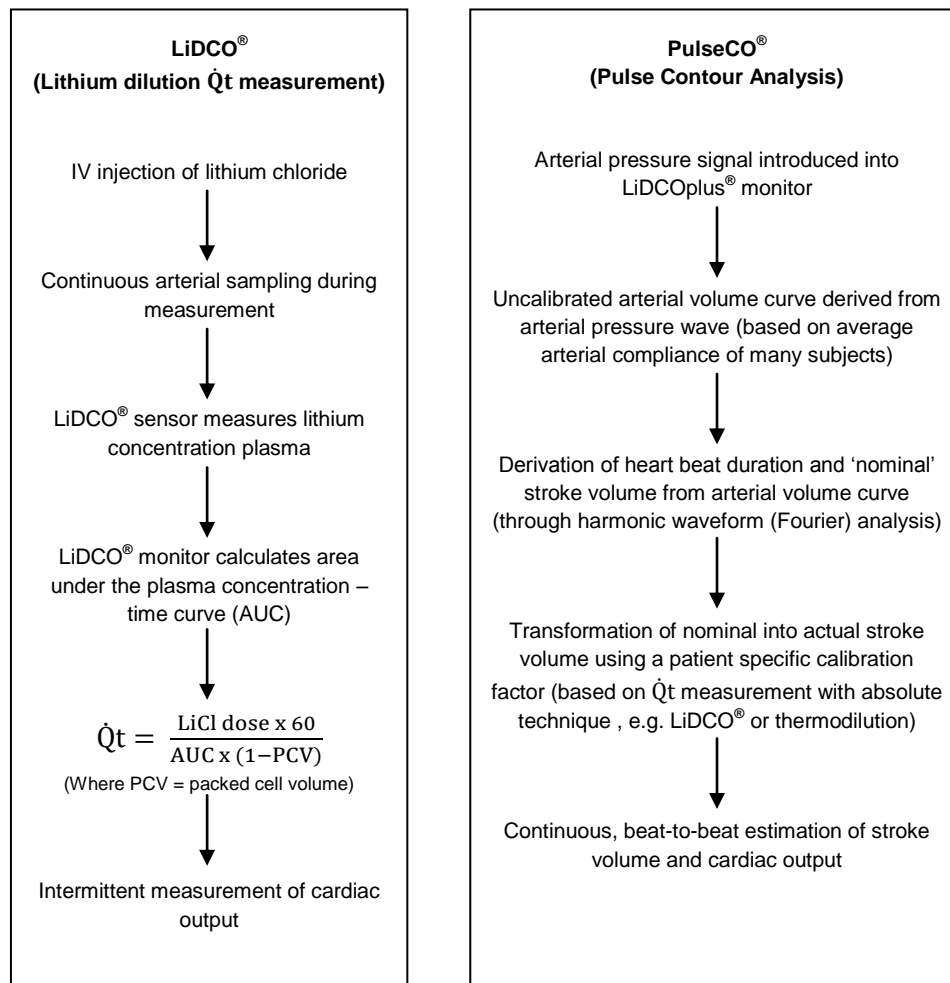
perfusing tissues with high extravascular (intracompartmental) pressures, such as the muscles of recumbent horses (Lindsay et al. 1980).

Compared to other species, horses appear to be more susceptible not only to the respiratory, but also to the cardiovascular depressant effects of general anaesthesia (Eberly et al. 1968, Gillespie et al. 1969, Hall 1971). Combined with their high body weight and their propensity to develop ventilation-perfusion mismatch when anaesthetized and placed in a recumbent position, this means that tissue oxygenation is often inadequate in anaesthetized horses. Sufficient monitoring is therefore needed to detect signs of cardiopulmonary deterioration at an early stage and appropriate measures must be taken to avoid or treat any problems.

### **Detecting cardiovascular depression during equine anaesthesia**

During equine anaesthesia, cardiovascular monitoring usually consists of clinical assessment (pulse rate/quality, mucous membrane colour, capillary refill time, skin turgor, etc.), electrocardiography, pulse oximetry and invasive measurement of arterial blood pressure. Since the latter requires placement of an arterial catheter, blood sampling for arterial blood gas analysis, which is useful to detect hypoxaemia, is also often performed. Although arterial pressure is important in the prevention of severe complications, measurement of  $\dot{Q}_t$  allows a better assessment of cardiovascular function and additional parameters such as stroke volume, oxygen delivery and systemic vascular resistance (provided right atrial pressure is known) can be calculated (Table 1). Numerous techniques have been described to measure  $\dot{Q}_t$ , including the Fick principle (Fick 1870), indicator dilution methods (Lagerlof et al. 1950), rebreathing of carbon dioxide (Klausen 1965), electromagnetic flowmetry (Brunsting et al. 1970), pulse contour analysis (Kouchoukos et al. 1970), Doppler echocardiography (Steingart et al. 1980) and thoracic electrical bioimpedance (Mattar et al. 1986). A continuous thermodilution method, using readings from a thermistor incorporated into the pulmonary catheter was developed, mainly for intensive care purposes in man (Luchette et al. 2000). However, the response time in sheep was reported to be rather slow (Siegel et al. 1996).

In horses, the indicator dilution techniques have been used most frequently (Muir et al. 1976). When performed carefully, the dilution techniques are as accurate as an electromagnetic flowmeter placed around the aorta (Kouchoukos et al. 1970), but usually



**Fig. 2: Short description of cardiac output ( $\dot{Q}t$ ) measurements using the lithium dilution and pulse contour analysis techniques**

require placement of a central venous and/or pulmonary artery catheter. In 1993, Linton et al. described the use of lithium chloride for a new indicator dilution technique to measure  $\dot{Q}t$  (Fig. 2). This technique was later commercialized under the tradename LiDCO®. It was demonstrated that the technique was reliable in horses (Linton et al. 2000) and that measurements using a peripheral injection of lithium chloride were comparable to those after central venous injection in dogs, eliminating the need for central venous catheterization (Mason et al. 2002). However, the technique only allows intermittent assessments of  $\dot{Q}t$ . It has been reported that transoesophageal echocardiography is an effective and non-invasive method for measurement of  $\dot{Q}t$  in anaesthetized horses (Young et al. 1996). With this technique,  $\dot{Q}t$  is calculated as the product of the velocity-time integral of blood flow through the aorta, the cross-sectional area of the aorta and heart rate. However, a long, expensive device is needed in horses, the technique does not provide continuous measurements and technical experience is required. Also, the user may have difficulty to obtain a good alignment

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of the ultrasound beam, which should be parallel to the blood flow. This is even more difficult when performing transthoracic echocardiography. Finally, the technique is minimally invasive but does not allow calculation of certain parameters derived from  $\dot{Q}_t$ , such as SVR, unless arterial and central venous pressures are simultaneously monitored.

Cardiac output is rarely measured in horses anaesthetized for clinical purposes because no 'ideal' measurement technique is available, i.e. one that is accurate, continuous, easy to perform and minimally invasive. However, the estimation of  $\dot{Q}_t$  based on analysis of the arterial pressure wave seems to fulfil most of these criteria, as it allows continuous, beat-to-beat assessment of  $\dot{Q}_t$  and only requires the insertion of an arterial catheter. Based on a mathematical model (Kouchoukos et al. 1970), these techniques allow calculation of changes in stroke volume or  $\dot{Q}_t$  from the arterial pressure wave, but require calibration in each patient using an absolute method, such as thermodilution or lithium dilution (Jansen et al. 1990). The accuracy of the original formulas was rather disappointing compared to other methods of measuring  $\dot{Q}_t$  in man, dogs and pigs (Alderman et al. 1972, Starmer et al. 1973, Verdouw et al. 1975, Wesseling et al. 1976). Later on, a more complicated, nonlinear, time-varying three-element model was developed, the "Modelflow" method, which was found to be more accurate (Wesseling et al. 1993). This formula was the basis for the commercial PiCCO<sup>®</sup> system, which needs an initial calibration using the thermodilution technique (Gödje et al. 2002).

The PulseCO<sup>®</sup> software (Fig. 2) uses yet another formula to calculate  $\dot{Q}_t$  during every heart beat from the beat duration, ejection duration, mean arterial pressure and the modulus and phase of the first harmonic of the arterial waveform. It is usually calibrated by the lithium dilution technique, which offers the advantage that no pulmonary catheterisation is needed and that the two techniques can be conveniently combined into one monitor, the LiDCO-Plus<sup>®</sup>. Another advantage is that PulseCO<sup>®</sup> incorporates a model of pressure transfer from the aorta to the radial artery, whereby wave reflections are taken into account, which should make the technique more accurate (Linton & Linton 2001). Compared to thermodilution and LiDCO<sup>®</sup> in man, PulseCO<sup>®</sup> reliably tracked changes in  $\dot{Q}_t$  for at least 8 hours after cardiac operations (Hamilton et al. 2002). Because the PulseCO<sup>®</sup> algorithm was developed for use in humans, the reliability in animals remains uncertain. If the technique proved to be reliable in horses, it would be an invaluable technique for  $\dot{Q}_t$  measurement in this species, where assessment of cardiovascular function is of fundamental importance to improve survival rate.

### Principles of treatment

To reduce the complication rate in equine anaesthesia, some preventive measures should be taken in all anaesthetized horses, including preoperative preparation of the horse (with correction of any abnormalities when possible, e.g. hypovolaemia), use of sufficient padding, careful positioning of the horse (to avoid myopathies), availability of equipment for artificial ventilation, reduction of anaesthesia duration if possible, etc. The anaesthetic protocol also has an important role, e.g. it has been reported that less muscular injury results from hypoxaemia during isoflurane compared to halothane anaesthesia (Whitehair et al. 1996). Although such measures are of fundamental importance to reduce the incidence and severity of problems resulting from anaesthesia-related cardiovascular depression, cardiovascular function *per se* must also be restored whenever it deteriorates during anaesthesia. Three general principles are the fundamentals of the prevention and treatment of cardiovascular depression in any species: reduction of anaesthetic depth (if possible), high-volume fluid therapy and use of drugs which stimulate the cardiovascular system. In daily practice, the aim is usually to maintain mean arterial pressure above 70 mm Hg in anaesthetized horses to reduce the incidence or severity of myopathy (Young 1993, Duke et al. 2006), since intracompartmental pressure in the dependent muscles of adult horses, on an adequately padded surface, reaches values of 30-40 mm Hg (White & Suarez 1986), while vascular transmural pressure needs to be greater than 30 mm Hg for adequate microcirculation (Young 1993). However, as stated above, not only maintaining blood pressure but additionally measuring and optimizing cardiac output would be desirable.

Volatile anaesthetics have only poor analgesic properties (Tomi et al. 1993, Petersen-Felix et al. 1995) and, depending on the circumstances, may even be anti-analgesic (Zhang et al. 2000). Consequently, reducing anaesthetic depth in response to cardiovascular depression is usually not possible when only an inhalant is used for maintenance of anaesthesia during painful surgical procedures. However, as a preventive measure, the use of locoregional anaesthetic/analgesic techniques (Tobias 1996, Tobias et al. 1996, Doherty et al. 1997, Morley et al. 2002, Haga et al. 2006) and/or systemically administered anaesthetics/analgesics (Brandl & Taeger 1991, Muir & Sams 1992, Doherty & Frazier 1998, Muir et al. 2003) can reduce the need for volatile anaesthetics by providing additional analgesia, hypnosis and/or muscle relaxation, the 3 cornerstones of anaesthesia. Similarly, intratesticular, intrafunicular and subcutaneous administration of lidocaine reduced the need for additional doses of

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ketamine and romifidine during total intravenous anaesthesia for field castration in horses (Portier et al. 2009). Combining anaesthetic drugs may result in less pronounced side effects, not only when dose requirements are reduced, but also when the anaesthetic agents have opposing effects on the cardiovascular system. As an example, the cardiovascular depressant effects of inhalants (Steffey & Howland 1980) might be partially offset by the administration of a constant rate infusion of ketamine (Muir & Sams 1992), which usually increases heart rate and arterial blood pressure by increasing sympathetic efferent activity (Wong & Jenkins 1974). It is therefore clear that, with respect to cardiovascular function, balanced anaesthetic techniques have many advantages over the use of a single agent for maintenance of anaesthesia.

In humans and small animals, high-volume fluid therapy can be an effective means of increasing circulating volume and cardiovascular performance. In horses and other large animals, this is less readily achieved because very large volumes need to be infused, especially when isotonic crystalloids are used. Indeed, 75 to 85 % of the administered volume moves to the interstitial space within the first hour after intravenous administration (Griffel & Kaufman 1992). In shock cases, the recommended administration rates of isotonic crystalloids in dogs and cats are respectively situated around 90 and 55 mL/kg within 10 to 15 min (Day 2000). In equine practice, even when using multiple, large-gauge, short catheters and pressurized infusion systems, such infusion rates are rarely, if ever, reached. Due to their larger molecular size, colloid solutions are better retained within the vasculature and are therefore more effective at quickly restoring plasma volume, because smaller volumes result in greater plasma volume expansion compared with crystalloids (Shoemaker et al. 1981). A cheaper alternative is the use of hypertonic saline (Danowski et al. 1946), which first causes a shift of water into the plasma from red blood cells and endothelium and then from the interstitium and tissue cells (Mazzoni et al. 1988). Although the increase in blood volume is transitory, it occurs in only a fraction of the time needed with iso-osmotic fluids at the same infusion rate. Furthermore, capillary hydraulic resistance may be reduced and tissue perfusion improved since hypertonic saline causes haemodilution and endothelial cell shrinkage, (Mazzoni et al. 1988). Use of hypertonic saline in horses or ponies has been reported by several authors (Bertone et al. 1990, Dyson & Pascoe 1990, Schmall et al. 1990, Gasthuys et al. 1992).

Despite the use of balanced anaesthetic protocols and fluid administration, cardiovascular stimulant drugs are often needed in anaesthetized horses. Among the drugs most often used in

anaesthetized horses are the sympathomimetic agents dobutamine, dopamine, ephedrine and noradrenaline, but many other drugs exist which exert a stimulating effect on the cardiovascular system. The following part of this chapter presents a general overview of the different classes of available drugs, with specific attention to the effects that have been reported in horses.

### **Conclusions**

Horses are prone to develop inadequate tissue oxygen supply during anaesthesia, a factor which contributes to the high mortality related with anaesthesia in this species. To optimize oxygen delivery, cardiovascular depression needs to be diagnosed and treated. No ideal method to measure cardiac output in anaesthetized horses under clinical circumstances is available, but the pulse contour analysis (PulseCO<sup>®</sup>) technique appears promising. When cardiac output is found to be low, reduction of anaesthetic depth and high volume fluid therapy are useful measures, but pharmacological support of the cardiovascular system is still often needed in horses.

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## **Cardiovascular stimulant drugs: a literature review with an emphasis on equine anaesthesia**



### SUMMARY

Cardiovascular stimulant drugs include antimuscarinics, inotropic drugs and vasopressors. Antimuscarinic drugs increase heart rate and, for many reasons, are not suitable to augment cardiac output ( $\dot{Q}_t$ ) unless it is decreased by bradycardia which is not related to hypertension. Inotropic drugs include digitalis glycosides,  $\beta$ -sympathomimetics, calcium salts, calcium sensitizers and phosphodiesterase III inhibitors. Although the mechanism of action differs between these agents, most inotropes increase the availability of calcium to the contractile apparatus of the cardiac muscle. For routine cardiovascular support during equine anaesthesia, digitalis glycosides seem to be of limited usefulness, because of their unfavourable pharmacokinetic properties and toxicity. Extensive research has been performed on the  $\beta$ -sympathomimetics, of which dobutamine appears to remain the most useful agent for use in anaesthetized horses. Calcium salts are not always effective, the effects depend on the cardiovascular situation of the individual horse. The use of calcium sensitizers has not been described in horses, but these drugs are quite expensive and long acting and are most likely best reserved for patients with specific cardiac diseases. Available data on the use of phosphodiesterase III inhibitors, i.e. inodilators, in horses is very limited. Vasopressors, such as vasopressin analogues, calcium salts and  $\alpha$ -sympathomimetics are useful only when hypotension is caused by vasodilation, e.g. induced by drugs or endotoxins, while myocardial contractility and  $\dot{Q}_t$  are normal or even increased and vascular transmural pressure needs to be restored to maintain a normal tissue perfusion.

# Cardiovascular stimulant drugs

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## Introduction

Cardiovascular depression frequently occurs and can induce detrimental effects in anaesthetized horses, especially because this species is also prone to hypoxaemia during anaesthesia. Despite the use of balanced anaesthetic techniques and intensive fluid therapy, additional pharmacological support is often needed to optimize cardiac output ( $\dot{Q}_t$ ) and blood pressure. This can be achieved by the use of chronotropic, inotropic or vasoactive drugs. The classification of these drugs into a single class is often not possible, e.g. noradrenaline exerts both positive inotropic (Garb 1950) and vasoconstrictive (Sutton et al. 1950) effects. Theoretically, vasodilators may also increase  $\dot{Q}_t$  by reducing afterload, but this approach will often induce hypotension with a reduction in tissue perfusion pressure.

The drugs most typically used to increase heart rate (HR) in equine clinical practice are the anticholinergics which competitively antagonize the muscarinic effects of acetylcholine without affecting the nicotinic receptors at the neuromuscular junction. These drugs are therefore more precisely referred to as antimuscarinic drugs (Calvey & Williams 2001b). Available inotropic drugs include digitalis glycosides,  $\beta$ -adrenergic agonists, calcium salts, calcium sensitizers and phosphodiesterase (PDE) inhibitors (Notterman 1991, Choudhury & Saxena 2003, Via et al. 2003). Except for vasopressin analogues and perhaps calcium salts, most vasopressors that are routinely used clinically are  $\alpha$ -adrenergic agonists (Kee et al. 2003).

## Antimuscarinics

Both naturally occurring and synthetic antimuscarinic drugs affect organs innervated by postganglionic parasympathetic fibres, such as the heart, non-vascular smooth muscle, the eyes and glandular tissues (Calvey & Williams 2001b). The anticholinergic drugs most often used in equine practice are atropine, glycopyrrolate and hyoscine. Atropine (or hyoscyamine), probably the best known anticholinergic drug, is an alkaloid that can be extracted from the plant *Atropa belladonna* (deadly nightshade). It has been suggested that the juice of the belladonna berry, which contains atropine, was already used by Cleopatra for cosmetic purposes, i.e. to induce mydriasis (Emsley 2008). Atropine has been used mostly for premedication and to antagonize the muscarinic effects of anticholinesterase drugs, but also for other specific indications, e.g. to produce mydriasis in humans with glaucoma (Derby



1868) or as an antisialagogue (Kentala et al. 1990). Heart rate was reported to increase two- to threefold after administration of atropine (0.04 mg/kg intravenously) in awake horses (Hamlin et al. 1972). The drug has been widely used in horses to antagonize the bradycardic effects of  $\alpha_2$  agonists (Alitalo et al. 1986, Gasthuys et al. 1990).

Glycopyrronium is another antimuscarinic drug often used by human and veterinary anaesthetists. Unlike atropine, it does not readily cross the blood brain barrier or the placenta because it is an ionized quaternary amine (Calvey & Williams 2001a). In humans, it is an effective antisialagogue with a long duration of action (approximately 6 hours) which does not tend to cause other antimuscarinic effects when used at moderate doses (e.g. 0.2 mg total dose). Indeed, clear effects on HR and pupillary size are only observed at higher doses (Calvey & Williams 2001a). In dogs (Richards et al. 1989) and horses (Singh et al. 1997, Dyson et al. 1999), the cardiac effects appear to be more comparable to those of atropine.

In humans, hyoscine (scopolamine) has a shorter duration of action, produces less tachycardia, is a more powerful antisialagogue and has less bronchodilator activity compared to atropine (Calvey & Williams 2001a). It is a useful drug in the prevention and treatment of motion sickness (Spinks et al. 2007) and has also been used in combination with opioids to produce 'twilight sleep' (Gauss 1906). In equids, hyoscine butylbromide, a quaternary ammonium derivative of scopolamine, is often used for its spasmolytic properties (Roelvink et al. 1991, Boatwright et al. 1996), although the drug can increase HR in horses (Geimer et al. 1995, Marques et al. 1998, Borer & Clarke 2006).

As mentioned earlier, the main cardiovascular effect of antimuscarinics is positive chronotropism. Although HR is one of the determinants of  $\dot{Q}_t$ , attempting to increase  $\dot{Q}_t$  using chronotropic drugs is usually not recommended unless a clear bradycardia is present. When high heart rates are pharmacologically induced, myocardial oxygen consumption increases (Van Citters et al. 1957), while the proportion of time spent in diastole diminishes. Since 80 % of the total coronary blood flow actually occurs during the diastolic phase (Power & Kam 2001a), tachycardia may compromise myocardial oxygen delivery. This effect will be attenuated by a reflex metabolic coronary arteriolar dilatation (Power & Kam 2001a), but hypoperfusion and hypoxia of the myocardium can still occur, e.g. when tachycardia is severe, cardiac disease is present or drugs affecting coronary vascular resistance have been administered. In those cases, cardiac oxygen supply can become insufficient, resulting in decreased myocardial contractility (Jose & Stitt 1969, Nayler et al. 1971) or arrhythmias

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(Senges et al. 1979, Hjalmarson 1980). Atropine has also been shown to increase the arrhythmogenicity of dobutamine in halothane anaesthetized horses (Light & Hellyer 1993). Finally, most antimuscarinic drugs have a negative effect on intestinal motility (Ducharme & Fubini 1983, Singh et al. 1996) and can induce signs of abdominal discomfort or colic in horses (Ducharme & Fubini 1983). These side effects might be avoided by using selective muscarinic type-2 antagonists such as methoctramine (Teixeira Neto et al. 2004). In equine anaesthesia, atropine has been widely used to counteract bradycardia and atrioventricular (AV) blocks after administration of  $\alpha_2$  agonists (Brouwer et al. 1980, Gasthuys et al. 1990). Atropine was also shown to reduce the dose of dobutamine needed in order to maintain mean arterial pressure (MAP) above 70 mm Hg (Weil et al. 1997), but this strategy is somewhat controversial. An important part of the bradycardia induced by  $\alpha_2$  agonists is attributable to a baroreceptor reflex in response to the initial hypertension associated with the administration of these drugs. Administering a positive chronotropic agent under such circumstances may be associated with even more pronounced increases in blood pressure. Cardiac work will also be higher since  $\dot{Q}_t$  increases in the presence of a high afterload, associated with  $\alpha_2$  agonist – induced vasoconstriction. Finally, any chronotropic effects of other drugs, e.g. dobutamine, will be accentuated and may lead to pronounced tachycardia. For all these reasons, the use of antimuscarinic drugs for cardiovascular support is preferably limited to horses with severe bradycardia unrelated to hypertension and which are not predisposed to develop gastrointestinal problems.

### **Inotropes**

All positive inotropic drugs, such as digitalis glycosides,  $\beta$ -sympathomimetics, calcium salts, calcium sensitizers and phosphodiesterase inhibitors, increase myocardial contractility. Although there are differences in the exact mode of action of these drugs, the end result is virtually always (except for calcium sensitizers) an increased availability of calcium ( $\text{Ca}^{2+}$ ) to the contractile myocardial apparatus (Choudhury & Saxena 2003). Because of differences in additional positive or negative effects, preferred route of administration, efficacy and/or pharmacokinetic properties, the suitability of these products for use during anaesthesia differs from drug to drug. Also, their effects in horses are not always the same as in other species. From a pharmacokinetic and pharmacodynamic point of view, an ideal inotropic drug for use during anaesthesia needs a rapid onset and short duration of action with a reliable dose-effect

relationship and no tendency to accumulate, irrespective of the duration of administration and the health status of the patient. Indeed, these properties allow administration as a constant rate infusion (CRI) with the ability to rapidly alter plasma concentrations and associated cardiovascular effects. Ideally, the drug should also not induce side effects or overly increase myocardial oxygen consumption.

### **Digitalis glycosides**

The digitalis glycosides form a group of more than 300 steroid-containing compounds that exert clear electrophysiologic effects on the heart. The most popular drugs are digoxin and digitoxin, which are used clinically, as well as ouabain, which is mostly used under laboratory conditions (Jortani & Valdes 1997). Cardiac glycosides increase the intracellular sodium concentration in the myocardial cells by inhibiting the  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase pump. This leads to a reduced extrusion of  $\text{Ca}^{2+}$  in exchange for  $\text{Na}^+$  and therefore an increased intracellular concentration of  $\text{Ca}^{2+}$ , resulting in an increased force of contraction (Calvey & Williams 2001b). A second effect of the inhibition of  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase is a reduced inward  $\text{K}^+$  transport and therefore a less negative resting membrane potential. This leads to increased automaticity and possibly impaired conduction and excitability, explaining the toxic arrhythmogenic activities of digitalis (Adams 2001). At therapeutic concentrations, digoxin also increases the initial rate and the amount of  $\text{Ca}^{2+}$ -induced  $\text{Ca}^{2+}$  release from cardiac sarcoplasmic reticulum (SR) vesicles, which may contribute directly to digoxin's inotropic effects (McGarry & Williams 1993).

Cardiac effects of digoxin include increased rate and peak force of contraction, as well as reduced time for generation of the peak force. Due to alterations in vagal and sympathetic function, digitalis therapy leads to reduced formation of impulses by the sinoatrial (SA) node and depression of conduction by the AV node, accompanied by an increase in the effective refractory period (Jortani & Valdes 1997). Its main use is in human and veterinary patients with congestive heart failure (CHF), where digitalization results in a broad scope of haemodynamic adjustments, including increased myocardial contractility and  $\dot{Q}_t$ , diuresis and diminution of oedema, control of cardiac arrhythmias and reductions in blood volume, venous pressures, heart size and HR. The improved myocardial contractility is the most important effect and the primary action on which the other effects depend (Adams 2001). Prophylactic preoperative digitalization has been used in humans to protect the heart against the negative inotropic effect of certain anaesthetic agents (Goldberg et al. 1961). Similarly, preanaesthetic

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digitalization in dogs offered some protection against the negative inotropic and hypotensive effects of 1 and 2 % halothane (Goldberg et al. 1962) and high doses of thiopental (45 and 60 mg/kg), although this could not be reproduced with smaller doses (15 and 30 mg/kg) (Goldberg et al. 1961). Prophylactic preoperative digitalization is not only useful for patients with overt heart failure, but has also been recommended in the late 1960's for patients with any history of cardiac failure (even when well compensated at the time of surgery), cardiac enlargement, ventricular hypertrophy, coronary artery disease or episodic atrial fibrillation (AF) or flutter, and for any patient undergoing cardiac surgery or for people over the age of 50 years undergoing major pulmonary surgery (Deutsch & Dalen 1969). Later on, preoperative digitalization of patients with coronary artery disease (but without cardiac failure) has indeed been shown to prevent the impairment in cardiac function during recovery from anaesthesia (Pinaud et al. 1983).

Despite possible protective effects against the negative inotropic effects of anaesthetic drugs, cardiac glycosides are rarely used in patients without a history or clinical evidence of cardiovascular abnormalities. Possible reasons include problems related to the pharmacokinetic profile of digoxin, its propensity to induce toxic side effects and perhaps the apparently lower effectiveness in healthy patients. As mentioned earlier, an inotropic drug for perianaesthetic use is preferred to have a rapid onset but short duration of action, two properties which digitalis glycosides do not appear to have. Although the positive inotropic response to digoxin and digitoxin can be detected within 15-30 minutes after intravenous (IV) administration in dogs, the maximal pharmacological effect is typically not obtained until 60 minutes after administration (Hamlin et al. 1971). This might make the drug sufficiently suitable for preoperative prophylactic use, but much less for treatment of cardiovascular depression occurring during anaesthesia. Digoxin disposition after IV injection in horses was reported to be tri-exponential. Both a rapid and slow distributive phase with half-lives of 15 minutes and 4.1 hours respectively, followed by a biological disposition phase with a half-life of 23.1 hours have been calculated (Button et al. 1980). Based on these data, prolonged effects can be expected after administration of these drugs. It has been stated that *'The basic procedure for digitalization usually involves the initial administration of a large amount of digitalis divided in several doses over a period of 24 – 48 hours to achieve the desired therapeutic effect quickly, but because of marked interpatient variation in the response to therapeutic and toxic actions of the glycosides, digitalization of each patient should be viewed as an individual and separate project involving some degree of trial and error during the*

*search for an efficacious dose without toxic side effects'* (Adams 2001). From this description, it seems reasonable to say that, even if these drugs can be used during preoperative preparation of patients with cardiac disease facing elective surgery, they are not suitable for perioperative use in emergency cases, nor feasible for routine use before elective surgery. Furthermore, cardiac glycosides are typically administered orally and although IV administration is justified during acute decompensation, this increases the likelihood for toxic arrhythmias (Adams 2001).

The narrow safety margin between the therapeutic and toxic levels of digoxin is a major drawback. Toxicity is initially manifested in horses as signs of anorexia, colic, and diarrhoea, but cardiac arrhythmias are another common and potentially life-threatening result of digitalis intoxication (Sage 2002). Digoxin is capable of producing paroxysmal atrial tachycardia, atrial fibrillation and flutter, AV block and junctional rhythm with slow rate (Jortani & Valdes 1997). Close monitoring of the clinical response and plasma digoxin concentration are needed in horses under digoxin treatment to avoid toxicity (Sage 2002), again rendering this drug less suitable for routine use during anaesthesia. Also, accurate measurement of digoxin concentrations has proven to be technically difficult and challenging (Jortani & Valdes 1997). Furthermore, hypokalaemia, -magnesaemia, and -calcaemia, can occur in anaesthetized patients and make the patient more sensitive to the toxic effects of digitalis glycosides. At the same time, digoxin also interacts with other drugs commonly used in the perioperative period, including phenylbutazone, quinidine, erythromycin, tetracyclines, omeprazole, etc. (Sage 2002). Digoxin further accentuates the cardiotoxicity of local anaesthetics (Roitman et al. 1993). Digitalis is not indicated in cases of circulatory shock because it may intensify tissue hypoxia by causing peripheral vasoconstriction in patients without congestive failure syndrome (Adams 2001).

Finally, digoxin was proven to be more effective in the diseased than in the normal heart, where  $\dot{Q}_t$  increases minimally and may even decrease slightly due to an increase in systemic vascular resistance (SVR), thus augmenting outflow impedance (Adams 2001). Although digitalis increases the contractility not only of the failing, but also of the normal heart (Adams 2001), the degree to which cardiac glycosides augment contractility is inversely related to the baseline contractile state (Braunwald 1985). Despite these observations, it may be argued that, during anaesthesia, contractility is depressed and should therefore be higher with prior digitalization, even in healthy patients. However, there is clear evidence suggesting that the effects of digoxin are diminished by certain anaesthetic drugs. Halothane was shown to

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increase the tolerance of the heart to digitalis, so digitalization may be less effective in patients anaesthetized with halothane, while the effects of an excessive dose of digitalis given during halothane anaesthesia may not become apparent until the patient awakens (Morrow 1970). Also, preoperative digitalization did not attenuate cardiac and haemodynamic changes occurring after induction and during balanced anaesthesia with phenoperidine, thiopentone, suxamethonium, pancuronium and N<sub>2</sub>O/O<sub>2</sub> in patients with ischaemic heart disease (Blanloeil et al. 1980).

In horses, digoxin can be used during treatment for CHF (Brumbaugh et al. 1982, Staudacher 1989) and AF (Reef et al. 1995, Gray 1999) and remains the most commonly used digitalis glycoside in the horse (Sage 2002). However, digitalis is best reserved for therapy of CHF and should not be used in attempts to treat cardiovascular depression during anaesthesia in healthy patients. To the authors' knowledge, reports in literature about perianaesthetic use of digoxin in equids are sparse, being limited to one experimental study about the combined use of digoxin and dopamine in ponies (Gasthuys et al. 1991b) and a case report about the use of digoxin during preoperative preparation of a horse with AF and reduced contractility (Schauvliege et al. 2005).

### **Sympathomimetics**

When  $\beta$ -adrenergic sympathomimetics bind to the  $\beta_1$ -receptor, a stimulatory protein (Gs), which is a heterotrimer of  $\alpha$ ,  $\beta$  and  $\gamma$  subunits, is activated (Hall 1993) and undergoes a conformational change. This results in high-affinity binding of guanosine triphosphate (GTP) (Gilman 1984) and dissociation of the  $\alpha$  subunit – GTP complex, which in turn stimulates adenylate cyclase. The latter enzyme converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) (Power & Kam 2008). Cyclic AMP then binds to a protein kinase comprised of two regulatory and two catalytic subunits, causing a dissociation of the regulatory subunits from the catalytic subunits. This activated protein kinase phosphorylates specific substrate proteins in the cells, including sarcolemmal proteins, phospholamban and troponin-I (TnI) (Evans 1986).

Phosphorylation of sarcolemmal proteins results in increased Ca<sup>2+</sup> influx through slow channels in response to membrane depolarization (Evans 1986). More specifically, the probability of slow Ca<sup>2+</sup> (L-type) channel opening and the mean open time of the channel are increased, an effect mediated by protein kinase A (Sperelakis et al. 1994). In addition to the slower, indirect, cAMP/protein kinase A pathway, a faster and more direct mechanism also

follows  $\beta$  receptor activation, which likely involves direct modulation of the L-type  $\text{Ca}^{2+}$  channel activity by the  $\alpha$  subunit of the Gs-protein (Sperelakis et al. 1994). Because  $\text{Ca}^{2+}$  flux across myocardial cell plasma membranes is facilitated (Osterrieder et al. 1982), intracellular  $\text{Ca}^{2+}$  levels increase, stimulating the release of more  $\text{Ca}^{2+}$  from the SR (' $\text{Ca}^{2+}$  induced  $\text{Ca}^{2+}$  release') (Fabiato 1983). This results in an increase of the contractile forces (Vernon et al. 1991).

Phosphorylation of phospholamban, a protein that regulates the  $\text{Ca}^{2+}$  pump of the SR, results in an increased velocity of  $\text{Ca}^{2+}$  reuptake by SR vesicles, an increased affinity of the transport protein for  $\text{Ca}^{2+}$  and an increased turnover of elementary steps of the ATPase reaction (Kranias & Solaro 1983). Consequently,  $\text{Ca}^{2+}$  transport by the cardiac SR is stimulated (Tada et al. 1975) and occurs at an increased rate (Davis et al. 1990, Luo et al. 1994), thus augmenting calcium sequestration by the SR (Tada et al. 1983). Because more  $\text{Ca}^{2+}$  is available for release during the next action potential, the net result is a higher force and rate of contraction (Luo et al. 1994). In phospholamban-deficient mice, contractility was as high as in wild-type mice maximally stimulated by the  $\beta$  agonist isoproterenol, while isoproterenol administration in the knockout mice did not further increase contractility (Luo et al. 1994). It has therefore been suggested that increases in the  $\text{Ca}^{2+}$  sensitivity of the SR transport system, through phosphorylation of phospholamban, might even be the main mechanism by which  $\beta$ -adrenergic agonists mediate a contractile response. A second consequence of the rise in the  $\text{Ca}^{2+}$  transport rate by the SR is an increased rate of myocardial relaxation, i.e. a positive lusitropic effect (Luo et al. 1994, Li et al. 2000).

Protein kinase A in ventricular myocytes also phosphorylates TnI, which helps to explain the positive lusitropic effects of catecholamines (Kögler & Rüegg 1997). Phosphorylation of TnI leads to a decreased affinity of troponin C for  $\text{Ca}^{2+}$  (Kranias & Solaro 1983, Kögler & Rüegg 1997) and an increased rate of  $\text{Ca}^{2+}$  dissociation from the myofilaments, thus accelerating myocardial relaxation (Li et al. 2000).

Negative aspects of  $\beta$ -adrenergic sympathomimetics are the increases in cardiac work and myocardial oxygen demand occurring after their administration (Notterman 1991), as well as sinus tachycardia, cardiac arrhythmias, muscular tremor and disturbances of organ perfusion caused by vasoconstriction (Swanson et al. 1985, Trim et al. 1985, Gasthuys et al. 1991c, Lee et al. 1998). The increase in HR seen after administration of  $\beta_1$ -adrenergic agonists is related to acceleration of voltage-sensitive sarcolemmal currents (the so-called 'voltage clock') and

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Ca<sup>2+</sup> release from the SR (the ‘calcium clock’) in cardiac pacemaker cells, such as the SA node (Eisner & Cerbai 2009, Joung et al. 2009). Individual differences between drugs do exist, not only in their pharmacokinetic properties but also in their selectivity for the different types of adrenergic receptors. Two classic examples of catecholamines are adrenaline and noradrenaline. However, dobutamine and dopamine are undoubtedly the most widely used agents in equine anaesthesia. A short overview of some  $\beta$ -sympathomimetics is presented in Table 1.

### *Adrenaline*

Adrenaline or epinephrine is an endogenous catecholamine secreted into the bloodstream by the adrenal medulla during stress periods. It exerts powerful  $\alpha$  and  $\beta_1$  and moderate  $\beta_2$  effects (Barnard & Linter 1993). At lower doses (0.04 – 0.1  $\mu\text{g}/\text{kg}/\text{min}$ ), the effects on  $\beta$ -adrenoreceptors predominate and HR, contractility and conduction velocity are increased ( $\beta_1$  effect), while SVR is lowered ( $\beta_2$  effect) or unchanged (Morrill 2000, Calvey & Williams 2001b). Consequently, systolic arterial pressure (SAP) increases, while diastolic arterial pressure (DAP) may even decrease due to vasodilation (Sanders et al. 1991, Calvey & Williams 2001b). At higher doses, the  $\alpha$ -effects become more dominant so both SVR and blood pressure increase (Barnard & Linter 1993, Morrill 2000). In halothane anaesthetized horses, IV administration of a bolus of adrenaline (3  $\mu\text{g}/\text{kg}$ ) resulted in a pronounced increase in blood pressure during approximately 8 minutes; HR initially increased markedly, but decreased when the pressor response became maximal (Lees & Tavernor 1970). The plasma half-life of adrenaline is very short (10-15 seconds) (Power & Kam 2001b), explaining the short duration of the effects. Consequently, adrenaline can be administered as a CRI, which has been described in halothane anaesthetized horses. Significant increases in blood pressure and HR were seen at rates of 0.25-1.2  $\mu\text{g}/\text{kg}/\text{min}$ , but ventricular premature contractions occurred at the higher end of the dose range (Gaynor et al. 1992).

In human medicine, adrenaline is mainly indicated for treatment of anaphylaxis, pulseless electrical activity, asystole and ventricular fibrillation (Morrill 2000) and plays an important role during cardiopulmonary resuscitation (Wenzel et al. 2006). The drug can be useful in cases of ventricular fibrillation where fine fibrillation (high-frequency, low-amplitude waves) needs to be coarsened prior to direct current cardioversion (Calvey & Williams 2001b). Adrenaline is also indicated in patients irresponsive to dobutamine or dopamine and in patients with life threatening hypotension, because its maximal effects are greater than those of other  $\beta$  agonists (Lees & Tavernor 1970, Barnard & Linter 1993).



Table 1: Dose-dependent effects of frequently used  $\beta$ - sympathomimetic agents (continues).

Drug	Patients	Dose	Receptor activity	Cardiovascular effects	References	
Epinephrine	General		Strong $\alpha$ and $\beta_1$ , moderate $\beta_2$	HR, contractility & ABP $\uparrow$ ; SVR $\uparrow, \downarrow$ or = (~dose) May cause tachycardia, arrhythmias, vasoconstriction, myocardial ischaemia, myocardial O <sub>2</sub> consumption $\uparrow$	Barnard & Linter 1993 Schechter et al. 1983	
	Humans	0.04 - 0.1 $\mu\text{g}/\text{kg}/\text{min}$	Mainly $\beta_1, \beta_2$	$\beta_1$ effect: HR, contractility & conduction velocity $\uparrow$ moderate $\beta_2$ effect: SVR $\downarrow$ or = SAP $\uparrow$ , DAP sometimes $\downarrow$	Sanders et al. 1991, Morrill 2000, Calvey & Williams 2001b	
		>0.1 $\mu\text{g}/\text{kg}/\text{min}$	$\alpha$ effect becomes more important	$\beta_1$ effect: $\uparrow$ HR, contractility & conduction velocity $\alpha$ effect: $\uparrow$ SVR ABP $\uparrow$	Barnard & Linter 1993, Morrill 2000	
	Horses	3 $\mu\text{g}/\text{kg}$			Pronounced $\uparrow$ ABP, HR initially $\uparrow$ , but $\downarrow$ when pressor response maximal Ventricular arrhythmias	Lees & Tavernor 1970
		0.25 - 1.2 $\mu\text{g}/\text{kg}/\text{min}$			ABP & HR $\uparrow$ VPC's at higher end of dose	Gaynor et al. 1992
Dopamine	General		DA <sub>1</sub> , DA <sub>2</sub> , $\alpha_1$ , $\alpha_2$ , $\beta_1$ Part of effect mediated by $\uparrow$ release and $\downarrow$ uptake of norepinephrine	$\beta_1$ effect: contractility & HR $\uparrow$ DA <sub>1</sub> effect: vascular relaxation, sodium excretion kidney $\uparrow$ Postsynaptic $\alpha_1$ & $\alpha_2$ effect: vasoconstriction	Murphy & Elliott 1990, Via et al. 2003	
	Humans	<2 - 4 $\mu\text{g}/\text{kg}/\text{min}$	Mainly DA <sub>1</sub> and DA <sub>2</sub>	renal plasma flow, GFR & Na <sup>+</sup> excretion $\uparrow$	Morrill 2000, Murphy & Elliott 1990, Via et al. 2003	
		3 - 10 $\mu\text{g}/\text{kg}/\text{min}$	Mainly $\beta_1$	HR & $\dot{Q}_t$ $\uparrow$ Sometimes tachycardia (e.g. underhydrated patients)		
		>10 $\mu\text{g}/\text{kg}/\text{min}$	Mainly $\alpha$	Vasoconstriction, arrhythmias likely	Calvey & Williams 2001b	
	Conscious horses	1 - 2.5 $\mu\text{g}/\text{kg}/\text{min}$			No effect on HR & ABP, but renal blood flow $\uparrow$ at 2.5 $\mu\text{g}/\text{kg}/\text{min}$	Trim et al. 1989
		5 $\mu\text{g}/\text{kg}/\text{min}$			HR $\uparrow$ & ABP $\downarrow$ No effect on HR & ABP, but renal blood flow $\uparrow$ & arrhythmias	Clark & Moore 1989a Trim et al. 1989

Abbreviations used: heart rate (HR), arterial blood pressure (ABP), systemic vascular resistance (SVR), oxygen (O<sub>2</sub>), systolic (SAP) and diastolic (DAP) arterial pressure, ventricular premature contraction (VPC), dopamine 1 and 2 receptor (DA<sub>1</sub> and DA<sub>2</sub> respectively), glomerular filtration rate (GFR), sodium (Na<sup>+</sup>), cardiac output ( $\dot{Q}_t$ ).

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**Table 1: Dose-dependent effects of frequently used  $\beta$ - sympathomimetic agents (continued).**

Drug	Patients	Dose	Receptor activity	Cardiovascular effects	References
Dopamine	Anaesthetized ponies	2.5 - 5 $\mu\text{g}/\text{kg}/\text{min}$		None	Gasthuys et al. 1991c, Lee et al. 1998
		10 - 20 $\mu\text{g}/\text{kg}/\text{min}$		CI, MAP & intramuscular blood flow $\uparrow$ , SVR $\downarrow$ Tachyarrhythmias & muscle tremor at highest dose	Lee et al. 1998
	Anaesthetized horses	0.5 - 3 $\mu\text{g}/\text{kg}/\text{min}$		None	Swanson et al. 1985, Trim et al. 1985
		2.5 $\mu\text{g}/\text{kg}/\text{min}$		$\dot{Q}t \uparrow$ & SVR $\downarrow$	Trim et al. 1985
		4 $\mu\text{g}/\text{kg}/\text{min}$		ABP $\downarrow$ & $\dot{Q}t \uparrow$ , minor $\uparrow$ HR	Young et al. 1998a
		5 $\mu\text{g}/\text{kg}/\text{min}$		$\dot{Q}t \uparrow$ , SVR $\downarrow$ , ABP =, HR =, arrhythmias	Swanson et al. 1985
	10 $\mu\text{g}/\text{kg}/\text{min}$		$\dot{Q}t \uparrow$ , SVR =, ABP $\uparrow$ , HR =, arrhythmias Variable effect on HR, arrhythmias	Swanson et al. 1985 Robertson et al. 1996	
Dopexamine	General		$\beta_2$ , DA <sub>1</sub> , DA <sub>2</sub> , weak $\beta_1$ $\downarrow$ norepinephrine reuptake	renal vascular resistance $\downarrow$ , neurogenic vasoconstriction $\downarrow$ some positive inotropism HR & CI $\uparrow$ , SVR $\downarrow$ Sinus tachycardia, tachyarrhythmias	Brown et al. 1985 Via et al. 2003 Leier et al. 1988 Calvey & Williams 2001b
	Ponies & horses	0.5 - 20 $\mu\text{g}/\text{kg}/\text{min}$		CI, contractility, MAP & HR $\uparrow$ , SVR $\downarrow$ $\uparrow$ intramuscular blood flow muscle tremor, sweating, excitement, shivering, colic 10 - 20 $\mu\text{g}/\text{kg}/\text{min}$ tachycardia & arrhythmias	Muir 1992a & b, Young et al. 1997, Lee et al. 1998  Muir 1992a, Lee et al. 1998
Fenoldopam	General		DA <sub>1</sub>	CI $\uparrow$ , SVR & ABP $\downarrow$ Tachycardia and hypotension	Barnard & Linter 1993 Clark & Moore 1989b, Hollis et al. 2006a
Dobutamine	General		Mainly $\beta_1$ , slight $\alpha_1$ and $\beta_2$	SV $\uparrow$ , $\dot{Q}t \uparrow$ , HR $\uparrow$ at higher doses	Tuttle & Mills 1975, Barnard & Linter 1993
	Humans	< 7.5 $\mu\text{g}/\text{kg}/\text{min}$	Mainly $\beta_1$	SV $\uparrow$ , $\dot{Q}t \uparrow$ , ABP $\uparrow$ , HR $\uparrow$ at higher doses	Morrill 2000
		> 7.5 $\mu\text{g}/\text{kg}/\text{min}$	$\beta_1$ and $\beta_2$ (overshadows $\alpha_1$ )	SVR $\downarrow$ , but usually ABP still $\uparrow$ , tachycardia	Tuttle & Mills 1975, Morrill 2000

Abbreviations used: cardiac index (CI), mean arterial pressure (MAP), systemic vascular resistance (SVR), cardiac output ( $\dot{Q}t$ ), arterial blood pressure (ABP), heart rate (HR), dopamine 1 and 2 receptor (DA<sub>1</sub> and DA<sub>2</sub> respectively).

Table 1: Dose-dependent effects of frequently used  $\beta$ - sympathomimetic agents (continued).

Drug	Patients	Dose	Receptor activity	Cardiovascular effects	References
Dobutamine	Ponies	1.25 - 5 $\mu\text{g}/\text{kg}/\text{min}$		SVR $\downarrow$ , CI, MAP & SV $\uparrow$ At 2.5 & 5 $\mu\text{g}/\text{kg}/\text{min}$ HR and PCV $\uparrow$ , some ponies severe tachycardia	Gasthuys et al. 1991c
		2.5 - 10 $\mu\text{g}/\text{kg}/\text{min}$		SVR $\downarrow$ , CI & MAP $\uparrow$ , highest dose arrhythmias & tachycardia intramuscular blood flow $\uparrow$	Lee et al. 1998
	Horses	0.5 - 1.0 $\mu\text{g}/\text{kg}/\text{min}$		ABP $\uparrow$ , $\dot{Q}_t$ $\downarrow$ , no changes in left ventricular systolic function or SVR	Raisis et al. 2000a, Swanson & Muir 1986
		3 - 10 $\mu\text{g}/\text{kg}/\text{min}$		ABP $\uparrow$ , $\dot{Q}_t$ $\uparrow$ , contractility $\uparrow$ , variable effect on HR ( $\uparrow$ , $\downarrow$ or $\downarrow$ ), effect on SVR small and not significant, PCV $\uparrow$ arrhythmias at higher doses (often limited to bradyarrhythmias, AV blocks, AV dissociation or APC's)	Swanson et al. 1985, Swanson & Muir 1986, Dyson & Pascoe 1990, Young et al. 1998b, Swanson et al. 1985, Donaldson 1988, Light et al. 1992
Xamoterol	General		Partial $\beta_1$ agonist	Contractility and HR $\uparrow$ Effect depends on sympathetic tone: moderate inotropism at rest, but attenuates $\beta$ -adrenergic response during exercise SVR and ABP $\uparrow$ (through $\beta_2$ vascular blocking action?)	Nuttall & Snow 1982 Calvey & Williams 2001b Galiè et al. 1989
Ephedrine	General		Direct $\alpha_1$ effect and also causes synaptic release of norepinephrine and inhibits its metabolism	$\dot{Q}_t$ , SVR, ABP and HR $\uparrow$ Tachyphylaxis with continued use	Calvey & Williams 2001b
	Horses	0.06 mg/kg		ABP $\uparrow$ , HR & PCV $\downarrow$ , no arrhythmias	Hellyer et al. 1998
Isoprenaline	General		Very potent $\beta_1$ and $\beta_2$ , no $\alpha$ effect	Contractility and $\dot{Q}_t$ $\uparrow$ , HR $\uparrow$ (sometimes excessive tachycardia), peripheral & bronchial vasodilation, SVR, DAP & MAP $\downarrow$ , coronary perfusion may $\downarrow$ , myocardial $\text{O}_2$ consumption $\uparrow$ , arrhythmias	Mueller 1978, Chamberlain et al. 1980, Mansell et al. 1988, Morrill 2000
	Horses	0.85 $\mu\text{g}/\text{kg}$		HR $\uparrow$ $\uparrow$ , arrhythmias, ABP $\uparrow$ slightly	Lees & Tavernor 1970

Abbreviations used: systemic vascular resistance (SVR), cardiac index (CI), mean arterial pressure (MAP), stroke volume (SV), heart rate (HR), packed cell volume (PCV), arterial blood pressure (ABP), cardiac output ( $\dot{Q}_t$ ), atrioventricular (AV), atrial premature contraction (APC), diastolic arterial pressure (DAP), oxygen ( $\text{O}_2$ ).

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Adrenaline additionally produces many other effects throughout the body, including mydriasis, bronchodilation, lipolysis, glycogenolysis, increased blood glucose levels, sweating, etc. (Anderson & Aitken 1977, Morrill 2000). Traditionally, there has been concern about the association of adrenaline with tachycardia, vasoconstriction and myocardial ischaemia (Schechter et al. 1983). Adrenaline constricts coronary vessels due to its effects on  $\alpha$  adrenoceptors and although this direct effect is overshadowed by the dilatatory effect of metabolic changes induced by the increased work of the heart (Calvey & Williams 2001b), myocardial oxygen consumption rises due to increases in HR, contractility and SVR (Fawaz & Tutunji 1960). Myocardial oxygen supply may therefore become inadequate (Barnard & Linter 1993).

Another concern during treatment with adrenaline is its propensity to induce arrhythmias (Lenel et al. 1948), including premature ventricular depolarizations, ventricular tachycardia and atrial or ventricular fibrillation (Gaynor et al. 1992). Intravenous administration of 3  $\mu\text{g}/\text{kg}$  adrenaline produced ectopic beats of ventricular origin in 8 out of 13 conscious horses (Lees & Tavernor 1970). The arrhythmogenic activity of adrenaline is also influenced by the anaesthetic protocol. As an example, the risk for arrhythmias in response to adrenaline infusions in dogs was significantly higher with halothane compared to isoflurane or sevoflurane (Imamura & Ikeda 1987). Furthermore, halothane not only increased the incidence, but also the duration of ventricular arrhythmias occurring after IV adrenaline administration in horses (Lees & Tavernor 1970). In the latter study, 3  $\mu\text{g}/\text{kg}$  of adrenaline caused ventricular ectopic beats in all horses and ventricular or nodal tachycardia in 4 of 11 animals (Lees & Tavernor 1970). When hypercapnia occurs, this will further increase the risk of adrenaline-induced ventricular arrhythmias in halothane anaesthetized horses (Gaynor et al. 1993). Beside the choice of the inhalant agent, drugs used during premedication may also influence the arrhythmogenicity of adrenaline. Xylazine was reported to reduce the dose of adrenaline required to induce fibrillation in anaesthetized dogs (Muir et al. 1975). However, more recent studies in dogs (Lemke et al. 1993a & 1993b) and horses (Gaynor et al. 1992) failed to show significant alterations in the arrhythmogenic dose of adrenaline after xylazine administration (Gaynor et al. 1992). On the other hand, premedication with acepromazine may protect against the occurrence of arrhythmias in response to adrenaline (Muir et al. 1975). Consequently, low doses of acepromazine are often included in the premedication protocols of horses for elective surgical procedures.

### *Noradrenaline*

Although noradrenaline or norepinephrine is a  $\beta_1$  agonist which increases myocardial contractility (Garb 1950), it is a more potent  $\alpha$  agonist and is therefore best seen as a vasopressor with some inotropic properties. For this reason, the drug will be discussed later.

### *Dopamine*

Dopamine is a naturally occurring sympathetic amine and the precursor of noradrenaline. It is formed by metabolization of L-dihydroxyphenylalanine (= L-dopa) by dopa decarboxylase and is metabolized by dopamine  $\beta$  hydroxylase to noradrenaline (Blaschko 1939). Dopamine exerts a complex, dose-dependent action on the cardiovascular system since it stimulates a variety of receptors, including presynaptic dopamine 2 ( $DA_2$ ) and  $\alpha_2$  receptors and postsynaptic dopamine 1 ( $DA_1$ ),  $\alpha_1$ ,  $\alpha_2$  and  $\beta_1$  receptors (Murphy & Elliott 1990). Dopamine achieves part of its effects by causing the release and preventing the re-uptake of noradrenaline (Via et al. 2003). Because of the effects at postsynaptic  $\beta_1$  receptors, mediated by inducing noradrenaline release, dopamine has positive inotropic and chronotropic effects. Postsynaptic  $DA_1$  receptors on vascular smooth muscle cells mediate vascular relaxation and promote sodium excretion by the kidneys. Dopamine causes vasoconstriction by the effects exerted at postsynaptic  $\alpha_1$  and  $\alpha_2$  receptors. Presynaptic  $\alpha_2$  and  $DA_2$  receptors both inhibit noradrenaline release (Murphy & Elliott 1990). The half-life of dopamine is 2 minutes with a time to onset of action of 5 minutes and duration of effect of approximately 10 minutes (Morrill 2000).

In humans, low doses (< 2-4  $\mu\text{g}/\text{kg}/\text{min}$ ) predominantly activate  $DA_1$  and  $DA_2$  receptors, increasing renal plasma flow, glomerular filtration rate and sodium excretion (Murphy & Elliott 1990, Barnard & Linter 1993, Morrill 2000). Such 'renal' doses can be used to increase renal blood flow, e.g. during heart failure or acute tubular necrosis (Morrill 2000). However, this is no longer recommended as a routine strategy in human medicine. Although low-dose dopamine indeed augmented renal blood flow, glomerular filtration rate and natriuresis in different experimental models of ischaemic and nephrotoxic acute renal failure (ARF), most clinical studies in humans have failed to demonstrate convincingly that it prevents ARF in high risk patients, or improves renal function or outcome in patients with established ARF (Denton et al. 1996, Friedrich et al. 2005). Intermediate doses (3-10  $\mu\text{g}/\text{kg}/\text{min}$ ) predominantly stimulate  $\beta_1$  receptors, resulting in an increased HR and  $\dot{Q}_t$  (Murphy & Elliott 1990, Morrill 2000, Via et al. 2003). The inotropic effect is usually more pronounced than the

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chronotropic effect, but tachycardia can sometimes be a problem, particularly in underhydrated patients (Calvey & Williams 2001b). These moderate doses are used primarily to increase contractility in CHF (Morrill 2000). Higher doses ( $> 10 \mu\text{g/kg/min}$ ) mainly stimulate  $\alpha$  receptors, leading to vasoconstriction (Murphy & Elliott 1990, Morrill 2000), while arrhythmias become more likely (Calvey & Williams 2001b). Dopamine increases automaticity in Purkinje fibres, affects action potential duration and has been reported to induce sinus tachycardia and ventricular ectopic activity. However, the latter is usually asymptomatic and dopamine-associated ventricular tachycardia is relatively rare in humans (Tisdale et al. 1995). High dosages are mainly used to increase blood pressure in cases of hypotension or shock with evidence of hypoperfusion (e.g. mental status changes, oliguria, poor tissue perfusion). Dopamine administration is usually initiated when SAP is below 90 mm Hg (Morrill 2000). It should be remembered that the mentioned dose ranges are approximate and doses at which the different receptors are activated can vary considerably, depending largely on the patient's clinical status and particularly on the pre-existing level of sympathetic activity (Murphy & Elliott 1990).

Numerous authors reported on the cardiovascular effects of dopamine in conscious or anaesthetized ponies or horses. In conscious horses, dopamine at 1 and  $2.5 \mu\text{g/kg/min}$  did not affect HR, carotid arterial pressure (Clark & Moore 1989a, Trim et al. 1989), lateral caecal arterial blood flow (Clark & Moore 1989a) or fractional excretion of sodium and potassium, although a rate of  $2.5 \mu\text{g/kg/min}$  did increase renal blood flow (Trim et al. 1989). In the study by Clark & Moore (1989a), significant increases in lateral caecal arterial blood flow and HR and decreases in carotid arterial pressure were found when dopamine was administered at a rate of  $5 \mu\text{g/kg/min}$ . In contrast, Trim et al. (1989) did not observe any changes in HR, blood pressure or fractional excretion of sodium and potassium with a similar dose, although increases in renal blood flow and urine volume, decreases in urine osmolality and dysrhythmias occurred.

In halothane anaesthetized ponies, dopamine CRI's at doses of 2.5 and  $5.0 \mu\text{g/kg/min}$  failed to induce any significant cardiovascular changes (Gasthuys et al. 1991c, Lee et al. 1998). Higher doses ( $10 - 20 \mu\text{g/kg/min}$ ) decreased SVR and increased CI, MAP and intramuscular blood flow in the dependent muscles of halothane anaesthetized ponies, but the highest dose ( $20 \mu\text{g/kg/min}$ ) was associated with tachyarrhythmias and muscular tremor (Lee et al. 1998). After pretreatment with digoxin, dopamine did not produce significant changes in cardiovascular function at doses of 1.25 and  $2.5 \mu\text{g/kg/min}$ , but administration of  $5 \mu\text{g/kg/min}$

caused increases in blood pressure and  $\dot{Q}t$ , while SVR tended to decrease and HR and total pulmonary resistance remained constant (Gasthuys et al. 1991b).

In halothane anaesthetized healthy horses, a dopamine CRI at rates between 0.5 and 3  $\mu\text{g}/\text{kg}/\text{min}$  also failed to produce any cardiovascular effects (Swanson et al. 1985, Trim et al. 1985), except for an increase in  $\dot{Q}t$  and a decrease in SVR at a dose of 2.5  $\mu\text{g}/\text{kg}/\text{min}$  (Trim et al. 1985), which was not detected at 3  $\mu\text{g}/\text{kg}/\text{min}$  (Swanson et al. 1985). Using a CRI rate of 4  $\mu\text{g}/\text{kg}/\text{min}$ , Young et al. (1998a) reported significant decreases in mean aortic pressure and increases in  $\dot{Q}t$ , together with a small but significant increase in HR. Using a CRI of 5  $\mu\text{g}/\text{kg}/\text{min}$ , dopamine had no effect on blood pressure, most likely because it reduced SVR while increasing  $\dot{Q}t$  by augmenting the rate of increase in left ventricular pressure (dP/dt) (Swanson et al. 1985). At 10  $\mu\text{g}/\text{kg}/\text{min}$ , increases in blood pressure were recorded, mainly because of an increase in  $\dot{Q}t$  and dP/dt, while SVR returned to baseline values. Heart rate was not affected by either of these doses. Robertson et al. (1996), using the same administration rates, reported variable effects on HR, with either no change, an increase or a decrease in individual horses. In the study of Swanson et al. (1985), 2<sup>nd</sup> degree AV blocks, in some cases accompanied by increases in HR, were noted in 1 out of 9 horses receiving 5  $\mu\text{g}/\text{kg}/\text{min}$  and in 3 of 9 horses receiving 10  $\mu\text{g}/\text{kg}/\text{min}$ . Other authors have also reported arrhythmias in halothane anaesthetized horses receiving dopamine, including supraventricular premature contractions (Trim et al. 1985, Robertson et al. 1996) and episodes of tachycardia at 5  $\mu\text{g}/\text{kg}/\text{min}$  (Trim et al. 1985), as well as sino-atrial block, atrial premature contractions, ventricular premature contractions, ventricular tachycardia and ventricular fibrillation with death in 1 horse at 10  $\mu\text{g}/\text{kg}/\text{min}$  (Robertson et al. 1996).

Based on the available data from literature, it can be concluded that the situation in equids is comparable to human medicine, i.e. the cardiovascular effects of dopamine are dose-dependent and results between various studies are not always consistent. Low dose rates ( $\leq 3$   $\mu\text{g}/\text{kg}/\text{min}$ ) do not produce clear changes, while higher doses can be used to increase  $\dot{Q}t$  and perhaps also blood pressure. However, by increasing the dose, the risk of inducing arrhythmias becomes higher. As in human medicine, the response of each individual patient to dopamine may vary depending on the degree of sympathetic stimulation and the health status of the patient. After infusion with *Escherichia coli* endotoxins in anaesthetized horses, dopamine appeared to produce more pronounced effects than previously mentioned. A CRI of 5  $\mu\text{g}/\text{kg}/\text{min}$  increased CI and blood pressure and decreased diastolic pulmonary arterial

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pressure (PAP), SVR and pulmonary vascular resistance (PVR), although it had no effect on the development of metabolic acidosis (Trim et al. 1991). One more possible indication for the use of dopamine was mentioned in a case report where 4 anaesthetized foals with AV block unresponsive to atropine sulphate and supportive treatment were treated successfully with dopamine hydrochloride (Whitton & Trim 1985).

### *Dopexamine*

Dopexamine is a synthetic catecholamine with agonistic activity at  $\beta_2$  adrenoreceptors and peripheral dopamine receptors (Brown et al. 1985, Calvey & Williams 2001b). The drug's potency at  $\beta_2$  receptors is approximately 60 times higher than that of dopamine, but the activity at dopamine receptors is lower. Nevertheless, dopexamine causes a fall in renal vascular resistance and reduces neurogenic vasoconstriction through its activity at vascular  $DA_1$  and prejunctional  $DA_2$  receptors respectively (Brown et al. 1985). Although it is only a weak  $\beta_1$  receptor agonist, dopexamine has positive inotropic effects, partly due to its direct effects on cardiac  $\beta_2$  adrenoreceptors, but also by inhibiting the neuronal reuptake of noradrenaline (Uptake<sub>1</sub>), which increases the effects of released noradrenaline at  $\beta_1$  receptors (Calvey & Williams 2001b, Via et al. 2003).

Dopexamine was reported to increase HR and CI and to reduce SVR and PVR (Leier et al. 1988). In humans, it can be used as an alternative to dobutamine to increase  $\dot{Q}t$  and produce vasodilation, hereby increasing splanchnic blood flow and urinary output (Barnard & Linter 1993, Via et al. 2003). Besides sinus tachycardia, dopexamine can also induce tachyarrhythmias in humans (Calvey & Williams 2001b).

In halothane anaesthetized ponies and horses, the cardiovascular effects of dopexamine CRI's varying between 0.5 and 20  $\mu\text{g}/\text{kg}/\text{min}$  were usually characterized by increases in CI, MAP, HR and maximal rate of increase in left ventricular pressure (dP/dtmax), together with a reduction in SVR (Muir 1992a & b, Young et al. 1997, Lee et al. 1998). It was also demonstrated that dopexamine infusions of 1 and 5  $\mu\text{g}/\text{kg}/\text{min}$  in anaesthetized ponies increased intramuscular blood flow in the nondependent limb (Lee et al. 1998). However, several undesirable side effects have been associated with dopexamine administration in equids, including muscular tremor (Lee et al. 1998), profuse sweating during administration, excitement and violent shivering during recovery and signs of colic a few hours after anaesthesia (Young et al. 1997, Lee et al. 1998). At the higher end of the dose range (10 – 20



$\mu\text{g}/\text{kg}/\text{min}$ ), several authors also reported sinus tachycardia, tachyarrhythmias and ventricular arrhythmias (Muir 1992a, Lee et al. 1998).

### *Fenoldopam*

Fenoldopam, a  $\text{DA}_1$  receptor agonist with no  $\alpha$  or  $\beta$  effects, increases CI, but reduces SVR and blood pressure dose-dependently (Barnard & Linter 1993). Lateral caecal arterial blood flow (Clark & Moore 1989b), renal blood flow (Aronson et al. 1990) and urine output (Hollis et al. 2006a) also increase during administration of fenoldopam. However, the drug was reported to induce hypotension and tachycardia in anaesthetized rats (Sengupta & Lokhandwala 1985), dogs (Aronson et al. 1990), horses (Clark & Moore 1989b) and foals (Hollis et al. 2006a). Consequently, fenoldopam seems less useful for cardiovascular support in anaesthetized horses.

### *Dobutamine*

Dobutamine, a synthetic catecholamine chemically related to dopamine (Calvey & Williams 2001b), is one of the most potent positive inotropes available (Morrill 2000). It was developed by systematic modification of isoproterenol's chemical structure to reduce its chronotropic, arrhythmogenic and vascular side effects (Tuttle & Mills 1975). The resulting drug, dobutamine, was shown to have an inotropic efficacy in dogs as great as the one of adrenaline, due to a direct action on  $\beta_1$  cardiac receptors, combined with only a slight effect on  $\alpha$  and  $\beta_2$  vascular receptors (Tuttle & Mills 1975). The drug is marketed as a racemic mixture, in which the (-) isomer has some  $\beta$  agonist properties but is predominantly an  $\alpha$  agonist, while the (+) isomer is a  $\beta_1$  and  $\beta_2$  agonist and a competitive  $\alpha$  blocker (Ruffolo et al. 1981). The racemic mixture has a predominant  $\beta_1$  activity and a balanced peripheral  $\beta_2$  and  $\alpha_1$  effect (Via et al. 2003). Therefore, lower dosages mainly stimulate  $\beta_1$  receptors, while both  $\beta_1$  and  $\beta_2$  effects are seen at higher dosages ( $> 7.5 \mu\text{g}/\text{kg}/\text{min}$ ). The effects at  $\alpha_1$  receptors (vasoconstriction) are usually antagonized by the drug's  $\beta_2$  effects (vasodilation) (Morrill 2000). In humans, the plasma half-life of dobutamine is very short (2 – 3 minutes), due to rapid metabolism in the liver (Calvey & Williams 2001b). The time to onset of action is 1 to 10 minutes, with a peak effect seen within 10 to 20 minutes (Morrill 2000).

In humans, dobutamine is administered to increase  $\dot{Q}_t$  in patients with CHF and other states of decreased  $\dot{Q}_t$  (Morrill 2000). This increase in  $\dot{Q}_t$  is the result of an increase in stroke volume (SV) and, at higher doses, HR (Barnard & Linter 1993). Dobutamine has been

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suggested as the agent of choice in septic shock patients with low  $\dot{Q}_t$  despite adequate fluid resuscitation, but should be combined with vasopressor therapy when blood pressure is low (Beale et al. 2004). The drug is contraindicated in human patients with hypovolaemia and is usually not administered if the patient's SAP is below 90 mm Hg (Morrill 2000), because dobutamine can decrease blood pressure slightly because of its vasodilating properties. This vasodilatory effect is mainly observed at higher dosages, which activate  $\beta_2$  receptors, causing a decrease in afterload, SVR (Morrill 2000) and total pulmonary resistance (Thuillez et al. 1993). Nonetheless, dobutamine restored blood pressure despite reducing SVR slightly in dogs with experimentally induced hypotension and low  $\dot{Q}_t$  and contractility (Tuttle & Mills 1975). Dobutamine has also been shown to increase myocardial oxygen supply and coronary blood flow, but this favourable effect may be lost when the drug causes tachycardia (Via et al. 2003), which is mainly observed at higher dosages (Morrill 2000). Dobutamine may also induce arrhythmias, but its arrhythmogenic activity has been shown to be weaker than that of other catecholamines such as dopamine, isoproterenol and noradrenaline (Ueda et al. 1977).

In equine anaesthesia, dobutamine is undoubtedly the most widely used catecholamine for cardiovascular support. Many authors have reported on the cardiovascular effects of different doses of dobutamine in both ponies and horses, usually under experimental circumstances. In halothane anaesthetized ponies, dobutamine (1.25, 2.5 & 5.0  $\mu\text{g}/\text{kg}/\text{min}$ ) did not significantly alter SVR but dose-dependent increases in cardiac index (CI), MAP, mean PAP and SV were reported. This was in contrast with dopamine infusions of 2.5 and 5.0  $\mu\text{g}/\text{kg}/\text{min}$ , which did not affect any of these variables. At the 2 highest doses of dobutamine, packed cell volume (PCV) and HR also increased, and in some ponies a severe tachycardia was observed (Gasthuys et al. 1991c). Lee et al. (1998) obtained similar results in ponies, with dose-dependent increases in CI and MAP and decreases in SVR at CRI rates of 2.5, 5.0 and 10  $\mu\text{g}/\text{kg}/\text{min}$ . In 2 out of 8 ponies, the highest dose caused tachycardia and ventricular arrhythmias. Additionally, it was shown that dobutamine increased intramuscular blood flow in both the dependent and nondependent forelimbs more consistently than dopamine, dopexamine or phenylephrine (Lee et al. 1998).

In halothane or isoflurane anaesthetized healthy horses, blood pressure invariably increased in response to dobutamine infusions at doses ranging between 0.5 and 10  $\mu\text{g}/\text{kg}/\text{min}$  (Swanson et al. 1985, Dyson & Pascoe 1990, Young et al. 1998b, Raisis et al. 2000a, Gehlen et al. 2006). As reported in ponies, these increases occurred at lower infusion rates of

dobutamine compared to dopamine and were not accompanied by changes in SVR (Swanson et al. 1985). Although  $\dot{Q}_t$  does not seem to be affected by doses of 0.5 (Raisis et al. 2000a) and 1.0  $\mu\text{g}/\text{kg}/\text{min}$  (Swanson & Muir 1986), higher doses of dobutamine (3 – 10  $\mu\text{g}/\text{kg}/\text{min}$ ) have been shown to increase  $\dot{Q}_t$  (Swanson et al. 1985, Swanson & Muir 1986, Dyson & Pascoe 1990, Young et al. 1998b). In agreement with these findings, no changes were found in left ventricular systolic function when dobutamine was administered at a rate of 0.5  $\mu\text{g}/\text{kg}/\text{min}$  (Raisis et al. 2000a), while doses between 3 and 10  $\mu\text{g}/\text{kg}/\text{min}$  were shown to increase the maximal rate of left ventricular pressure development ( $dP/dt_{\text{max}}$ ) (Swanson et al. 1985), maximal acceleration and velocity of aortic blood flow and left ventricular velocity time integral, while left ventricular pre-ejection period and ejection time significantly decreased (Young et al. 1998b). Dobutamine's effect on HR in anaesthetized normotensive horses appears to be variable, with some authors reporting increases (Gehlen et al. 2006) and others decreases (Swanson et al. 1985) at doses of 3 – 5  $\mu\text{g}/\text{kg}/\text{min}$ . At 10  $\mu\text{g}/\text{kg}/\text{min}$ , HR was not significantly different from baseline values (Swanson et al. 1985). Most likely, the actual effect in an individual horse will depend on the prevailing autonomic nervous system activity, blood pressure and HR of the horse before initiating dobutamine administration. In contrast to reports in human medicine, most authors found only small and non-significant effects of dobutamine on SVR in horses (Swanson et al. 1985, Raisis et al. 2000a). Other effects of dobutamine administration include increased pulmonary capillary wedge pressure (PCWP) (Gehlen et al. 2006), PAP (Young et al. 1998b) and PCV (Dyson & Pascoe 1990). Additionally, low dose dobutamine infusions (0.5  $\mu\text{g}/\text{kg}/\text{min}$ ) significantly increased femoral arterial flow, most likely due to local vasodilation, which may however not be associated with improved perfusion of skeletal muscles since microvascular perfusion, recorded using laser Doppler flowmetry, was not altered (Raisis et al. 2000a). Although dobutamine CRI's are usually found to have a quick onset and short duration of action, Young et al. (1998b) demonstrated that, in halothane anaesthetized horses, dobutamine at a dosage of 4  $\mu\text{g}/\text{kg}/\text{min}$  did not achieve peak effects on many haemodynamic variables within 40 minutes of the start of the infusion while effects of a 60-minute infusion persisted for at least 30 minutes after the infusion was discontinued (Young et al. 1998b).

Dobutamine is a weaker proarrhythmic drug than most other catecholamines (Ueda et al. 1977). Arrhythmias have been reported with the use of dobutamine in horses under experimental conditions, including supraventricular tachycardia in 2 of 8 horses receiving dobutamine at a rate of 4  $\mu\text{g}/\text{kg}/\text{min}$  (Young et al. 1998b). However, in most horses the

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arrhythmias observed during dobutamine administration are limited to bradyarrhythmias, 2<sup>nd</sup> degree AV blocks and isorhythmic AV dissociation at doses of 3 – 5 µg/kg/min (Swanson et al. 1985, Light et al. 1992). This agrees with the results of a study involving 200 horses anaesthetized for elective or emergency surgery, where a CRI of 1.5 to 3.2 µg/kg/min dobutamine as treatment of hypotension effectively increased blood pressure, while a cardiac arrhythmia developed in 28 % of the horses (60 % sinus bradycardia, 32 % AV block, 4 % premature atrial contractions and 4 % AV dissociation) (Donaldson 1988).

Caution is advised when combining parasympatholytic drugs with dobutamine. After prior atropine administration, the risk for tachyarrhythmias in response to dobutamine administration was higher (Light et al. 1992), while the dose of dobutamine required to induce repeated premature ventricular complexes or sustained narrow-complex tachyarrhythmia was almost threefold lower (Light & Hellyer 1993).

Many authors investigated the effects of dobutamine in anaesthetized horses under experimental conditions, but only a few reports describe the effects during routine clinical use. In horses anaesthetized for different surgical procedures, 1 – 4 µg/kg/min dobutamine significantly increased blood pressure and PCV, while HR tended to decrease (Hellyer et al. 1998). No arrhythmias were noted in the latter study. In another clinical study, in isoflurane anaesthetized horses, dobutamine administered to effect (average dose of 1 µg/kg/min) effectively increased blood pressure, CI and HR, although some of these changes may have been accentuated by surgical stimulation (De Vries et al. 2009). Because the increase in CI was only significant 30 minutes but not 15 minutes after the start of the infusion, the authors suggested that the initial increase in blood pressure may have resulted from the peripheral vasoconstrictive ( $\alpha_1$ ) effects of dobutamine; since SVR was not measured or calculated, this hypothesis could not be confirmed.

Dobutamine appears to be an effective and rather safe drug for cardiovascular support in horses and seems to be more effective than dopamine at improving blood pressure and  $\dot{Q}_t$ . Some additional evidence favouring dobutamine over dopamine in equine anaesthesia was provided by Duke et al. (2006), who reported that a combination of high-volume fluid therapy and dobutamine for cardiovascular support, with the aim to maintain MAP above 70 mm Hg, reduced the increase in muscle enzymes after halothane anaesthesia compared to the use of low-volume fluid therapy and dopamine with the aim to maintain MAP above 60 mm Hg.

### *Xamoterol*

Xamoterol is a selective partial agonist of the  $\beta_1$  adrenoreceptors and produces dose-dependent positive inotropic and chronotropic effects upon the dog heart (Nuttall & Snow 1982). In pigs, a more potent positive inotropic than chronotropic effect was illustrated under basal conditions (Galiè et al. 1989). However, the drug is also a competitive antagonist of the chronotropic and vasodilator effects of isoprenaline on the heart and blood vessels and of the chronotropic effects on noradrenaline on the heart (Nuttall & Snow 1982). When sympathetic tone is low, xamoterol has additive effects with released noradrenaline, but when it is high, it will antagonize the effects of the neurotransmitter, such that xamoterol has moderate inotropic effects at rest, but partly attenuates the  $\beta$ -adrenergic response during exercise (Calvey & Williams 2001b). In pigs with a maximal sympathetic tone, xamoterol indeed antagonized the chronotropic, though not the inotropic, effect of noradrenaline, while increasing SVR and blood pressure, possibly through a  $\beta_2$  vascular blocking action (Galiè et al. 1989). In humans, xamoterol may be beneficial in patients with poor left ventricular function but can cause clinical deterioration in patients with extremely poor left ventricular function when sympathetic drive is high (Molajo & Bennett 1985). To the authors' knowledge, the use of xamoterol has not been described in horses or ponies.

### *Ephedrine*

For more than 5000 years, the Chinese have used a vegetable drug, derived from a plant called Ma Huang (= *Ephedra sinica*), as a circulatory stimulant, antipyretic and cough suppressant. Towards the end of the 19<sup>th</sup> century, an alkaloid, named ephedrine, was isolated from this plant by a Japanese chemist and subsequently shown to have marked chemical and pharmacological similarity with adrenaline (Stehle 1925). Like adrenaline, ephedrine increases HR, contractility and blood pressure (Stehle 1925). Ephedrine occurs naturally in various other plants, but nowadays it is usually synthesized (Calvey & Williams 2001b). The drug has direct and indirect sympathomimetic activity (Trendelenburg et al. 1962). It directly stimulates postsynaptic  $\alpha_1$ -receptors, but is also actively taken up by sympathetic nerve endings (Uptake<sub>1</sub>), where it displaces noradrenaline from its storage granules into the synapse and inhibits the intraneuronal metabolism of noradrenaline by mitochondrial monoamine oxidase (Calvey & Williams 2001b). Tachyphylaxis occurs with the continued use of ephedrine (Valette et al. 1960), because of depletion of noradrenaline stores in sympathetic neurones (Calvey & Williams 2001b). Similarly, the effect of ephedrine may be diminished when the sympathetic nervous system is already maximally stimulated before administration.

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Compared to most other sympathomimetics, the cardiovascular effects of ephedrine are more prolonged, e.g. the effect on blood pressure usually lasts at least 15 minutes (Stehle 1925). Therefore this drug is often administered as a bolus instead of a CRI.

In halothane anaesthetized horses, ephedrine (0.06 mg/kg IV) increased  $\dot{Q}_t$ , SV and blood pressure, without affecting HR or cardiac rhythm (Grandy et al. 1989). Ephedrine (0.06 mg/kg IV, 1 – 2 boluses) significantly increased blood pressure without significantly altering HR or inducing arrhythmias (Hellyer et al. 1998). In the latter study, dobutamine 1 – 4  $\mu\text{g}/\text{kg}/\text{min}$  tended to increase MAP to a greater extent than ephedrine, suggesting that dobutamine is more efficacious than ephedrine at increasing arterial blood pressure in anaesthetized horses. However, the study was not designed to compare equipotent doses of the two drugs. Ephedrine did not affect PCV, in contrast to dobutamine (Hellyer et al. 1998).

### *Isoprenaline*

Isoprenaline or isoproterenol (N-isopropylnorepinephrine) is a synthetic catecholamine which differs from adrenaline in that it has an isopropyl group substituted for the methyl group of adrenaline (Nathanson & Miller 1952). Of all catecholamines available to the clinician, isoprenaline has the most potent direct  $\beta_1$  and  $\beta_2$  effects, but no  $\alpha$  effects (Barnard & Linter 1993). The drug therefore increases  $\dot{Q}_t$  and myocardial contractility and produces a pronounced increase in HR (Mueller 1978, Chamberlain et al. 1980, Mansell et al. 1988), in some cases even an excessive tachycardia (Morrill 2000). The  $\beta_2$  activity leads to peripheral and bronchial vasodilation, resulting in a reduction in SVR (Mueller 1978, Chamberlain et al. 1980), DAP (Mansell et al. 1988, Barnard & Linter 1993) and MAP (Morrill 2000, Calvey & Williams 2001b). The potent  $\beta_1$  activity leads to a significant increase in myocardial oxygen consumption (Parratt & Wadsworth 1970, Mueller 1978), while coronary perfusion may become compromised because of tachycardia and reduced DAP (Parratt & Wadsworth 1970). Undesirable effects include tachycardia, arrhythmias (Mueller 1978, Morrill 2000) and a diversion of blood flow from vital organs to muscle and skin (Barnard & Linter 1993). Isoprenaline is nevertheless useful in patients with bradycardia and AV block (Nathanson & Miller 1952, Barnard & Linter 1993), as well as in patients with pulmonary hypertension and right ventricular failure (Barnard & Linter 1993). The half-life of isoproterenol is 2.5 to 5 minutes with an onset of action after 30 to 60 seconds and a duration of action of 8 to 50 minutes (Morrill 2000).

To the authors' knowledge, only one study reported the use of isoprenaline during anaesthesia in horses. Intravenous injection of 0.85 µg/kg isoprenaline to 6 halothane anaesthetized horses produced great increases in HR, with a much slower return to baseline compared to adrenaline. Ventricular ectopic beats were observed in all animals and ventricular or nodal tachycardia in 3 cases. In most horses, blood pressure increased slightly (Lees & Tavernor 1970).

### **Calcium salts**

As indicated earlier, inotropic drugs usually act by increasing the availability of  $\text{Ca}^{2+}$  to the contractile apparatus, but an alternative approach is to directly increase circulatory calcium levels (Choudhury & Saxena 2003). Total calcium in the blood consists of three distinct forms: protein bound, ionized (free) and complexed with ions such as phosphate and citrate (Simesen 1980). In the open-chest dog, differences in ionized calcium levels accounted for significant alterations in  $\text{dP/dt}$ , suggesting that fluctuations in ionized calcium were primarily involved in the regulation of the contractile state of the heart (Bristow et al. 1977). This finding led the authors to propose that ionized calcium should replace total calcium as a routine clinical test. It is now indeed generally accepted that ionized calcium is the biologically active form. Intravenous therapy that is aimed at increasing circulatory calcium levels is therefore best done by administering calcium salts which increase serum ionized calcium levels. Typically,  $\text{CaCl}_2$  or calcium gluconate are used. The choice between both forms may depend on considerations regarding differences in urinary excretion, rapidity of dissociation, concentration of the salt in solution and bioavailability of the calcium ion provided (Cote et al. 1987). However, in both dogs and children, Cote et al. (1987) demonstrated that equal elemental calcium doses of calcium gluconate and  $\text{CaCl}_2$  were equivalent in their ability to raise ionized calcium levels, rapidity of ionization and cardiovascular effects. On the other hand, Hempelmann et al. (1978) found that, while both  $\text{CaCl}_2$  and calcium gluconate significantly increased blood pressure, left ventricular pressure, SVR, CI, stroke index (SI), peak  $\text{dP/dt}$  and myocardial oxygen consumption, the positive inotropic effects of  $\text{CaCl}_2$  were more pronounced.

In man,  $\text{CaCl}_2$  effectively improved cardiac function when it was depressed by anaesthesia, underlying cardiac disease, or both (Eriksen et al. 1983). Similarly, calcium salts produced positive inotropic effects in cats (Bosnjak and Kampine 1986), dogs (Pagel et al. 1993), calves (Stanley et al. 1976) and horses (Grubb et al. 1996, Grubb et al. 1999a) and attenuated or

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completely reversed the negative lusitropic actions of halothane and isoflurane in horses (Grubb et al. 1999b). Furthermore,  $\dot{Q}_t$  and/or SV increased when calcium salts were administered in conscious (Grubb et al. 1996) and anaesthetized horses (Grubb et al. 1999a) and ponies (Gasthuys et al. 1991a), hypocalcaemic dogs (Drop and Scheidegger 1980) and human patients with cardiac disease (Eriksen et al. 1983). In anaesthetized dogs, calcium gluconate increased myocardial contractility and myocardial oxygen consumption, but in contrast to the adrenergic stimulation induced by isoprenaline, myocardial uptake of free fatty acids remained low, indicating a possibly lower oxygen cost for similar haemodynamic performance (Bugge-Asperheim 1972). Heart rate decreased in halothane anaesthetized ponies (Gasthuys et al. 1991a) and horses (Grubb et al. 1999a) during the administration of calcium, while blood pressure increased when calcium was administered to anaesthetized ponies (Gasthuys et al. 1991a), horses (Grubb et al. 1999a), dogs (Drop and Scheidegger 1980) and humans (Marone et al. 1981, Eriksen et al. 1983, Zaloga et al. 1990, Butterworth et al. 1992, Royster et al. 1992). In most of these reports, the increase in blood pressure was not due to an increase in  $\dot{Q}_t$ , but rather to an increase in SVR.

However, while calcium administration may slightly improve MAP, it significantly increased mortality associated with endotoxic shock (Malcolm et al. 1989) and septic peritonitis (Zaloga et al. 1992) in rats. Furthermore, several researchers failed to demonstrate significant changes in cardiovascular function after calcium administration. Calcium gluconate infusion did not influence blood pressure in conscious horses (Grubb et al. 1996) and  $\dot{Q}_t$  was not affected by calcium administration in dogs (Scheidegger et al. 1980), healthy people (Marone et al. 1981, Eriksen et al. 1983) or patients recovering from cardiac surgery (Zaloga et al. 1990, Butterworth et al. 1992, Royster et al. 1992). Possibly, these conflicting results may be explained by differences in health status, cardiovascular function and pre-existing serum calcium concentrations between the different studies. Indeed, serum calcium concentrations were found to be lower during inhalation anaesthesia than in conscious horses (Gasthuys et al. 1985, Grubb et al. 1999a). Also, Drop and Scheidegger (1980) reported significant increases in  $\dot{Q}_t$  and SV when calcium was administered in hypocalcaemic, but not in normocalcaemic dogs. Similarly, Mathru et al. (1993) found that during normocalcaemia, the predominant effect of  $\text{CaCl}_2$  is peripheral vasoconstriction, while calcium infusion during hypocalcaemia significantly increased left ventricular contractile performance. It can be concluded that the usefulness of calcium salts for cardiovascular support differs between individual patients.



### **Calcium sensitizers**

Most cardiostimulant agents, such as digitalis, catecholamines and phosphodiesterase III inhibitors, induce a positive inotropic effect by facilitating  $\text{Ca}^{2+}$  mobilization through cAMP-dependent or -independent mechanisms in myocardial cells. These agents are therefore sometimes referred to as 'Ca<sup>2+</sup> mobilizers'. On the other hand, 'Ca<sup>2+</sup> sensitizers' increase the Ca<sup>2+</sup> binding affinity of troponin C or stability of the Ca<sup>2+</sup>-troponin C complex and/or facilitate thin filament regulation of cross-bridge cycling and/or directly facilitate cross-bridge cycling (Endoh 2008). Some of these agents (e.g. EMD 57033, CGP 48506) are pure Ca<sup>2+</sup> sensitizers, while others also weakly (Org 30029, SCH00013) or clearly (pimobendan, levosimendan) inhibit PDE III, hereby increasing intracellular cAMP levels in the myocardium (Endoh 2008). Advantages of Ca<sup>2+</sup> sensitizers include the stimulation of cardiac contractility without increasing myocardial oxygen demand (Parissis et al. 2008), without the risks for arrhythmias, cell injury, apoptosis or necrosis due to Ca<sup>2+</sup> overload. Even more, these agents are able to reverse contractile dysfunction under pathophysiological conditions where other agents may be less effective (Endoh 2008). Levosimendan enhances myocardial contractility by Ca<sup>2+</sup> sensitization and causes peripheral vasodilation through ATP-dependent potassium channels (Perrone & Kaplinsky 2005); it also has immunomodulatory, antioxidant and anti-apoptotic properties, whereby lower levels of oxidative stress markers have been reported compared to placebo treatment (Parissis et al. 2008). In dogs with CHF secondary to dilated cardiomyopathy or chronic degenerative valvular disease, pimobendan was found to be safe and well tolerated. Pimobendan enhanced the quality of life when used in combination with furosemide or other conventional therapies and reduced mortality from CHF associated with dilated cardiomyopathy (Gordon et al. 2006). Although Ca<sup>2+</sup> sensitizers appear promising for use in patients with heart failure, they do have long-lasting haemodynamic effects (Lehtonen et al. 2004) and are quite expensive. It appears unlikely that these specific drugs will ever be used for routine cardiovascular support during anaesthesia in patients without cardiac disease. To the authors' knowledge, the effects of pimobendan and levosimendan have not been investigated in horses or ponies.

### **Phosphodiesterase III inhibitors**

As explained earlier, the inotropic and chronotropic effects of  $\beta$  sympathomimetics are mediated by increasing the synthesis of cAMP by adenylate cyclase. At the same time however, cAMP is broken down by phosphodiesterase enzymes, which in this way play an important role in modulating the amplitude and duration of the cyclic nucleotide second

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messenger signal, the response of cells to prolonged agonist stimulation and cross-talk between different second messenger signalling pathways (Beavo 1995). More than 25 PDE's of 7 different families have been recognized in humans (Beavo 1995). Some drugs, including the methylxanthines theophylline, theobromine and caffeine (Butcher & Sutherland 1962), but also papaverine (Kukovetz & Pösch 1970) and pentoxifylline (Cortijo et al. 1993), nonselectively inhibit PDE's of the different families. One example of the clinical use of methylxanthines is as bronchodilators for treatment of asthma (Shenfield 1982). However, these agents also affect the central nervous system, gastrointestinal tract and cardiovascular system (Slapke et al. 1988). Other drugs more specifically inhibit a certain family of PDE enzymes and produce effects that depend on the type of PDE inhibited. There is some evidence to suggest that selective PDE I inhibitors increase cognitive function (Beavo 1995) and certain PDE IV inhibitors may have antidepressant (Bobon et al. 1988) or anti-inflammatory (Teixeira et al. 1994) effects. PDE V inhibitors such as sildenafil can have a role in the treatment of pulmonary hypertension (Michelakis et al. 2002). However, the greatest number of commercially available compounds, including e.g. amrinone, milrinone, vesnarinone, enoximone, pimobendan, etc. primarily inhibit the PDE III family. These drugs have been developed as antithrombotic (reduction of platelet aggregation) (Shintani et al. 1985), antihypertensive (vasodilation) and/or inotropic agents (Beavo 1995).

The inotropic effects of PDE III inhibitors result from increased cAMP levels in the myocardial cell, the effects of which have already been described for the  $\beta$  sympathomimetic agents. However, PDE III inhibitors also increase the cAMP levels in vascular smooth muscle cells, causing a vasorelaxation through three different mechanisms. Cyclic AMP decreases myoplasmic  $\text{Ca}^{2+}$  concentrations (McDaniel et al. 1991, Itoh et al. 1993) by inhibiting the slow, L-type  $\text{Ca}^{2+}$  channels (Sperelakis et al. 1994), reducing  $\text{Ca}^{2+}$  influx in vascular smooth muscle cells (Ishikawa et al. 1993, Orlov et al. 1996) and enhancing  $\text{Ca}^{2+}$  pump activity by phosphorylation of phospholamban (Kimura et al. 1991, Sasaki et al. 1992). Secondly, PDE inhibitors may decrease the  $\text{Ca}^{2+}$  sensitivity of contractile elements in vascular smooth muscle cells (Itoh et al. 1993). Finally, a cAMP-dependent protein kinase catalyzes the phosphorylation of myosin light chain kinase, which interferes with the binding of  $\text{Ca}^{2+}$ -calmoduline to myosin light chain kinase, reducing the activity of this enzyme (Adelstein et al. 1982). In turn, this causes reduced myosin light chain phosphorylation, which is needed for actin-myosin interaction and vascular smooth muscle contraction.

There are three groups of PDE III inhibitors: the bipyridines (amrinone, milrinone), imidazole derivatives (enoximone, piroximone) and benzimidazole derivatives (sulmazole, pimobendan, adibendan) (Barnard & Linter 1993). Comparative studies failed to show clinically relevant differences between most PDE III inhibitors (Via et al. 2003). They all induce an inotropic effect, pulmonary and systemic vasodilation, less chronotropic effects than dobutamine, no increase in myocardial oxygen consumption (Baim 1989) and improved diastolic properties of the left ventricle, such as relaxation, compliance and filling (Barnard & Linter 1993). Because of their inotropic and vasodilating effects, PDE III inhibitors such as amrinone, milrinone and enoximone are sometimes referred to as inodilators. These drugs cause peripheral vasodilation and therefore reduce ventricular wall stress and counteract the increased oxygen requirement normally needed to support enhanced contractility (Colucci 1991). Their lusitropic effect appears to be more pronounced than that of the  $\beta$  sympathomimetics, e.g. the lusitropic action of milrinone was greater than that of adrenaline (Lobato et al. 2000). Potential drawbacks include the long duration of action and a possibly excessive vasodilator effect associated with bolus administration (Via et al. 2003). High doses may indeed substantially reduce MAP, but this effect can be minimized by volume expansion, slower administration of loading doses and the administration of vasopressors (Barnard & Linter 1993). In human medicine, the main indications of these drugs are in patients with heart failure and during weaning from cardiopulmonary bypass (Lehtonen et al. 2004). Reports about the use of PDE III inhibitors in horses are sparse, only the effects of milrinone have been described in this species (Muir 1995). Because of the abundance of information about the many PDE III inhibitors available, only a short overview of some properties of three well known inodilators will be provided here, i.e. amrinone, milrinone and enoximone.

### *Amrinone*

Amrinone was the first PDE III inhibitor approved for clinical human use. In 1978, Benotti et al. investigated its cardiovascular effects and found significant increases in CI and dP/dtmax together with decreases in left ventricular end-diastolic, pulmonary capillary and right atrial pressures, without a change in HR and only a slight decline in mean aortic pressure. Amrinone also improved myocardial systolic and diastolic function in endotoxaemic rabbits and even reduced the systemic inflammatory response syndrome after IV administration of endotoxins (Takeuchi et al. 1999). Amrinone has a half-life of more than 3 hours in humans (Park et al. 1983). Reported side effects include thrombocytopenia, gastrointestinal effects,

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hypotension, fever, liver enzyme elevation and anaphylactoid responses (Treadway 1985). Accumulation can also occur in critically ill patients (Notterman 1991). Although the incidence and/or importance of most of these side effects appear to be limited (Treadway 1985), amrinone is used less frequently compared to newer agents such as milrinone and enoximone.

### *Milrinone*

Milrinone is a second generation bipyridine derivative of amrinone and is 15 times more potent (Barnard & Linter 1993). Milrinone increases left ventricular dP/dt, ameliorates cardiac pump function, improves diastolic filling and accelerates isovolumic myocardial relaxation, without altering myocardial oxygen demand (Colucci 1991). Milrinone was also shown to have less proarrhythmic effects than dobutamine (Caldicott et al. 1993) and may even have anti-inflammatory properties (Möllhoff et al. 1999). Slow administration over 10-15 minutes is recommended for all PDE III inhibitors to avoid sudden decreases in SVR and venous return, which may result in hypotension, especially in hypovolaemic patients (Choudhury & Saxena 2003). When milrinone was administered to halothane anaesthetized horses, increases in HR, MAP,  $\dot{Q}t$ , ejection fraction and maximum rate of increase and decrease of left ventricular pressure were observed (Muir 1995).

### *Enoximone*

Enoximone (MDL 17,043) is an imidazole derivative which mainly inhibits PDE III, although PDE IV inhibition may also contribute to the observed inotropic effects (Szilágyi et al. 2005). Beside the positive inotropic effect, enoximone increases coronary blood flow and reduces SVR and PVR in humans, without significant increases in myocardial oxygen consumption (Dage and Okerholm 1990, Ghio et al. 2003). Myocardial oxygen consumption, as reflected by heart rate-pressure product, was indeed significantly lower in patients after the administration of enoximone compared to patients receiving dobutamine following cardiopulmonary bypass (Lancon et al. 1990). In patients with moderate to severe CHF, enoximone infusion markedly improved left ventricular performance while HR tended to rise and MAP to decrease (Vernon et al. 1991). In similar populations of patients, oral (Leier et al. 1987) and intravenous (Winkle et al. 1990) enoximone increased  $\dot{Q}t$  and decreased SVR, but had minimal or no effects on HR and blood pressure. Furthermore, Leier et al. (1987) reported

that, while the flow through and resistance of the renal and hepatic-splanchnic vascular beds were not altered, enoximone seemed to preferentially reduce limb vascular resistance and augment blood flow to the peripheral musculoskeletal system.

In patients with cardiogenic shock persisting despite the use of adrenergic agents, the addition of enoximone resulted in significant increases in CI and SI and a significant decrease in PCWP, without consistent changes in MAP (Vincent et al. 1990). Of perhaps greater interest for equine practitioners are the effects of inotropic drugs in patients with other types of shock. In contrast to dobutamine, enoximone improved hepatosplanchnic function and had anti-inflammatory properties in fluid-optimized septic shock patients (Kern et al. 2001). In patients with severe and prolonged catecholamine and volume refractory endotoxin shock, even with electromechanical uncoupling and complete myocardial arrest, enoximone was able to immediately restore myocardial contractility and blood pressure (Ringe et al. 2003). In a rat endotoxaemia model, despite contributing to systemic hypotension, enoximone prevented mucosal hypoperfusion (Schmidt et al. 2001).

In humans, enoximone is extensively metabolized into enoximone sulphoxide, very little unchanged drug appears in the urine (Okerholm et al. 1987). Enoximone sulphoxide has the same inotropic and vasodilator activities as the parent molecule, but is only 0.13-0.14 times as potent (Dage & Okerholm 1990). The terminal half-lives of both enoximone and its sulphoxide metabolite were 2.0-2.7 hours and did not appear to be dose related (Morita et al. 1995). Administering 4 consecutive doses at 3h-intervals did not affect pharmacokinetic parameters and no accumulation was observed (Morita et al. 1995).

Adverse effects associated with long term oral enoximone therapy include central nervous (insomnia, headache and anxiety), gastrointestinal (diarrhoea, dyspepsia, vomiting, nausea, abdominal pain, increased liver enzymes mainly in patients with previous liver disease or diabetes) and cardiovascular side effects (usually mild ventricular or supraventricular arrhythmias) (Gilfrich & Dieterich 1991, Vernon et al. 1991). Vernon et al. (1991) mentioned that the gastrointestinal effects were the most common and could be resolved with a reduction in dosage, while Gilfrich & Dieterich (1991) found that cardiovascular side effects were the most frequent (10 % of patients), followed by gastrointestinal complaints in 3 % of the patients. On the other hand, Treese et al. (1991) found that in most patients with advanced chronic heart failure, even long-term enoximone therapy was not associated with an important increase in the incidence of ventricular arrhythmias.

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Most studies investigating the safety and side effects of enoximone have been performed in cardiac patients receiving the drug orally for prolonged periods of time, but its short-term use, e.g. in the intensive care unit (Sicignano et al. 1994) or following cardiac surgery (Gonzalez et al. 1988, Zeplin et al. 1990) was usually reported to be safe, with a low incidence of side effects. In patients with acute myocardial infarction, enoximone was tolerated better and produced fewer side-effects than dobutamine using doses which produced similar increases in  $\dot{Q}t$  (Caldicott et al. 1993). When used during weaning from cardiopulmonary bypass, one of the main concerns with PDE III inhibitors is the occurrence of excessive vasodilation, which can be reduced by slow administration, but often has to be compensated for by volume supplementation and alpha-mimetic stimulation (Kruger et al. 1996). After extracorporeal circulation, enoximone reduced platelet levels and was associated with supraventricular arrhythmias and ventricular tachyarrhythmias (Ferrara et al. 1993). However, an inhibitory effect on platelet aggregation might in fact be beneficial in patients with cardiovascular disease (Buerke et al. 1997). On the other hand, Boldt et al. (1992) reported that platelet aggregation after cardiopulmonary bypass decreased to a similar extent with enoximone treatment as in the control group and concluded that enoximone did not affect platelet function in cardiac surgery patients. In contrast with the report of Ferrara et al. (1993), Pop et al. (1986), who investigated the electrophysiologic effects of enoximone, concluded that, despite its positive chronotropic and dromotropic effects, enoximone did not appear to be arrhythmogenic. Similarly, Brembilla-Perrot et al. (1990) found that enoximone has no supraventricular arrhythmogenic effects and does not facilitate the induction of ventricular arrhythmias in subjects without inducible sustained ventricular tachycardia under basal conditions, although it can accelerate the ventricular tachycardia rhythm in patients who have inducible sustained ventricular tachycardia under basal conditions.

### Vasopressors

Vasopressors cause vasoconstriction and can be used to increase blood pressure through an increase in SVR. Many vasopressors are also positive inotropes and/or chronotropes at the same time. However, even pure vasopressors, which do not affect HR or myocardial contractility, may still have an influence on  $\dot{Q}t$ . When vasoconstriction mainly occurs on the venous side of the circulation, mean systemic filling pressure and venous return will increase and this will tend to augment  $\dot{Q}t$  through an increased preload. On the other hand, arterial

vasoconstriction will increase afterload and may actually reduce  $\dot{Q}_t$ , especially when contractility is already compromised, e.g. by underlying cardiac disease, sepsis or anaesthetic drugs. With regard to tissue perfusion, the effect of vasopressors will depend on the pre-existing arteriolar tone. Arteriolar vasoconstriction will increase blood pressure but reduce perfusion of the tissues distal to constricted arterioles. This may lead to ischaemia of vulnerable organs such as the kidneys and the gut. However, arterial hypotension can be associated with a collapse of vessels perfusing tissues with high extravascular (intracompartmental) pressures, such as the muscles of recumbent horses (Lindsay et al. 1980), because transmural pressure becomes inadequate. Under these circumstances, vasopressors may help to increase transmural pressure and actually restore patency of blood vessels and peripheral tissue perfusion. Vasopressors are therefore usually reserved for situations where hypotension is caused by a reduction in SVR (e.g. due to drug- or endotoxin-induced vasodilation), myocardial contractility and  $\dot{Q}_t$  are normal (or already increased by sympathetic stimulation, fluids and inotropic support) and vascular transmural pressure needs to be restored to maintain (or re-establish) vessel patency and assure tissue perfusion.

Different types of vasopressors are available, which can largely be subdivided into three groups, i.e. vasopressin, calcium salts and sympathomimetics. Although the exact mechanism of action differs somewhat between these groups, they all increase intracellular  $\text{Ca}^{2+}$  levels in vascular smooth muscles. Calcium induces vascular smooth muscle contraction by binding to calmodulin and activating the enzyme myosin light chain kinase, which then phosphorylates myosin, initiating contraction. Calcium would further enhance smooth muscle contractile activity by binding directly to myosin and finally by activating protein kinase C, which phosphorylates smooth muscle myosin at a different site than myosin light chain kinase (Adelstein & Sellers 1987).

### **Vasopressin analogues**

Endogenous vasopressin or antidiuretic hormone is synthesized in the hypothalamus and stored and released into the bloodstream by the posterior pituitary, mainly in response to increases in plasma osmolarity, but also when the arterial baroreceptors detect large decreases in blood pressure (Power & Kam 2001b). The most important physiological effects of vasopressin are water retention by the kidneys, mediated via  $V_2$  receptors on the basolateral surface of cells of the distal convoluted tubules and medullary collecting ducts in the kidney, and vasoconstriction, mediated via  $V_1$  receptors on vascular smooth muscle cells (Mutlu &

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Factor 2004). Activation of  $V_1$  receptors stimulates phospholipase C, promoting hydrolysis of phosphatidylinositol 4,5-bisphosphate ( $PIP_2$ ), which results in formation of inositol triphosphate ( $IP_3$ ) and diacylglycerol (DAG). Inositol triphosphate in turn promotes mobilization of  $Ca^{2+}$  from the endoplasmic reticulum, leading to vascular smooth muscle contraction (Mutlu & Factor 2004). Diacylglycerol stimulates protein kinase C, an enzyme which increases the influx of extracellular  $Ca^{2+}$  through L-type  $Ca^{2+}$  channels (Marshall et al. 1999). Vasoconstriction mainly occurs in nonvital organ systems such as the skin, skeletal muscles and intestines (Vanhoutte et al. 1984, Rajani et al. 2009), while vasodilation occurs in other vessels such as the cerebral and coronary arteries (Vanhoutte et al. 1984). Vasopressin may additionally have some inotropic effects after stimulation of myocardial  $V_1$  receptors (Fujisawa & Iijima 1999), but this is usually overshadowed by a baroreflex-mediated reduction in  $\dot{Q}_t$ . This baroreflex is even facilitated by vasopressin, both through a central action of the hormone and a sensitizing influence on arterial baroreceptors and cardiac afferents (Abboud et al. 1990).

The time required for synthesis, transport and storage of vasopressin in the neurohypophysis is about 1 to 2 hours (Sklar & Schrier 1983), while the plasma half-life of endogenous vasopressin is short, only 6-10 minutes (Morelli et al. 2009). Prolonged stimulation, e.g. during haemorrhagic shock, exhausts the endogenous supply of vasopressin in approximately 1 hour, which leads to vasodilation and hypoperfusion of end organs and may be a contributing factor to the morbidity and mortality associated with haemorrhagic shock (Rajani et al. 2009). Similarly, endogenous vasopressin plasma levels were found to be inappropriately low in vasodilatory septic shock. Except for depletion of endogenous vasopressin stores, it has been suggested that this may also be due to an impaired baroreflex-mediated secretion of vasopressin (Landry et al. 1997). Administering vasopressin or one of its analogues may thus be useful in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressors (Beale et al. 2004). Furthermore, vasopressin receptors remain available despite maximal binding of adrenoceptors by endogenous or exogenous catecholamines.

Examples of arginine vasopressin (AVP) analogues are terlipressin and F-180. Terlipressin is a non-selective, synthetic AVP analogue, which has the nonapeptide sequence of the natural hormone lysine-vasopressin (Morelli et al. 2009). It has a somewhat greater preference for vascular  $V_1$  receptors than vasopressin, which has equal affinity for  $V_1$  and  $V_2$  receptors (Mutlu & Factor 2004). It is less expensive than vasopressin and has a long half-life, making



single bolus dosing possible (Mutlu & Factor 2004). Another, perhaps less known vasopressin analogue is F-180, a long-acting drug with selective effects on the  $V_1$  receptor (Bernadich et al. 1998).

Although arginine vasopressin and terlipressin are potent adjunct vasopressor agents which effectively increase SVR and blood pressure and reduce catecholamine requirements in patients with advanced vasodilatory or haemorrhagic shock, who remain hypotensive despite adequate fluid resuscitation and infusions of catecholamines (Jochberger et al. 2005, Tsuyenoshi et al. 2005, Krismer et al. 2006, Ertmer et al. 2008), the influence on the final outcome will remain uncertain until large scale, prospective studies have been performed (Jochberger et al. 2005). A second possible indication for vasopressin is during treatment of cardiac arrest. Vasopressin's effects were similar to those of adrenaline in the management of ventricular fibrillation and pulseless electrical activity and were even superior to those of adrenaline in patients with asystole (Krismer et al. 2006). Furthermore, vasopressin followed by adrenaline resulted in significantly higher rates of survival to hospital admission and discharge (Krismer et al. 2006). In a porcine cardiac arrest model, with severe hypotension induced by blood loss, vasopressin redirected blood from bleeding sites to more vital organs and resulted in sustained vital organ perfusion, less metabolic acidosis and prolonged survival, in contrast with large-dose adrenaline or saline administration (Voelckel et al. 2000).

Nevertheless, AVP should not be used as the sole vasopressor agent (Krismer et al. 2006). Especially when used in higher doses, AVP and terlipressin can reduce  $\dot{Q}_t$ , oxygen delivery ( $DO_2$ ) and mixed venous oxygen saturation, with impaired perfusion and ischaemic injury of tissues such as the gut, liver and skin (Ertmer et al. 2008). Also, while the efficacy of catecholamines is often markedly reduced in vasodilatory shock states, exogenous vasopressin receptor agonists appear to be more efficacious and even moderate doses may lead to an exaggerated increase in SVR (Ertmer et al. 2008). In septic rats, high dose AVP infusion severely compromised gut mucosal blood flow, which may be related to arteriolar vasoconstriction, a reduction in  $\dot{Q}_t$ , or both (Westphal et al. 2004). The inflammatory response to the septic injury was also increased (Westphal et al. 2004). On the other hand, during long-term hyperdynamic endotoxaemia in pigs, a 12 hour low-dose infusion of terlipressin increased MAP and SVR and decreased  $\dot{Q}_t$  and global oxygen consumption, without any detrimental effect on hepatosplanchnic perfusion, oxygen exchange and metabolism. Nevertheless, a marked hyperlactataemia occurred, which did not originate from the

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hepatosplanchnic organs, but from other tissues, possibly muscles and skin (Asfar et al. 2005). Ischaemic skin lesions are indeed another common complication during continuous infusion of AVP in patients with catecholamine-resistant vasodilatory shock (Dünser et al. 2003). Hyponatraemia and tissue oedema in response to anti-diuresis and water reabsorption may also occur, as well as decreases in platelet counts and increases in aminotransferase activity and bilirubin concentrations (Ertmer et al. 2008).

To avoid side effects, high volume fluid therapy is recommended when infusing AVP or terlipressin (Ertmer et al. 2008). When using terlipressin, a continuous infusion appears to be superior to bolus administration, since intermittent bolus injections of terlipressin caused decreases in HR and CI and increases in PVR, while continuous low-dose infusion of the drug stabilized haemodynamics and improved myocardial performance in endotoxaemic sheep (Lange et al. 2007). Platelet count, surrogate variables of hepatic dysfunction, electrolytes and osmolality should also be strictly monitored in patients treated with vasopressin analogues (Ertmer et al. 2008).

Literature describing the cardiovascular effects of exogenous AVP or its analogues in equids is scarce. In hypotensive, isoflurane anaesthetized foals, vasopressin (0.3 and 1.0 mU/kg/min) increased SVR and blood pressure without affecting CI and  $\text{DO}_2$ , but increased the gastric to arterial  $\text{CO}_2$  gap, which is indicative for reduced splanchnic perfusion (Valverde et al. 2006).

### **Calcium salts**

As already mentioned, calcium chloride or gluconate administration increased blood pressure in anaesthetized ponies (Gasthuys et al. 1991a), horses (Grubb et al. 1999a), dogs (Drop and Scheidegger 1980) and humans (Marone et al. 1981, Eriksen et al. 1983, Zaloga et al. 1990, Butterworth et al. 1992, Royster et al. 1992). In most of these reports this was not due to an increase in  $\dot{Q}_t$ , but rather to an increase in SVR, illustrating the vasoconstrictive effects of calcium administration.

### **Sympathomimetics**

Many sympathomimetics have vasoconstrictive properties through their effects at  $\alpha_1$  adrenergic receptors, which are G-protein coupled receptors. Many different types of  $\alpha_1$  adrenoceptors exist in different tissues and many different intracellular signaling effectors have been described, including phospholipase A<sub>2</sub>, phospholipase D and activation of  $\text{Ca}^{2+}$  and

K<sup>+</sup> channels (Marshall et al. 1999). However, most  $\alpha_1$  adrenoceptors, including those on vascular smooth muscle cells, are linked to phospholipase C via a G protein. When activated, the  $\alpha$  subunit of the heterotrimeric G protein, G<sub>q</sub>, binds GTP and dissociates from the  $\beta\gamma$  subunits and activates phospholipase C, which hydrolyzes PIP<sub>2</sub> to IP<sub>3</sub> and DAG (Marshall et al. 1999), with effects on Ca<sup>2+</sup> transients as already described for vasopressin. Many sympathomimetic drugs not only induce vasoconstriction but also have inotropic and/or chronotropic properties. Furthermore, the vasoconstrictive effect of some drugs, such as adrenaline and dopamine, depends on the dose administered. Subdivision of the catecholamines as pure inotropes or pure vasopressors is therefore not always possible. Only the agents with clear vasoconstrictive and less inotropic effects will be discussed (Table 2).

### *Noradrenaline*

Noradrenaline or norepinephrine is an endogenous catecholamine secreted by the adrenal medulla and is the main neurotransmitter at sympathetic postganglionic fibres. It is a rather potent  $\beta_1$  and very potent  $\alpha_1$  and  $\alpha_2$  agonist which mainly functions as a vasopressor (Barnard & Linter 1993, Morrill 2000). Systemic vascular resistance and arterial pressure are raised because of generalized vasoconstriction. This causes a vagally mediated baroreceptor response, which usually obscures the direct effects of noradrenaline on the heart and rather tends to cause slight bradycardia (Barnard & Linter 1993, Calvey & Williams 2001b). Also, noradrenaline directly increases myocardial contractility (Garb 1950), but  $\dot{Q}_t$  may in fact decrease due to the substantial increase in SVR (Barnard & Linter 1993, Morrill 2000).

Noradrenaline is used when the importance of increasing perfusion pressure outweighs the disadvantages of a lower  $\dot{Q}_t$ , or to counterbalance the vasodilatory effects of other agents (Barnard & Linter 1993, Via et al. 2003). Additionally, the effects of noradrenaline on  $\alpha$  and  $\beta_1$  receptors in the myocardium may complement the positive inotropic effects of other drugs, and when relatively low doses are used (0.5-1.5  $\mu\text{g}/\text{kg}/\text{min}$ ), excessive vasoconstriction is not a problem and there are no deleterious effects on renal function (Calvey & Williams 2001b). Time to onset of action of noradrenaline is 1 to 2 minutes and because the half-life is very short (20-30 seconds) (Power & Kam 2001b), the duration of the effect is limited to 1-2 minutes (Morrill 2000).

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**Table 2: Sympathomimetic agents with primarily a vasopressor action.**

Drug	Patients	Dose	Receptor activity	Cardiovascular effects	References
Norepinephrine	General		Very potent $\alpha_1$ and $\alpha_2$ Additional $\beta_1$ effect	Mainly vasopressor effect, SVR & ABP $\uparrow$ Usually slight bradycardia (vagal mediated) Contractility $\uparrow$ but $\dot{Q}_t$ may $\downarrow$ due to $\uparrow\uparrow$ SVR May cause arrhythmias, $\uparrow$ myocardial $O_2$ consumption, renal, abdominal visceral and skeletal muscle ischaemia	Barnard & Linter 1993, Morrill 2000  Friedrichs & Merrill 1991, Morrill 2000
	Horses	3 $\mu\text{g}/\text{kg}$		MAP $\uparrow$ during 6 minutes but less pronounced than with epinephrine, HR initially $\uparrow$ slightly, but pronounced $\downarrow$ during maximal pressor response Ventricular arrhythmias in 2 of 4 animals	Lees & Tavemor 1970
	Foals	0.05 - 0.40 $\mu\text{g}/\text{kg}/\text{min}$		ABP & SVR $\uparrow$ , HR & CI $\downarrow$	Hollis et al. 2006b, Craig et al. 2007, Hollis et al. 2008
		0.3 - 1 $\mu\text{g}/\text{kg}/\text{min}$		During deep isoflurane anaesthesia (with hypotension) in neonatal foals: SVR & ABP $\uparrow$ , CI & $DO_2$ also $\uparrow$ but less pronounced than with dobutamine	Valverde et al. 2006
Phenylephrine	General		Selective $\alpha_1$ agonist Little effect on $\beta$ receptors	SVR & ABP $\uparrow$ , minimal direct effect on HR and contractility, vagal mediated bradycardia may occur	Hardy et al. 1994
	Conscious horses	1 - 6 $\mu\text{g}/\text{kg}/\text{min}$		RAP, SAP, DAP, MAP & PCV $\uparrow$ , HR & $\dot{Q}_t$ $\downarrow$ , SV =, AV blocks	Hardy et al. 1994
	Anaesthetized ponies and horses	0.25 - 2 $\mu\text{g}/\text{kg}/\text{min}$		MAP, CVP, SVR & PCV $\uparrow$ , muscle blood flow & CI =	Lee et al. 1998, Raisis et al. 2000b
Methoxamine	General		Selective $\alpha_1$ agonist	As for phenylephrine	Calvey & Williams 2001b
	Horses	40 $\mu\text{g}/\text{kg}$ before induction		No change in cardiopulmonary function during anaesthesia	Dyson & Pascoe 1990
	Ponies	13 $\mu\text{g}/\text{kg}$ , then 5 $\mu\text{g}/\text{kg}/\text{min}$		SVR & ABP $\uparrow$ , $\dot{Q}_t$ $\downarrow$	Brodgelt et al. 1998
Metaraminol	General		Direct effect on vascular adrenergic receptors Stimulates norepinephrine release	SVR & ABP $\uparrow$	Calvey & Williams 2001b, Kee 2003

Abbreviations used: systemic vascular resistance (SVR), arterial blood pressure (ABP), cardiac output ( $\dot{Q}_t$ ), oxygen ( $O_2$ ), mean arterial pressure (MAP), heart rate (HR), cardiac index (CI), oxygen delivery ( $DO_2$ ), right atrial pressure (RAP), systolic (SAP) and diastolic arterial pressure (DAP), packed cell volume (PCV), stroke volume (SV), atrioventricular (AV), central venous pressure (CVP).

However, caution is advised when using this drug. Like adrenaline, noradrenaline has arrhythmogenic properties (Friedrichs & Merrill 1991). Myocardial oxygen consumption is invariably increased (Barnard & Linter 1993, Morrill 2000), ischaemia may be exacerbated and ventricular function can be compromised (Barnard & Linter 1993). Because of generalized vasoconstriction, renal, abdominal visceral and skeletal muscle ischaemia may also occur (Morrill 2000) and, if used in shock patients, the state of shock may actually be worsened (Calvey & Williams 2001b). In human medicine, noradrenaline is usually not recommended for patients with hypovolaemia, because *“There must be adequate volume to generate pressure, and clinicians should remember to ‘fill up the tank’ before attempting to constrict the vessels”* (Morrill 2000).

Although some clinicians commonly use noradrenaline in anaesthetized horses when blood pressure is not responsive to dobutamine and/or in vasodilatory shock states (e.g. endotoxaemia), little information is available on the effects in adult horses. A bolus of noradrenaline (3 µg/kg) in halothane anaesthetized horses increased MAP during 6 minutes, but this increase was less pronounced than with adrenaline at the same dose. Heart rate initially increased slightly, followed by a more pronounced bradycardia shortly after the time of the maximal pressor response. In 2 of 4 animals receiving noradrenaline, ventricular arrhythmias were observed (Lees & Tavernor 1970). Using a total dose of 50 – 200 µg in conscious adult horses, Sanders et al. (1991) reported increases in blood pressure and decreases in bronchial artery flow after noradrenaline administration.

In contrast to the paucity of data in adult horses, several researchers have studied the effects of noradrenaline in young foals (Hollis et al. 2006b, Valverde et al. 2006, Craig et al. 2007, Hollis et al. 2008). Noradrenaline (0.1–0.3 µg/kg/min) increased blood pressure and SVR and decreased HR and CI compared to a placebo treatment with saline in normotensive conscious foals (Hollis et al. 2006b, Hollis et al. 2008). No significant differences in urine output, creatinine clearance or fractional excretion of electrolytes were found using a dose of 0.1 µg/kg/min in Thoroughbred foals (Hollis et al. 2006b), but urine output and creatinine clearance increased when administering a dose of 0.3 µg/kg/min in pony foals (Hollis et al. 2008). In the latter report, the authors concluded that noradrenaline may be useful for hypotensive foals, because it increases SVR and blood pressure without negatively affecting renal function. Similar results were found in 1 – 2 week old, isoflurane anaesthetized foals, where noradrenaline (0.05-0.40 µg/kg/min) increased blood pressure, PAP, SVR and PVR, while HR decreased (Craig et al. 2007). Cardiac index and DO<sub>2</sub> also decreased, but the

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changes were not significant. Oxygen consumption, oxygen extraction, mixed venous oxygen tension and standard base excess, all markers of inadequate tissue perfusion, did not change (Craig et al. 2007). In neonatal hypotensive foals during deep isoflurane anaesthesia, noradrenaline (0.3 and 1.0  $\mu\text{g}/\text{kg}/\text{min}$ ) increased not only SVR and blood pressure, but also CI and  $\text{DO}_2$ , while the oxygen extraction ratio decreased. However, as would be expected, the increases in CI and  $\text{DO}_2$  were much less pronounced than after dobutamine administration (Valverde et al. 2006).

### *Phenylephrine*

Phenylephrine is closely related structurally to adrenaline and noradrenaline. It is a selective  $\alpha_1$ -adrenergic agonist (Calvey & Williams 2001b) and has little effect on  $\beta$  adrenoreceptors of the heart (Kee 2003). It therefore has minimal direct effects on HR and contractility, but bradycardia can be observed in response to the increase in blood pressure (Hardy et al. 1994). In septic shock patients, hepatosplanchnic blood flow and oxygen delivery were lower during treatment with phenylephrine compared to noradrenaline (Reinelt et al. 1999).

Phenylephrine infusion (1, 3 or 6  $\mu\text{g}/\text{kg}/\text{min}$ ) in conscious horses significantly increased PAP, RAP, SAP, DAP, MAP and PCV and significantly decreased HR and  $\dot{Q}_t$ , but SV did not change significantly. At the highest dosage, the rate-pressure product increased. At all doses, bradycardia was observed, while 2<sup>nd</sup> degree AV block was present in 88 % of horses (Hardy et al. 1994). In halothane anaesthetized ponies, doses of 0.25-2  $\mu\text{g}/\text{kg}/\text{min}$  dose-dependently increased MAP, central venous pressure (CVP), PVR, PCWP and SVR, without improving intramuscular blood flow or CI (Lee et al. 1998). Similarly, Rasis et al. (2000b) reported that phenylephrine decreased femoral arterial and venous blood flow and  $\dot{Q}_t$  and increased MAP, SVR and PCV in anaesthetized horses. Besides its use as a vasopressor, phenylephrine is also commonly used in horses during treatment of nephrosplenic entrapment of the large colon, where splenic contraction is the therapeutic target (Hardy et al. 2000).

### *Methoxamine*

Methoxamine has similar effects to phenylephrine because of its highly selective agonist effects on  $\alpha$ -adrenoceptors. The drug is commonly used in the management of untoward hypotension occurring during anaesthesia, particularly following subarachnoid or extradural blockade or when ganglion-blocking drugs have been employed (Calvey & Williams 2001b). Only a few reports are available about the use of methoxamine in horses or ponies. When

given before induction of anaesthesia, methoxamine 40 µg/kg did not significantly affect cardiopulmonary function during halothane anaesthesia in horses (Dyson & Pascoe 1990). However, when given during anaesthesia in halothane anaesthetized ponies, methoxamine 13 µg/kg followed by 5 µg/kg/min was able to maintain normotension, while  $\dot{Q}_t$  was lower and SVR higher compared to the saline group (Brodbelt et al. 1998).

### *Metaraminol*

Metaraminol is a sympathomimetic drug with a direct effect on vascular-adrenergic receptors and an indirect mechanism of action related to the stimulation of noradrenaline release (Holmes 2005). It can be used for the prevention and treatment of acute hypotension, e.g. caused by epidural or spinal anaesthesia, surgical complications or drug reactions (Calvey & Williams 2001b, Kee 2003). To the authors' knowledge, the use of metaraminol in horses has not been described.

## **Combinations**

Under certain circumstances, it may be advantageous to combine agents which exert different effects (e.g. vasopressors and inotropic drugs) or agents which exert similar effects through a different mechanism of action (e.g. sympathomimetics with calcium salts, phosphodiesterase inhibitors with sympathomimetics, vasopressin analogues with sympathomimetic vasopressors, etc.). Since extensive research has been performed in this area, it is only possible to give a few examples here.

During treatment of vasodilatory shock, increased myocardial contractility, peripheral vasoconstriction and preservation of renal function are concomitant objectives which might be achieved using CRI's of noradrenaline (inotropic and vasoconstrictor) and low dose dopamine (renal and splanchnic blood flow) (Schaer et al. 1985). However, it remains uncertain whether this combination is superior to dopamine alone (Beale et al. 2004). Similarly, 'renal doses' of dopamine are sometimes used in combination with dobutamine in the treatment of shock states with a low  $\dot{Q}_t$  (e.g. septic or cardiogenic shock) in an attempt to improve both renal and cardiac function (Calvey & Williams 2001b). Another example of combined use of different sympathomimetic agents is the administration of noradrenaline (0.1 µg/kg/min) with dobutamine (5 µg/kg/min), which increased blood pressure and SVR and decreased HR and CI compared to saline administration in normotensive neonatal foals, without differences in urine output, creatinine clearance or fractional excretion of electrolytes (Hollis et al. 2006b).

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Because inotropic drugs exert their effect through increased  $\text{Ca}^{2+}$  influx in the myocardium, the effects of  $\beta$ -adrenergic agonists might be enhanced when these drugs are administered together with  $\text{Ca}^{2+}$  (d'Hollander et al. 1982, Abernethy et al. 1995). However, calcium salts rather tended to attenuate the cardiotoxic effects of  $\beta$ -adrenergic agonists in man (Zaloga et al. 1990, Butterworth et al. 1992, Abernethy et al. 1995), most likely due to a negative effect of free  $\text{Ca}^{2+}$  ions on the activity of adenylyl cyclase in the myocardial cells (Drummond & Duncan 1970, Colvin et al. 1991, Yu et al. 1993, Abernethy et al. 1995). At the same time,  $\text{Ca}^{2+}$  decreased the inotropic effects of milrinone in rat heart preparations (Goyal and McNeill 1986), possibly by stimulating the activity of PDE, thereby increasing cAMP degradation (Teo & Wang 1973).

Because inotropic  $\beta$ -sympathomimetics and PDE III inhibitors increase the intracellular concentration of cAMP through independent mechanisms, they may produce more powerful increases in contractility when used in combination. At the same time, PDE III inhibitors have vasodilatory properties, while many  $\beta$ -sympathomimetics act as vasopressors, which may be useful to prevent or treat exaggerated decreases in SVR after administration of PDE III inhibitors. In humans, a combination of adrenaline and amrinone produced additive effects on SV after cardiopulmonary bypass surgery (Royster et al. 1993). Also, enoximone's cardiovascular effects were additive to those produced by dobutamine, with larger increases in CI, left ventricular stroke work index and HR and more pronounced decreases in RAP, PAP, PCWP, SVR and PVR (Gilbert et al. 1995). Other authors have described beneficial effects of combinations of amrinone with dobutamine (Uretsky et al. 1987), noradrenaline (Robinson & Tchervenkov 1987) and dopamine (Olsen et al. 1988).

## Conclusions

In anaesthetized horses, adequate perfusion of peripheral tissues is important to avoid possibly lethal complications such as myopathies. Although balanced anaesthesia and fluid support are useful, cardiovascular stimulant drugs are often needed to achieve this. These include antimuscarinics, inotropic drugs and vasopressors. Antimuscarinic drugs are preferably used to treat bradycardia unrelated to hypertension and are not suitable to augment  $\dot{Q}_t$  under other circumstances, for many reasons. Vasopressors are useful in patients with hypotension caused by vasodilation, e.g. induced by drugs or endotoxins, where myocardial contractility and  $\dot{Q}_t$



are normal or high. Under such circumstances, the benefit of restoring vascular transmural pressure often outweighs the disadvantage of not improving  $\dot{Q}_t$  and possibly compromising perfusion of certain tissues because of excessive vasoconstriction. However, in most cases, inotropic drugs are preferable to improve tissue perfusion. Digitalis glycosides, calcium salts and calcium sensitizers are less suitable for routine cardiovascular support during anaesthesia, because of different reasons including a lack of effectiveness, cost, toxicity and/or pharmacokinetic considerations. Extensive research has been performed on the  $\beta$  sympathomimetic agents, of which dobutamine appears to remain the most useful agent for clinical use in anaesthetized horses. In humans, dobutamine typically causes inotropic effects, combined with some vasodilation, effects which are quite similar to those of PDE III inhibitors in humans. These agents therefore might be useful during equine anaesthesia, but have received very little attention in literature.

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## **Scientific aims**





Treatment of cardiovascular depression is important to reduce anaesthetic related mortality in horses. However, to detect cardiovascular depression and to monitor the response to treatment, an easily applicable, continuous, noninvasive and reliable method to measure cardiac output in anaesthetized horses is needed. Pulse contour analysis using the LiDCO-Plus<sup>®</sup> monitor appears attractive for this purpose. The first aim of the experimental part of this PhD thesis was therefore to evaluate the reliability of this monitor in ponies or horses.

When cardiac output is low, treatment with positive inotropes is often needed during anaesthesia in horses. While extensive literature is available on the effects of sympathomimetic drugs in horses, there is very limited information on the effects of phosphodiesterase III inhibitors. In humans, these agents are potent inotropes and induce little serious side effects during short term use. As described in chapter 1.2, amrinone may induce some side effects and is used less frequently compared to milrinone and enoximone in human medicine. Since the effects of milrinone had already been investigated in horses, the second aim of the present PhD thesis was to evaluate the cardiovascular effects and safety of enoximone in ponies and/or horses, alone or combined with other inotropic and vasoactive drugs.

To achieve these aims, both an experimental and a clinical study were set up. The specific aims of the experimental trial were to:

- assess the reliability of the Pulse Contour analysis logarithm used in the LiDCO-Plus<sup>®</sup> monitor to measure cardiac output by comparing it to the lithium dilution technique.
- evaluate the cardiovascular effects and side effects of a bolus of enoximone in isoflurane anaesthetized ponies, alone or in combination with dobutamine or calcium chloride.

The aim of the clinical study was to

- explore enoximone's usefulness in horses undergoing colic surgery.



## **Comparison between lithium dilution and pulse contour analysis techniques for cardiac output measurement in isoflurane anaesthetized ponies: influence of different inotropic drugs**

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**SUMMARY**

Cardiac output ( $\dot{Q}t$ ) measurements using lithium dilution (LiDCO) and pulse contour analysis (PulseCO) techniques were compared in isoflurane anaesthetized ponies before and during the administration of different inotropic/vasoactive drugs. Six ponies aged  $5.0 \pm 1.6$  years and weighing  $286 \pm 53$  kg were enrolled in a prospective, randomized, experimental cross-over trial. After sedation (romifidine) and induction (midazolam + ketamine), anaesthesia was maintained with isoflurane in oxygen. After 90 minutes (= T0), 1 of 4 treatments was administered: saline 0.1 mL/kg (S), enoximone 0.5 mg/kg intravenously (E), enoximone followed by dobutamine (0.5  $\mu$ g/kg/min for 120 minutes) (ED) or enoximone followed by a calcium chloride infusion (0.5 mg/kg/min for 10 minutes) (EC). Data were recorded for 120 minutes after T0. The PulseCO (recorded from carotid artery) was calibrated before T0, no further recalibrations were performed.  $\dot{Q}t$  was determined with LiDCO ( $\dot{Q}t_{\text{LiDCO}}$ ) and PulseCO ( $\dot{Q}t_{\text{PulseCO}}$ ) simultaneously at T5, T10, T20, T40, T60, T80, T100 and T120. Systemic vascular resistances ( $\text{SVR}_{\text{LiDCO}}$  and  $\text{SVR}_{\text{PulseCO}}$ ) were calculated.

In the saline group,  $\dot{Q}t_{\text{PulseCO}}$  was  $4.9 \pm 12.3$  % lower than  $\dot{Q}t_{\text{LiDCO}}$  ( $P < 0.01$ ), whereas  $\text{SVR}_{\text{PulseCO}}$  was  $6.9 \pm 14.4$  % higher than  $\text{SVR}_{\text{LiDCO}}$  ( $P < 0.01$ ). These differences increased over time,  $\dot{Q}t$  by 0.06 % per minute ( $P=0.042$ ) and SVR by 0.08 % per minute ( $P=0.018$ ).  $\dot{Q}t_{\text{PulseCO}}$  was higher than  $\dot{Q}t_{\text{LiDCO}}$  in the EC group ( $1.8 \pm 23.3$  %), but lower than  $\dot{Q}t_{\text{LiDCO}}$  in groups E ( $-11.7 \pm 20.4$  %) and ED ( $-10.0 \pm 25.9$  %) (significant difference between treatments,  $P < 0.01$ ). The differences in SVR in groups E ( $20.4 \pm 32.0$  %) and ED ( $20.7 \pm 35.3$  %) were significantly higher than in groups S ( $6.9 \pm 14.4$  %) and EC ( $3.1 \pm 22.2$  %) ( $P < 0.01$ ). It can be concluded that the PulseCO values deviated significantly from the LiDCO measurements in isoflurane anaesthetized ponies and that this difference was influenced by inotropic/vasoactive drugs.

### Introduction

During equine anaesthesia, cardiovascular monitoring usually consists of an electrocardiogram and invasive measurement of arterial blood pressure. Indeed, supporting mean arterial blood pressure (MAP) is important in the prevention of severe complications, such as myopathies. However, measurement of cardiac output ( $\dot{Q}_t$ ) would allow an even better assessment of cardiovascular function. Ideally, the measurement technique must be easy to perform, accurate, continuous and minimally invasive. Numerous techniques have been described, such as the Fick principle (Fick 1870), electromagnetic flowmetry (Brunsting et al. 1970), indicator dilution methods (Lagerlof et al. 1950), Doppler echocardiography (Steingart et al. 1980), thoracic electrical bioimpedance (Mattar et al. 1986), pulse contour analysis (Kouchoukos et al. 1970) and rebreathing of carbon dioxide (Klausen 1965). While many of these methods have been used in horses (Waugh et al. 1980, Evans et al. 1988, Young et al. 1996, Giguère et al. 2005), the indicator dilution techniques have been used most frequently (Muir et al. 1976), but only allow an intermittent assessment of  $\dot{Q}_t$ . A continuous thermodilution method has been developed (Luchette et al. 2000), but its response time was reported to be rather slow (Siegel et al. 1996) and to the authors' knowledge, the use of the technique has not been described in depth in the horse. Transoesophageal echocardiography has also been reported as an effective and non-invasive method for measurement of  $\dot{Q}_t$  in anaesthetized horses (Young et al. 1996), but this technique requires experience and a long, expensive device is needed in horses.

Several other techniques have been developed, but one of the most attractive alternatives was the estimation of  $\dot{Q}_t$  based on an analysis of the arterial pressure wave, which would allow continuous, beat-to-beat assessment of  $\dot{Q}_t$  and only requires the insertion of an arterial catheter. Most of these pulse contour analysis methods are based on the "Windkessel" theory (Kouchoukos et al. 1970) and relate the arterial pressure or pressure difference to a flow or volume by taking the impedance through which the flow is driven into account (Jansen et al. 1990). Numerous researchers developed countless linear models to assess stroke volume (SV) or  $\dot{Q}_t$  based on this theory, with rather disappointing results (Alderman et al. 1972, Starmer et al. 1973, Verdouw et al. 1975, Wesseling et al. 1976). Later, an extended version of the Windkessel model was developed: the "Modelflow" method (Wesseling et al. 1993). This nonlinear, time-varying, three-element model was able to maintain reliable determinations of  $\dot{Q}_t$  for a 24 hour period in humans, provided that no profound fluctuations in blood pressure

occurred (Gödje et al. 1999). An improved version of this algorithm has been implemented in the current PiCCO<sup>®</sup> software (Pulsion Medical Systems AG, Munich, Germany) (Gödje et al. 2002).

In the LiDCO-Plus<sup>®</sup> monitor (LiDCO-plus Hemodynamic Monitor<sup>®</sup>, LiDCO Ltd., London, UK), continuous arterial pulse contour analysis is performed using a different formula compared to the previous methods. Cardiac output is calculated during each heart beat from the beat duration, ejection duration, MAP and the modulus and phase of the first harmonic of the waveform (Fig. 2 Chapter 1.1). The PulseCO<sup>®</sup> technique incorporates a model of the pressure transfer from the aorta to the radial artery and uses a model of the arterial system in which wave reflections are well represented. The technique was therefore expected to be more accurate and less sensitive to changes in systemic vascular resistance (SVR) than the “Windkessel” model, where aorta and radial artery pressures are assumed to be equal and wave travel phenomena are not characterized (Linton & Linton 2001). Compared to thermodilution and LiDCO<sup>®</sup>, PulseCO<sup>®</sup> reliably tracked changes in  $\dot{Q}t$  in haemodynamically stable patients for at least 8 hours after cardiac surgery in humans, without performing recalibration (Hamilton et al. 2002).

As the PulseCO<sup>®</sup> algorithm was developed for use in humans, the reliability in animals can be questioned. In anaesthetized dogs, the PulseCO<sup>®</sup> provided directional tracking of  $\dot{Q}t$  measurements but poor accuracy when the haemodynamic conditions were altered appreciably from those during the initial calibration with the LiDCO<sup>®</sup> system (Chen et al. 2005). Although Martin-Bouyer et al. (2006) did not report significant differences between LiDCO<sup>®</sup> and PulseCO<sup>®</sup> in anaesthetized dogs after epidural administration of romifidine, the difference between the two methods gradually increased over time. One study in 24 horses undergoing elective or colic surgery reported a good correlation between LiDCO<sup>®</sup> and PulseCO<sup>®</sup> (Hallowell & Corley 2005). The objective of the present investigation was to further evaluate the accuracy of the PulseCO<sup>®</sup> software in ponies by comparing LiDCO<sup>®</sup> and PulseCO<sup>®</sup> measurements under changing haemodynamic conditions.

## Materials & Methods

### Animals

After approval by the Ethical Committee of the Faculty of Veterinary Medicine of the University of Ghent (EC 2005/48), 6 ponies were used for the study: 5 geldings and 1 mare, aged  $5.0 \pm 1.6$  years and weighing  $286 \pm 53$  kg. The left carotid artery had been transposed to a subcutaneous position at least two months before the experiment. Based on a physical and general blood examination, all ponies were regarded as ASA (American Society of Anesthesiologists) class I (normal and healthy).

### Anaesthetic protocol and instrumentation

The ponies were fasted for 12 hours before anaesthesia. After sedation (80 µg/kg romifidine intravenously (IV) (Sedivet<sup>®</sup>, Boehringer Ingelheim, Brussels, Belgium)), a 12 gauge catheter (Intraflon 2<sup>®</sup>, Vygon, Ecoen, France) was placed in the right jugular vein. Fifteen minutes later, general anaesthesia was induced with 0.06 mg/kg midazolam IV (Dormicum<sup>®</sup>, Roche, Brussels, Belgium) and 2.2 mg/kg ketamine IV (Anesketin<sup>®</sup>, Eurovet, Heusden-Zolder, Belgium). After endotracheal intubation (24 - 26 mm OD Soft rubber tracheal tube, Rüsich AG, Kernen, Germany), the ponies were placed in right lateral recumbency. The endotracheal tube was connected to a large animal anaesthetic unit (Matrix medical inc., Orchard Park, New York, USA + Sulla 909V<sup>®</sup>, Dräger, Lübeck, Germany) with a large animal respirator (Smith respirator LA 2100<sup>®</sup>, model 2002, Veterinary Technics/BDO-Medipass, Hoogezand, the Netherlands).

General anaesthesia was maintained with isoflurane (Isoflo<sup>®</sup>, Abbott Laboratories Ltd., Queenborough, Kent, United Kingdom) in oxygen, delivered through an out-of-circuit vaporizer (Drägerwerk AG, Lübeck, Germany). During the first 10 minutes of anaesthesia, the oxygen flow was set at 6 L/min, after which it was decreased to 10 mL/kg/min. Inspiratory and expiratory CO<sub>2</sub>, O<sub>2</sub> and isoflurane concentrations were monitored with a calibrated, methane-insensitive, multi-gas analyzer (HP M1025B<sup>®</sup>, Hewlett Packard Company, Houston, USA). The end-tidal isoflurane concentration was maintained at 1.7 %. Respiration mode was assisted-controlled, with a tidal volume of 10 mL/kg, a respiratory frequency of 10 breaths/min, a peak inspiratory pressure of 1.96 kPa (20 cm H<sub>2</sub>O) and an inspiration time of 2 seconds. When necessary, these settings were adapted to maintain PaCO<sub>2</sub> between 4.66 and 6.00 kPa (35 - 45 mm Hg). Lactated Ringer's solution



(Haemofiltration Formula E2, Clear-Flex<sup>®</sup>, Bieffe Medital, Grosotto, Italy) was infused at a rate of 3 mL/kg/hour.

After preparation of the skin over the left jugular vein and transposed carotid artery, a 20 gauge catheter (Vasocan<sup>®</sup> Braunüle Luer Lock, B. Braun Melsungen AG, Melsungen, Germany) was placed in the left carotid artery. Using the Seldinger technique, a 7 French thermodilution catheter (3-lumen, Abbott Laboratories, North Chicago, IL60064, USA) was placed in the left jugular vein, with the distal port in the right atrium to measure right atrial pressure (RAP). Correct positioning of the catheter was confirmed by the characteristic waveforms. Both the arterial and right atrial catheters were connected to a pressure transducer, zeroed at the level of the right atrium. Both catheters were regularly flushed during anaesthesia using a heparinized saline solution (100 IU heparin per mL (Heparine LEO<sup>®</sup>, Leo Pharma B.V., Breda, the Netherlands)). Pressures were monitored with a CMS-Patientenmonitor<sup>®</sup> (HP M1165A<sup>®</sup>, model 56S, Hewlett-Packard GmbH, Böblingen, Germany), which was also used to record the electrocardiogram (ECG) (base-apex lead), to perform pulse-oximetry (probe placed on tongue) and to measure body temperature using an oesophageal probe. The pressure monitoring system was calibrated against a mercury manometer before each experiment. Cardiac output was determined with both the lithium dilution technique ( $\dot{Q}_{\text{LiDCO}}$ ) and with Pulse Contour Analysis ( $\dot{Q}_{\text{PulseCO}}$ ) (LiDCO-plus Hemodynamic Monitor<sup>®</sup>, LiDCO Ltd., London, UK). For LiDCO measurements, a 1 to 1.5 mmol bolus of lithium chloride was injected through the proximal port of the thermodilution catheter, while arterial blood for detection of lithium chloride by the LiDCO sensor (CM10 LiDCO sensor<sup>®</sup>, LiDCO Ltd.) was withdrawn from the carotid artery by the LiDCO Flow Regulator. The LiDCO-plus<sup>®</sup> monitor then calculated  $\dot{Q}_t$  using the following formula:  $\dot{Q}_t = (\text{LiCl dose} \times 60) / [\text{Area} \times (1 - \text{PCV})]$  (where Area = integral of primary concentration versus time curve and PCV = packed cell volume). The monitor requires the user to enter the blood haemoglobin (Hb) concentration and calculates PCV from this value ( $\text{PCV(L/L)} = \text{Hb (g/dL)} / 34$ ) (Linton et al. 2000). Since we measured PCV by centrifugation before each LiDCO determination, but not the Hb concentration, we calculated Hb from PCV using the same formula. The plasma sodium concentration is also required by the LiDCO-plus<sup>®</sup> monitor and was determined on a blood sample withdrawn from the right jugular vein before sedation (AVL 9180 Electrolyte Analyzer<sup>®</sup>, AVL scientific corporation, Roswell, Georgia, USA 30076). Dilution curves rejected by the LiDCO-plus<sup>®</sup> software were repeated immediately. For Pulse Contour Analysis, the pressure waveform from the catheter in the

## LiDCO & PulseCO in ponies

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carotid artery was analyzed by the LiDCO-plus<sup>®</sup> monitor. During LiDCO measurements, PulseCO values were temporarily unavailable, as the arterial catheter had to be disconnected from the pressure transducer to allow blood flow towards the lithium sensor. Therefore,  $\dot{Q}t_{\text{PulseCO}}$  was taken as the mean of the PulseCO values during the last 5 seconds before and the first 5 seconds after each LiDCO measurement. PulseCO calibration, based on a LiDCO measurement, was performed after 60 minutes of anaesthesia and repeated 10 and 20 minutes later if LiDCO and PulseCO values differed by more than 5%. No further recalibrations were performed during the remaining anaesthetic period (120 minutes). At each of these three time points (T-30, T-20 and T-10), baseline values for heart rate (HR), systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP) and RAP were also recorded.

### Experimental design

Ninety minutes after induction, 1 of 4 treatments was administered: an IV bolus of 0.5 mg/kg enoximone 0.5% at a rate of 20 mL/min (treatment E), an equivalent volume of saline (0.1 mL/kg) at 20 mL/min (treatment S), an IV bolus of enoximone 0.5 mg/kg at 20 mL/min, followed by a constant rate infusion of 0.5  $\mu\text{g}/\text{kg}/\text{min}$  dobutamine (Dobutamine Mayne<sup>®</sup>, Mayne Pharma, Brussels, Belgium) for 120 minutes (treatment ED) or an IV bolus of enoximone 0.5 mg/kg at 20 mL/min, followed by an infusion of calcium chloride at 0.5 mg/kg/min (Calcii chloridum 10%, Federa, Brussels, Belgium) from T5 to T15 (treatment EC). T0 was defined as the end of the injection of saline or enoximone, after which data were recorded for 120 minutes. In a randomized order, each pony received all 4 treatments in a crossover trial setting, with a wash-out period of at least 2 weeks between treatments.

Heart rate, SAP, DAP, MAP, RAP,  $\dot{Q}t_{\text{LiDCO}}$  and  $\dot{Q}t_{\text{PulseCO}}$  were recorded at T5, T10, T20, T40, T60, T80, T100 and T120 (time expressed in minutes), except in the EC group, where LiDCO measurements were not performed at T5.

Stroke volume ( $SV_{\text{LiDCO}}$  and  $SV_{\text{PulseCO}}$ ) and SVR ( $SVR_{\text{LiDCO}}$  and  $SVR_{\text{PulseCO}}$ ) were calculated as follows:

$$SV \text{ (mL/beat)} = \frac{1000 * \dot{Q}t \text{ (L/min)}}{HR \text{ (beats/min)}}$$

$$SVR \left( \text{dyne} \cdot \frac{\text{sec}}{\text{cm}^5} \right) = \frac{80 * (\text{MAP (mm Hg)} - \text{RAP (mm Hg)})}{\dot{Q}t \text{ (L/min)}}$$

### Statistical analysis

Statistical analysis was performed using a statistical software programme (S-Plus<sup>®</sup> 7.0 for Windows, Insightful Corp., Seattle, USA). Data are expressed as mean  $\pm$  1 standard deviation (SD). For each pair of  $\dot{Q}t$  measurements after T0, the absolute and relative differences in  $\dot{Q}t$  (AbsDiff $\dot{Q}t$  and RelDiff $\dot{Q}t$  respectively) were calculated as:

$$AbsDiff\dot{Q}t (L/min) = \dot{Q}t_{LiDCO}(L/min) - \dot{Q}t_{PulseCO}(L/min)$$

$$RelDiff\dot{Q}t (\%) = 100\% * \frac{\dot{Q}t_{LiDCO}(L/min) - \dot{Q}t_{PulseCO}(L/min)}{\dot{Q}t_{LiDCO}(L/min)}$$

$$AbsDiffSVR (dyne.sec/cm^5)$$

$$= SVR_{LiDCO}(dyne.sec/cm^5) - SVR_{PulseCO}(dyne.sec/cm^5)$$

$$RelDiffSVR (\%) = 100\% * \frac{SVR_{LiDCO}(dyne.sec/cm^5) - SVR_{PulseCO}(dyne.sec/cm^5)}{SVR_{LiDCO}(dyne.sec/cm^5)}$$

To assess whether these differences were significant during treatment with saline, a paired t-test was performed. The evolution of these differences over time in the control group was assessed using a mixed model ANOVA with pony as random effect and time as continuous fixed effect.

The influence of treatment was analyzed using a mixed model ANOVA with pony as random effect, treatment as categorical fixed effect and time and its interaction with treatment as continuous fixed effects. To further document bias and precision, Bland-Altman plots were obtained and mean bias and limits of agreement between LiDCO and PulseCO techniques were calculated for each treatment group (Bland & Altman 1986).

To assess whether RelDiff $\dot{Q}t$  during treatment S was influenced by changes in HR, SAP, DAP, MAP, RAP, PCV or  $SVR_{LiDCO}$ , mixed models were fitted with pony as random effect and the respective variable as continuous fixed effect. Differences were considered significant if  $P < 0.05$ .

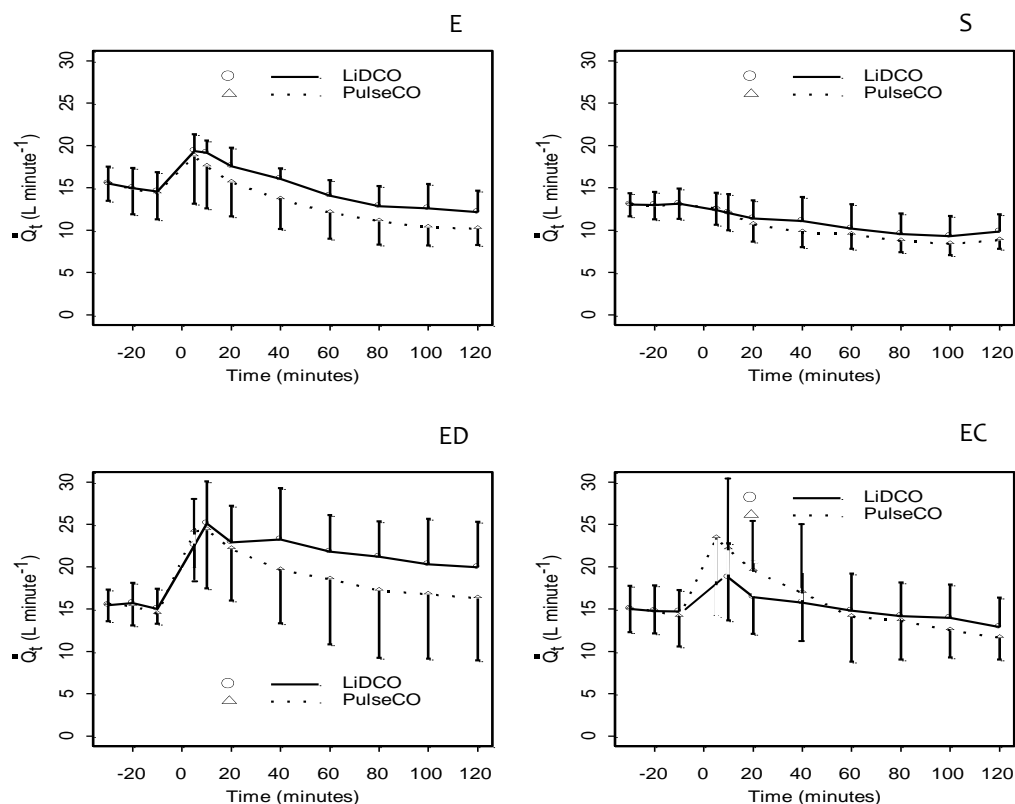
### Results

In total, 186 comparisons between LiDCO and PulseCO values for  $\dot{Q}t$  and SVR were obtained. The mean total lithium chloride dose per pony was  $0.056 \pm 0.011$  mmol/kg, with a

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maximum of 0.068 mmol/kg in one pony. Overall, during saline treatment (Fig. 1 & 2, Table 1), PulseCO underestimated  $\dot{Q}t_{LiDCO}$  by  $0.70 \pm 1.33$  L/min ( $P < 0.001$ ) (mean bias  $4.9 \pm 12.3$  %, limits of agreement -19.7 and +29.5 %) and overestimated overall SVR by  $22.0 \pm 58.0$  dyne.sec/cm<sup>5</sup> ( $P = 0.011$ ) or  $6.9 \pm 14.4$  % ( $P = 0.002$ ) (mean  $\pm$  SD). The difference also increased over time: each minute, the absolute difference between  $\dot{Q}t_{LiDCO}$  and  $\dot{Q}t_{PulseCO}$  increased by 0.007 L/min ( $P = 0.023$ ), while the relative difference increased by 0.06 % per minute ( $P = 0.042$ ). The difference between  $SVR_{LiDCO}$  and  $SVR_{PulseCO}$  increased by 0.29 dyne.sec/cm<sup>5</sup> ( $P = 0.027$ ) or 0.08 % ( $P = 0.018$ ) each minute.

While  $\dot{Q}t_{PulseCO}$  was usually lower than  $\dot{Q}t_{LiDCO}$  during treatments S and E, PulseCO initially overestimated LiDCO values in groups ED and EC, but gradually became lower than LiDCO values during the remaining period of the anaesthesia (Fig. 1 & 2, Table 1). Consequently, there were significant differences between treatments in AbsDiff $\dot{Q}t$  ( $P < 0.001$ ), AbsDiffSVR ( $P = 0.009$ ), RelDiff $\dot{Q}t$  ( $P = 0.001$ ) and RelDiffSVR ( $P = 0.006$ ).



**Fig. 1:** Cardiac output ( $\dot{Q}t$ ) measured using lithium dilution (LiDCO) and Pulse Contour Analysis (PulseCO) in 6 anaesthetized ponies, receiving a bolus of enoximone (E), saline (S), enoximone followed by a dobutamine infusion during 120 minutes (ED) or enoximone followed by a calcium chloride infusion during 10 minutes (EC). T0 = end of administration of saline or enoximone; PulseCO calibration performed at T-30, T-20 and T-10.

Data are represented as mean  $\pm$  1 standard deviation.

**Table 1: Cardiac output ( $\dot{Q}_t$ ), stroke volume (SV) and systemic vascular resistance (SVR) measured by lithium dilution (LiDCO) and pulse contour analysis (PulseCO) in 6 anaesthetized ponies, during treatment (Trt) with saline (S), enoximone (E), enoximone followed by a dobutamine infusion (ED) or enoximone followed by a calcium chloride infusion (EC).**

Variable	Unit	Trt	Measurement Technique	PulseCO calibration			Time after treatment (min)								
				T-30	T-20	T-10	T10	T20	T40	T60	T80	T100	T120		
$\dot{Q}_t$	L/min	S	LiDCO	13.02 ± 1.37	12.97 ± 1.54	13.13 ± 1.79	12.05 ± 2.21	11.40 ± 2.10	11.08 ± 2.86	10.18 ± 2.91	9.55 ± 2.45	9.28 ± 2.38	9.83 ± 2.04		
			PulseCO	13.02 ± 1.37	12.83 ± 1.54	13.03 ± 1.71	12.02 ± 2.02	10.62 ± 1.95	9.73 ± 1.74	9.45 ± 1.65	8.70 ± 1.30	8.33 ± 1.28	8.82 ± 1.03		
		E	LiDCO	15.49 ± 2.04	14.96 ± 2.41	14.57 ± 2.28	19.13 ± 1.44	17.53 ± 2.22	16.04 ± 1.26	14.05 ± 1.86	12.83 ± 2.41	12.56 ± 2.90	12.11 ± 2.54		
			PulseCO	15.49 ± 2.04	14.82 ± 2.94	14.32 ± 3.04	17.50 ± 4.94	15.60 ± 3.98	13.63 ± 3.50	12.03 ± 3.04	11.05 ± 2.76	10.28 ± 2.09	10.12 ± 1.88		
		ED	LiDCO	15.45 ± 1.86	15.69 ± 2.38	15.03 ± 2.35	25.13 ± 4.95	22.89 ± 4.32	23.21 ± 6.09	21.76 ± 4.32	21.18 ± 4.20	20.3 ± 5.38	19.96 ± 5.34		
			PulseCO	15.45 ± 1.86	15.33 ± 2.26	14.42 ± 1.15	24.30 ± 6.86	22.05 ± 6.05	19.6 ± 6.29	18.48 ± 7.65	17.13 ± 7.88	16.72 ± 7.60	16.27 ± 7.31		
		EC	LiDCO	15.00 ± 2.73	14.75 ± 3.06	14.70 ± 2.54	18.72 ± 4.08	16.41 ± 4.20	15.74 ± 4.57	14.80 ± 4.38	14.14 ± 3.99	13.98 ± 3.92	12.89 ± 3.47		
			PulseCO	15.00 ± 2.73	14.73 ± 2.61	14.05 ± 3.46	22.01 ± 8.36	19.47 ± 7.42	16.88 ± 7.56	14.08 ± 5.29	13.58 ± 4.53	12.47 ± 3.19	11.58 ± 2.54		
		SV	mL	S	LiDCO	322 ± 25	330 ± 29	335 ± 37	313 ± 39	303 ± 42	302 ± 76	281 ± 66	268 ± 58	264 ± 54	279 ± 48
					PulseCO	322 ± 25	327 ± 30	333 ± 34	313 ± 44	283 ± 44	266 ± 49	264 ± 44	247 ± 36	240 ± 36	252 ± 25
E	LiDCO			387 ± 54	374 ± 50	373 ± 47	425 ± 51	406 ± 73	395 ± 50	363 ± 56	340 ± 63	340 ± 78	334 ± 69		
	PulseCO			387 ± 54	370 ± 69	367 ± 79	385 ± 107	357 ± 89	333 ± 85	308 ± 67	291 ± 61	278 ± 55	279 ± 54		
ED	LiDCO			388 ± 99	408 ± 74	393 ± 33	494 ± 50	466 ± 33	458 ± 46	432 ± 42	444 ± 63	407 ± 82	403 ± 100		
	PulseCO			388 ± 99	401 ± 86	382 ± 57	478 ± 113	451 ± 113	392 ± 107	356 ± 82	346 ± 81	323 ± 55	313 ± 51		
EC	LiDCO			378 ± 78	375 ± 91	381 ± 71	413 ± 99	373 ± 88	369 ± 82	366 ± 103	349 ± 95	350 ± 104	327 ± 100		
	PulseCO			378 ± 78	374 ± 77	364 ± 94	480 ± 178	442 ± 158	392 ± 147	345 ± 115	332 ± 96	310 ± 78	293 ± 72		
SVR	dyne.sec/cm <sup>5</sup>			S	LiDCO	285 ± 45	271 ± 49	269 ± 58	307 ± 77	344 ± 83	406 ± 133	429 ± 111	444 ± 97	436 ± 99	440 ± 126
					PulseCO	285 ± 45	275 ± 53	270 ± 54	306 ± 70	369 ± 83	443 ± 100	446 ± 85	472 ± 72	476 ± 95	474 ± 77
		E	LiDCO	244 ± 23	267 ± 75	270 ± 84	232 ± 66	257 ± 85	282 ± 77	352 ± 90	394 ± 114	400 ± 143	395 ± 143		
			PulseCO	244 ± 23	276 ± 99	282 ± 107	290 ± 179	323 ± 190	368 ± 186	439 ± 178	471 ± 154	476 ± 127	461 ± 130		
		ED	LiDCO	225 ± 12	221 ± 33	228 ± 41	206 ± 37	231 ± 37	262 ± 79	296 ± 71	318 ± 98	356 ± 170	355 ± 180		
			PulseCO	225 ± 12	225 ± 25	235 ± 31	228 ± 90	252 ± 82	316 ± 94	388 ± 152	444 ± 190	458 ± 189	458 ± 192		
		EC	LiDCO	228 ± 49	228 ± 59	228 ± 45	208 ± 46	240 ± 70	248 ± 80	268 ± 73	288 ± 67	295 ± 60	328 ± 64		
			PulseCO	228 ± 49	227 ± 50	241 ± 44	191 ± 70	215 ± 87	255 ± 122	300 ± 122	313 ± 109	333 ± 86	362 ± 76		

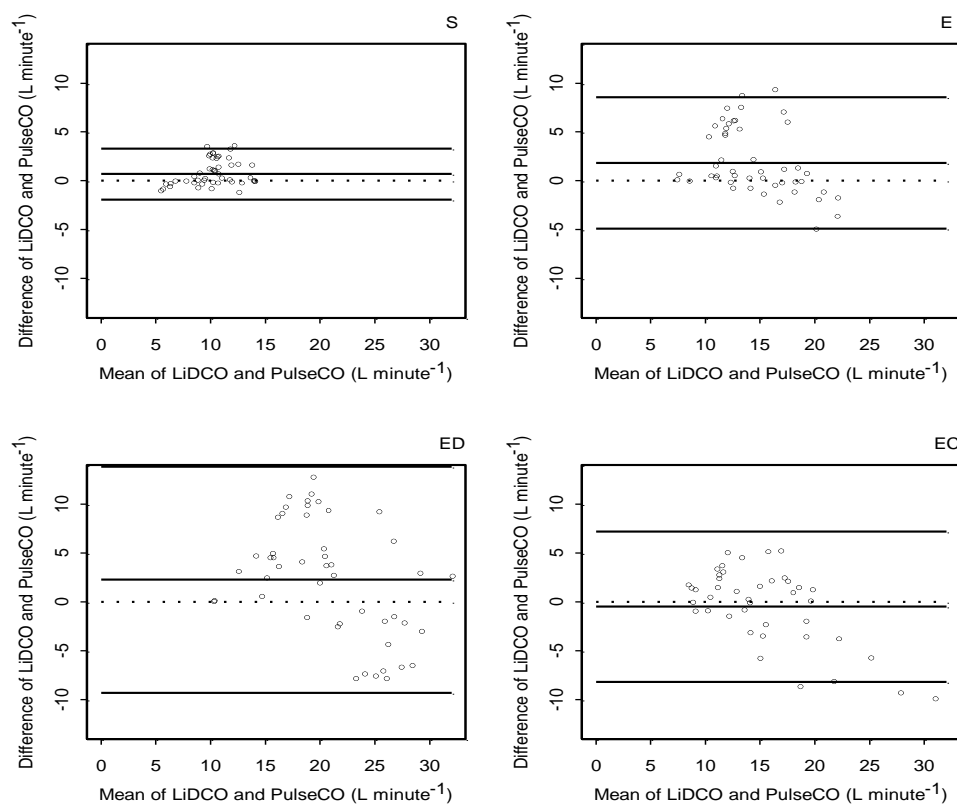
Data are represented as mean ± SD.

T0 = end of administration of saline or enoximone

PulseCO calibration performed at T-30, T-20 and T-10.

## LiDCO & PulseCO in ponies

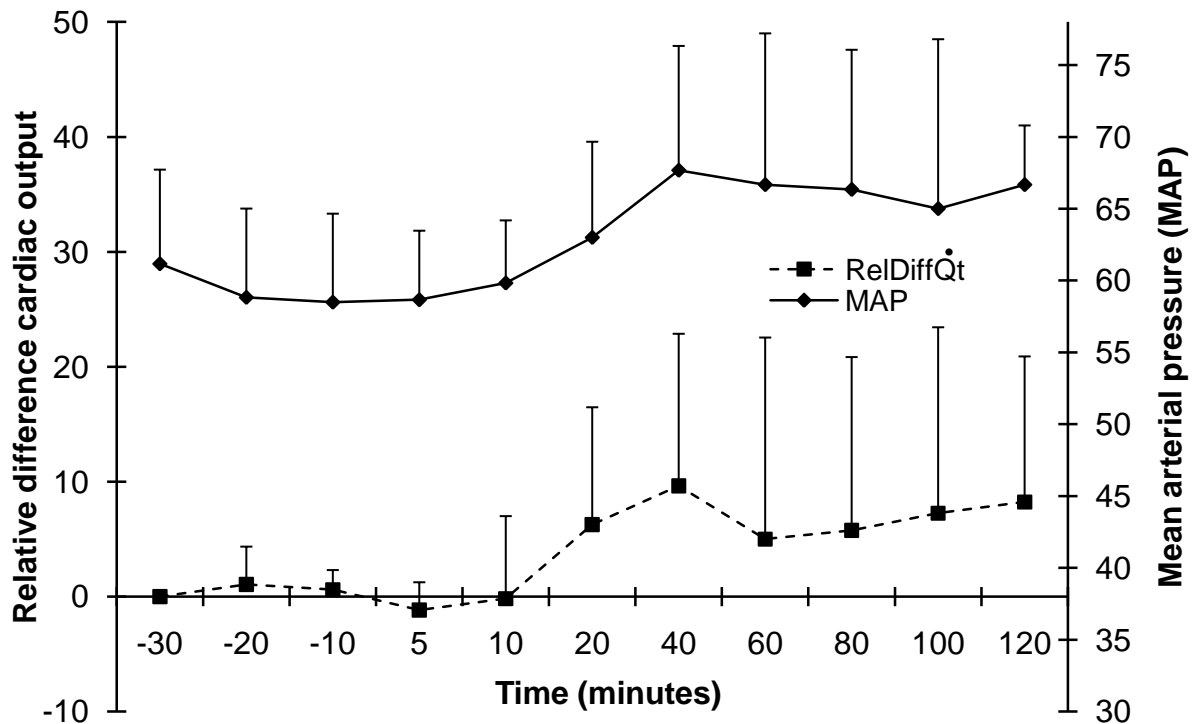
Overall, the largest absolute difference in  $\dot{Q}_t$  was in the enoximone/dobutamine treatment, with PulseCO underestimating  $\dot{Q}_{t_{LiDCO}}$  (mean bias  $2.28 \pm 5.90$  L/min, limits of agreement -9.52 and +14.08 L/min), especially from T40 onwards, when  $\dot{Q}_t$  was also clearly higher compared to the other treatments. However, when looking at the relative differences, the largest overall difference in  $\dot{Q}_t$  was found after treatment E, where  $\dot{Q}_{t_{PulseCO}}$  was lower than  $\dot{Q}_{t_{LiDCO}}$  (mean bias  $11.7 \pm 20.4$  %, limits of agreement -40.8 and +52.5 %). Mean bias during treatment ED was  $10.0 \pm 25.9$  %. The smallest relative difference was found in the enoximone/calcium combination group, where overall PulseCO overestimated LiDCO values (mean bias  $-1.8 \pm 23.3$  %, limits of agreement -48.4 and +44.8%). RelDiffSVR in groups ED ( $20.7 \pm 35.3$  %) and E ( $20.4 \pm 32.0$  %) was significantly higher than in groups S ( $6.9 \pm 14.4$  %) ( $P < 0.01$ ) and EC ( $3.1 \pm 22.2$  %) ( $P < 0.001$ ).



**Fig. 2:** Bland-Altman plots of cardiac output measured using lithium dilution (LiDCO) and Pulse Contour Analysis (PulseCO) in 6 anaesthetized ponies, receiving a bolus of enoximone (E), saline (S), enoximone followed by a dobutamine infusion during 120 minutes (ED) or enoximone followed by a calcium chloride infusion during 10 minutes (EC).

Mean bias (middle line) and limits of agreement (upper and lower line) are indicated.

Systolic arterial pressure, DAP and MAP had a significant effect on  $\text{RelDiff}\dot{Q}_t$  during treatment S: as these pressures increased,  $\text{RelDiff}\dot{Q}_t$  became higher ( $P < 0.001$ ) (Fig. 3). No significant influence of HR, RAP, PCV or SVR on  $\text{RelDiff}\dot{Q}_t$  could be detected.



**Fig. 3:** Mean arterial pressure and relative differences between lithium dilution and pulse contour analysis measurements of cardiac output ( $\text{RelDiff}\dot{Q}_t$ ) in 6 anaesthetized ponies receiving a bolus of saline at T0 (treatment S). Values are represented as mean  $\pm$  SD.

## Discussion

In the present study, significant differences between LiDCO and PulseCO estimations of both the  $\dot{Q}_t$  and the SVR were found in isoflurane anaesthetized ponies, even when no drugs were administered. Furthermore, these differences significantly increased over time and were influenced by the different treatments. These results indicate that in a clinical setting, relevant differences may occur if recalibration is not performed regularly, especially in haemodynamically unstable patients receiving inotropic/vasoactive drugs.

Although the thermodilution technique (TDCO) is widely used for  $\dot{Q}_t$  measurements in horses, the LiDCO technique was chosen as reference to validate PulseCO measurements in the present study. Indeed, comparison of TDCO and LiDCO measurements has demonstrated

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that the LiDCO technique is reliable, not only in humans (Linton et al. 1997), but also in anaesthetized horses (Linton et al. 2000) and foals (Corley et al. 2002). Although it has been shown in pigs that a peripheral injection site can be used for lithium chloride administration, a better correlation with an electromagnetic flowmeter around the aorta was found using a central injection site (Kurita et al. 1999). Therefore, a central venous injection of lithium chloride was preferred in the present study, in order to increase the accuracy of the reference technique.

In dogs and foals, LiDCO progressively exceeded TDCO over time. This was attributed to a decrease in the sensitivity of the older types of the LiDCO sensor (which had a relatively thin membrane) over time (Mason et al. 2001, Corley et al. 2002). However, newer sensors (as used in the present study) have a thicker membrane, which should increase their performance over longer time periods (Mason et al. 2001). Alternatively, increased background serum lithium concentrations can reduce the sensitivity of the sensor, leading to a smaller lithium peak and a consequent overestimation of true  $\dot{Q}_t$ . In the present study, 11 measurements were performed over 150 minutes. Although 20 successive 3 mmol bolus injections given at 3-minute intervals to adult Standardbred horses did not interfere with the performance of the LiDCO, Hatfield et al. (2001) recommended a maximum of 10 measurements in 2 hours. According to the manufacturer of LiDCO-plus<sup>®</sup>, increased background serum lithium only becomes important when serum lithium concentrations increase above 0.2 mmol/L. Corley et al. (2002) reported that the cumulative lithium dose to achieve this concentration in foals was approximately  $0.08 \pm 0.03$  mmol/kg. In the present study, this mean dose was never exceeded, even in the pony receiving the highest dose (0.068 mmol/kg).

It is also possible that the use of plasma sodium concentrations of the standing non-sedated ponies for LiDCO measurements during anaesthesia would affect the accuracy of the LiDCO measurements. However, plasma sodium concentrations have not been reported to change after induction of anaesthesia in horses (Tevik et al. 1968, Gasthuys et al. 1986). Furthermore, plasma sodium concentrations during anaesthesia should have been stable after the initial calibration, since none of the treatments should have affected plasma sodium concentrations. Therefore, the comparison between the 2 techniques should be reliable. Finally, calculation is less accurate than measurement of the haemoglobin concentration. However, as explained in the materials and methods section, the LiDCO-plus<sup>®</sup> monitor uses



PCV and not haemoglobin in the formula applied to calculate  $\dot{Q}_t$  and actually derives PCV from the entered haemoglobin value using the same formula as the one used in the present study to calculate haemoglobin from PCV (Linton et al. 2000). In conclusion, the LiDCO measurements in the present study can be assumed to be as accurate as previously described (Linton et al. 2000, Corley et al. 2002). Consequently, the actual  $\dot{Q}_t$  was likely to be progressively underestimated by the PulseCO software.

During saline treatment, isoflurane anaesthesia was kept stable using the expiratory isoflurane concentration and a constant  $\text{PaCO}_2$ . Nevertheless,  $\dot{Q}_{t\text{PulseCO}}$  became significantly lower than  $\dot{Q}_{t\text{LiDCO}}$  with a mean bias of 4.9%. Relative differences between the 2  $\dot{Q}_t$  measurement techniques were calculated because Critchley and Critchley (1999) argued that these are more relevant compared to absolute differences. According to their report, limits of agreement of  $\pm 30\%$  between the new and the reference technique are acceptable. The limits of agreement were -19.7 and 29.5 % in the control treatment of the present study. As the difference was significantly larger during the other treatments (limits of agreement during enoximone treatment -40.8 and +52.5 %), PulseCO became more unreliable as the haemodynamic conditions changed.

Several hypotheses are possible to explain why PulseCO values were lower than LiDCO measurements during saline treatment and why this difference became larger over time. In the saline group, gradual but significant increases in  $\text{SVR}_{\text{LiDCO}}$  and blood pressure and decreases in HR occurred over time (Chapter 4.1). Changes in blood pressure and especially in SVR were proven to affect the accuracy of various linear pulse contour analysis techniques (Kouchoukos et al. 1970, Starmer et al. 1973). Even the Modelflow method, although it takes aortic characteristic impedance, arterial compliance and SVR into account (Wesseling et al. 1993), was found to be less accurate when pronounced changes in blood pressure and/or SVR occurred (Gödje et al. 1999, Rödig et al. 1999). The PulseCO software incorporates a model of pressure transfer from the aorta to peripheral arteries, takes wave reflection into account and should therefore be less sensitive to changes in SVR, as backward flow, resulting in augmentation of the pressure but retardation of the flow, is partly determined by SVR. In humans, PulseCO<sup>®</sup> was accurate in conditions when the SVR changed but MAP remained constant and in conditions where the changes in SVR were small compared to changes in MAP (Linton & Linton 2001). In the present study, no significant influence of SVR on the difference between LiDCO and PulseCO could be demonstrated, although SVR increased

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substantially and significantly during saline treatment (see chapter 4.1). However, statistical analysis confirmed that the difference in  $\dot{Q}t$  estimated by the 2 methods became larger when blood pressure increased, possibly because aortic compliance decreased substantially in a non-linear way when pressure increased (Jansen et al. 2001). The respective curves during treatments E, ED and EC illustrated the same trend: after an initial increase in  $\dot{Q}t$  following administration of enoximone, which was reliably tracked by the PulseCO, blood pressure gradually increased in all groups, accompanied by an increasing difference between LiDCO and PulseCO values. Similar to the present study, Chen et al. (2005) reported an underestimation of  $\dot{Q}t$  by the PulseCO when blood pressure increased in dogs.

To the authors' knowledge, there is only one report about the accuracy of the PulseCO software in horses (Hallowell & Corley 2005). These authors reported a mean difference between LiDCO and PulseCO of 0.2%, with limits of agreement of -10.6 to + 11%, which was far better than the results of the present study. Although we did not use a continuous flushing device for the arterial catheter, it was frequently flushed manually using a heparinized saline solution and no obvious signs of dampening of the arterial waveform were observed in any of the ponies. Secondly, blood pressure was recorded from the carotid artery, while either the facial or metatarsal arteries were used by Hallowell and Corley (2005). To a certain degree, the accuracy of pulse contour analysis techniques may differ according to the artery from which it is recorded (Gödje et al. 2002). However, PulseCO was designed for use with radial artery pressure in man, because it incorporates a model of the pressure transfer from the aorta to the radial artery (Linton & Linton 2001). Therefore, inaccuracy would mainly be expected with pressures monitored from the hind limb, as the most important sites of wave reflection are the vascular beds of the trunk (Karamanoglu et al. 1994). Changes in the reflection coefficient of these beds might change the relationship between the pressures in the ascending and abdominal aorta as well as arteries distal to this vessel (Linton & Linton 2001). The accuracy of pulse contour analysis from the carotid artery should thus be comparable to the one from the facial artery.

Results of the present study indicated that the difference between the 2 methods increased over time. In the study of Hallowell and Corley (2005), LiDCO measurements were performed at 20-30 minute intervals and compared to the PulseCO readings immediately before each measurement. However, it is not mentioned whether the PulseCO was recalibrated with each LiDCO measurement. If recalibration was performed at 20-30 minute

intervals, differences between both techniques would be minimized. Furthermore, the number of comparisons per horse varied between 2 and 6, with 20 to 30 minute intervals between recordings, indicating that even if no recalibrations were performed, a large part of the comparisons was performed within the first hour after the initial calibration. As the present study was performed over a longer time period (120 minutes after calibration), a larger difference between the two methods was expected. Other factors which may affect PulseCO measurements, such as an aortic aneurysm or aortic valve abnormalities, were not present in these experimental ponies.

The LiDCO-plus<sup>®</sup> user's manual recommends checking the calibration in humans every 8 hours and each time a significant change is instituted in the haemodynamic management of the patient, when the arterial catheter or pressure line is changed or when the patient is moved to a new location. However, despite such measures, clinically relevant differences between TDCO and PulseCO (Linton and Linton 2001, Yamashita et al. 2005) or PiCCO (Halvorsen et al. 2006) have been reported in human patients during and after coronary artery bypass surgery and it has been recommended to check or redo the calibration before major clinical decisions are taken (Linton & Linton 2001). Based on the results of the present study, this can also be recommended in horses, since the accuracy of the PulseCO was significantly different between treatments, indicating that possible differences may be magnified in case of pronounced haemodynamic changes. Especially in these animals, where accurate knowledge of  $\dot{Q}t$  would be of great value to the clinician, the PulseCO may thus become less reliable if recalibration is not performed.

Significant differences in SVR were expected between treatments, because enoximone induced vasodilation in humans (Vernon et al. 1991), dobutamine tended to reduce SVR in ponies (Gasthuys et al. 1991, Lee et al. 1998) and may increase SVR at higher doses in horses (Taylor & Clarke 1999), a combination of enoximone and dobutamine potentiated the systemic vasodilator effects of both drugs in humans (Thuillez et al. 1993) and administration of calcium increased SVR in anaesthetized ponies (Gasthuys et al. 1991). Nevertheless, in the present study, the only significant difference in SVR was found during treatment with enoximone and dobutamine, where  $SVR_{LiDCO}$  was lowest. Although the largest absolute difference between LiDCO and PulseCO values was also found during treatment ED, no significant correlation was found between SVR and the difference between both techniques. Most likely, the large absolute difference found during treatment ED can simply be explained

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by the fact that  $\dot{Q}_t$  values were also highest during this treatment. When relative differences were analyzed, the differences during treatments E and ED were comparable.

The smallest relative difference overall was found during treatment with a combination of enoximone and calcium chloride. PulseCO overestimated  $\dot{Q}_t$  in this group, especially during and immediately after calcium administration. It might be hypothesized that alterations in the concentration of ionized calcium have an influence on the voltage of the lithium sensor, thereby influencing LiDCO measurements. However, this is most unlikely, as the sensor should only be sensitive to ions with a single positive charge (like lithium and sodium) and not to ionized calcium, which carries a double positive charge. On the other hand, as HR, arterial blood pressure and  $SVR_{LiDCO}$  were all comparable in groups E and EC, it remains unclear how calcium administration influenced PulseCO readings. During treatment EC, standard deviation of the LiDCO measurements was higher than during treatment E. This indicates that, compared to treatment E, there was more variation in the response to treatment EC between the different ponies. As a result, standard deviation of the PulseCO measurements was also increased. The overestimation of  $\dot{Q}_t$  by the PulseCO might therefore simply be the result of statistical coincidence. The large overlap of the PulseCO measurements during treatments E and EC confirms this hypothesis.

In conclusion, the present study indicated that, over a period of 120 minutes after calibration, PulseCO can significantly differ from LiDCO measurements in haemodynamically stable, isoflurane anaesthetized ponies. Furthermore, this difference gradually increased over time and was influenced by inotropic/vasoactive drugs and by changes in arterial blood pressure. It is therefore recommended to check the calibration before major clinical decisions are taken.

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## **Cardiorespiratory effects of enoximone alone or combined with inotropic/vasoactive drugs in isoflurane anaesthetized ponies**



## **Cardiovascular effects of enoximone in isoflurane anaesthetized ponies**

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### SUMMARY

The cardiovascular effects of enoximone were examined in six healthy, isoflurane anaesthetized ponies, aged  $5.0 \pm 1.6$  years and weighing  $286 \pm 52$  kg. After sedation with romifidine ( $80 \mu\text{g}/\text{kg}$  intravenously (IV)), anaesthesia was induced with midazolam ( $0.06 \text{ mg}/\text{kg}$  IV) and ketamine ( $2.2 \text{ mg}/\text{kg}$  IV) and maintained with isoflurane in oxygen (F<sub>E</sub> Iso 1.7%). The ponies were ventilated to maintain normocapnia (PaCO<sub>2</sub> 4.66-6.00 kPa). Each pony was anaesthetized twice to receive either enoximone  $0.5 \text{ mg}/\text{kg}$  IV (E) or saline (S) 90 minutes after induction, with a minimal interval of 3 weeks between treatments. Heart rate (HR), arterial blood pressure and right atrial pressure (RAP), cardiac output ( $\dot{Q}_t$ ) (lithium dilution technique) and blood gases (arterial and central venous samples) were recorded at regular intervals during a period of 120 minutes after treatment. Stroke volume (SV), systemic vascular resistance (SVR), venous admixture ( $\dot{Q}_s/\dot{Q}_t$ ) and oxygen delivery (DO<sub>2</sub>) were calculated.

Enoximone induced significant increases in HR,  $\dot{Q}_t$ , SV,  $\dot{Q}_s/\dot{Q}_t$  and DO<sub>2</sub> and a significant decrease in RAP. No significant differences were detected for arterial blood pressure, SVR and blood gases. No cardiac arrhythmias or other side effects were observed. These results suggest that in isoflurane anaesthetized ponies, enoximone has beneficial effects on  $\dot{Q}_t$  and SV without significantly affecting blood pressure. Despite increases in  $\dot{Q}_s/\dot{Q}_t$ , DO<sub>2</sub> to the tissues was improved.

### Introduction

Johnston et al. (2002) pointed out that most causes of perianaesthetic death in horses are linked with cardiovascular depression. Horses appear to be more susceptible to the cardiovascular and respiratory depressant effects of the inhalation anaesthetics than other species (Eberly et al. 1968, Gillespie et al. 1969, Hall 1971). This results in hypotension and poor tissue perfusion. As a result, tissue oxygen supply is often inadequate in anaesthetized horses, as delivery of oxygen ( $DO_2$ ) to the tissues is determined not only by the arterial oxygen content ( $CaO_2$ ) (which is often low in the recumbent horse) but also, and even more important, by the cardiac output ( $\dot{Q}t$ ). In order to prevent postanesthetic myopathy, preventing myocardial depression and maintaining tissue blood flow are of major importance in the equine patient.

Reduction in anaesthetic depth, high-volume fluid therapy and inotropic support to maintain mean arterial pressure (MAP) above 70 mm Hg are recommended to reduce the severity of myopathy (Duke et al. 2006). Available inotropic drugs include digitalis glycosides, beta-adrenergic agonists, calcium sensitizers and phosphodiesterase (PDE) inhibitors (Notterman 1991, Via et al. 2003). Sympathomimetics are most frequently used in anaesthetized horses, although side-effects can occur, including sinus tachycardia, cardiac arrhythmias, muscular tremor and in some cases severe vasoconstriction (Swanson et al. 1985, Trim et al. 1985, Gasthuys et al. 1991, Lee et al. 1998).

PDE III inhibitors (amrinone, milrinone, enoximone) are nonglycoside, noncatecholamine agents with positive inotropic and vasodilating effects (Vernon et al. 1991) and less proarrhythmic effects than dobutamine (Caldicott et al. 1993). These drugs exert their action through inhibition of the enzymatic hydrolysis of cAMP. This leads to positive inotropic and lusitropic effects in the myocardium (Vernon et al. 1991) and systemic vasodilation (Evans 1989). Amrinone is used less frequently in man, because accumulation can occur in critically ill patients and thrombocytopenia has been observed (Notterman 1991). Fewer side effects have been reported in man using the newer PDE III inhibitors, such as milrinone and enoximone (Kikura et al. 1995). The haemodynamic effects of milrinone have been investigated in halothane anaesthetized horses, whereby increases in heart rate (HR), MAP,  $\dot{Q}t$ , ejection fraction and maximum rate of increase and decrease of left ventricular pressure ( $\pm dP/dt_{max}$ ) were observed (Muir 1995).

In man, enoximone increases coronary blood flow, reduces vascular resistances and has a positive inotropic effect, without significant increases in myocardial oxygen consumption (Dage and Okerholm 1990, Ghio et al. 2003). Myocardial oxygen consumption, as reflected by heart rate-pressure product, was significantly lower in patients who received enoximone than in patients receiving dobutamine following cardiopulmonary bypass (Lançon et al. 1990). Even more, in patients with acute myocardial infarction, enoximone was tolerated better and produced fewer side-effects than dobutamine using doses which produced similar increases in  $\dot{Q}_t$  (Caldicott et al. 1993). The aim of the present study was to determine the effects of a single bolus of enoximone in isoflurane anaesthetized ponies.

### **Materials & Methods**

#### **Animals**

After approval by the Ethical Committee of the Faculty of Veterinary Medicine of the University of Ghent (EC 2005/48), six ponies, aged  $5.0 \pm 1.6$  years and weighing  $286 \pm 52$  kg, were selected for this study (5 geldings and 1 mare). The left carotid artery was transposed to a subcutaneous position at least two months before the experiment. The ponies were regularly vaccinated and dewormed. Based on a physical and general blood examination, they were regarded as ASA (American Society of Anesthesiologists) class I (normal, healthy patient).

#### **Determination of baseline values in the standing ponies**

In the first phase of the experiment, values for HR, arterial blood pressure and  $\dot{Q}_t$  were determined in the standing, unsedated ponies. A 14 gauge catheter (Vasocan<sup>®</sup> Braunüle Luer Lock, B. Braun Melsungen AG, Melsungen, Germany) was placed in the right jugular vein and blood was withdrawn for measurement of plasma sodium level (AVL 9180 Electrolyte Analyzer<sup>®</sup>, AVL scientific corporation, Roswell, Georgia, USA 30076) and packed cell volume (PCV) (Haemofuge<sup>®</sup>, Heraeus Instruments, Osterode, Germany). A 20 gauge catheter (Vasocan<sup>®</sup> Braunüle Luer Lock) was placed in the left carotid artery and connected to a pressure transducer (ST-33<sup>®</sup>, PVB Critical Care GmbH, Kirchseeon, Germany), zeroed at the level of the right atrium. A haemodynamic monitor (CMS Patientenmonitor HP M1165A<sup>®</sup>, model 56S, Hewlett-Packard GmbH, Böblingen, Germany) was used to record the electrocardiogram (ECG, base-apex lead) and systolic, diastolic and mean arterial pressures

## Enoximone in ponies

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(SAP, DAP and MAP respectively). The pressure monitoring system was calibrated against a mercury manometer before the experiment. Cardiac output measurements were performed with the lithium dilution technique (LiDCO-plus Haemodynamic Monitor<sup>®</sup>, LiDCO Ltd., London, UK): a 1.5 mmol bolus of lithium chloride was injected through the jugular catheter, while arterial blood for detection of lithium chloride by the LiDCO sensor (CM10 LiDCO sensor<sup>®</sup>, LiDCO Ltd.) was withdrawn from the carotid artery by the LiDCO Flow Regulator (4.5 mL/min). Haemoglobin (Hb) concentration, required by the LiDCO-plus<sup>®</sup> monitor, was calculated from PCV ( $\text{Hb (g/dL)} = 34 * \text{PCV (L/L)}$ ) (Linton et al. 2000)).

The ponies were placed in a stock in a quiet environment. After 30 minutes of accommodation, values for HR, SAP, DAP, MAP and  $\dot{Q}_t$  were recorded twice with an interval of 10 minutes. Arterial blood samples were withdrawn anaerobically and analyzed immediately for oxygen and carbon dioxide partial pressures ( $\text{PaO}_2$  and  $\text{PaCO}_2$  respectively) and pH (ABL5<sup>®</sup>, Radiometer, Copenhagen, Denmark). Corrections for body temperature and inspiratory  $\text{O}_2$  fraction ( $\text{FIO}_2$ ) were performed. Haemoglobin saturation ( $\text{SO}_2$ ), bicarbonate, standard bicarbonate (SBC), total carbon dioxide ( $\text{tCO}_2$ ) and actual and standard base excess (ABE and SBE respectively) were calculated automatically by the ABL5<sup>®</sup> Radiometer. PCV was obtained by centrifugation.

### General anaesthesia

At least one week later, the second part of the study was performed in the anaesthetized ponies. Each pony was anaesthetized four times to receive one of four treatments 90 minutes after induction. The same anaesthetic protocol was used on all occasions. Food, but not water, was withheld during 12 hours before anaesthesia. Blood was withdrawn from the right jugular vein for measurement of plasma sodium level. Subsequently, the ponies were sedated with 80  $\mu\text{g/kg}$  romifidine IV (Sedivet<sup>®</sup>, Boehringer Ingelheim, Brussels, Belgium) and a 12 gauge catheter (Intraflon 2<sup>®</sup>, Vygon, Ecoen, France) was placed in the right jugular vein. Fifteen minutes after sedation, anaesthesia was induced with 0.06 mg/kg midazolam IV (Dormicum<sup>®</sup>, Roche, Brussels, Belgium) and 2.2 mg/kg ketamine IV (Anesketin<sup>®</sup>, Eurovet, Heusden-Zolder, Belgium). An orotracheal tube (24-26 mm OD, Soft rubber tracheal tube, Rüschi AG, Kernlen, Germany) was placed and the pony was positioned in right lateral recumbency, on a surgery table, with the legs upwards at an angle of 40° to the horizontal.



General anaesthesia was maintained with isoflurane (Isoflo<sup>®</sup>, Abbott Laboratories Ltd., Queenborough, Kent, United Kingdom) in oxygen, using a large animal anaesthetic unit (Matrx medical inc., Orchard Park, New York, USA + Sulla 909V<sup>®</sup>, Dräger, Lübeck, Germany) with an out-of-circuit vaporizer (Drägerwerk AG, Lübeck, Germany) and a large animal ventilator (Smith respirator LA 2100<sup>®</sup>, model 2002, Veterinary Technics/BDO-Medipass, Hoogezand, the Netherlands). The oxygen flow was started at 6 L/min and decreased to 10 mL/kg/min after 10 minutes. Respiration mode was assisted-controlled, with a tidal volume of 10 mL/kg. Respiratory frequency was set at 10 breaths/min, peak inspiratory pressure at 1.96 kPa (20 cm H<sub>2</sub>O) and inspiration time at 2 seconds. When necessary, these settings were adapted to maintain PaCO<sub>2</sub> between 4.66 and 6.00 kPa (35-45 mm Hg). Lactated Ringer's solution (Haemofiltration Formula E2, Clear-Flex<sup>®</sup>, Bieffe Medital, Grosotto, Italy) was infused throughout anaesthesia at a rate of 3 mL/kg/h. Air conditioning in the operating theatre maintained room temperature at 21 °C.

The skin over the left jugular vein and transposed carotid artery was surgically prepared. A 20 gauge catheter (Vasocan<sup>®</sup> Braunüle Luer Lock) was placed in the left carotid artery and connected to a pressure transducer, placed at the level of the right atrium. Using the Seldinger technique, a 7 French thermodilution catheter (3-lumen, Abbott Laboratories, North Chicago, IL60064, USA) was placed in the left jugular vein, with the distal port of the catheter in the right atrium to measure right atrial pressure (RAP). Correct positioning of the catheter was guided by the characteristic waveforms. The pressure monitoring system was zeroed at the level of the right atrium and calibrated against a mercury manometer before each experiment.

Inspiratory and expiratory CO<sub>2</sub>, O<sub>2</sub> and isoflurane concentrations were monitored with a calibrated, methane-insensitive, multi-gas analyzer (HP M1025B<sup>®</sup>, Hewlett Packard Company, Houston, USA). The CMS-Patientenmonitor (HP M1165A<sup>®</sup>, model 56S, Hewlett-Packard GmbH) was used to record the electrocardiogram (ECG) (base-apex lead), to monitor SAP, DAP, MAP and RAP and to measure body temperature. Cardiac output was measured with the lithium dilution technique (LiDCO-plus Haemodynamic Monitor<sup>®</sup>), using a 1.5 mmol bolus of lithium chloride, injected through the proximal port of the thermodilution catheter. As in the standing ponies, Hb concentration was estimated from the PCV, which was measured before each LiDCO determination. Plasma sodium level (determined before each anaesthetic episode) was entered into the LiDCO-plus<sup>®</sup> monitor.

## Enoximone in ponies

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The first 60 minutes of anaesthesia served as an instrumentation and stabilisation period to achieve an end-tidal isoflurane concentration of 1.7 % and a PaCO<sub>2</sub> between 4.66 and 6.00 kPa (ABL5<sup>®</sup> Radiometer). After this period, three baseline values were recorded for inspiratory and expiratory isoflurane, CO<sub>2</sub> and O<sub>2</sub>, HR, SAP, DAP, MAP, RAP, body temperature and  $\dot{Q}_t$ . Arterial (a) and central venous (v) blood samples were collected anaerobically from the carotid artery and the right atrium respectively, over a period of three breaths (both samples simultaneously), for determination of pH, PCO<sub>2</sub>, PO<sub>2</sub>, haemoglobin saturation with oxygen (SaO<sub>2</sub>), bicarbonate, SBC, tCO<sub>2</sub>, ABE, SBE and PCV (ABL5<sup>®</sup>, Radiometer). Time between baseline measurements was 10 minutes. Baseline values were calculated as the mean of these 3 recordings for each variable.

Ninety minutes after induction, one of four treatments was administered. Treatment S consisted of an IV bolus of 0.1 mL/kg saline (S). During treatments E, ED and EC, 0.5 mg/kg enoximone 0.5% (Perfan<sup>®</sup>, Myogen GmbH, Bonn, Germany) was administered at a rate of 20 mL/min using an infusion pump (Ohmeda 9000 Syringe Pump<sup>®</sup>, Ohmeda, West Yorkshire, England), followed by either no additional drugs (treatment E), a constant rate infusion (CRI) of 0.5 µg/kg/min dobutamine (Dobutamine Mayne<sup>®</sup>, Mayne Pharma, Brussels, Belgium) during 120 minutes (treatment ED) or an infusion of calcium chloride at 0.5 mg/kg/min (Calcii chloridum 10%, Federa, Brussels, Belgium) from T5 to T15 (treatment EC). For treatment ED, dobutamine was dissolved in saline to obtain a concentration of 0.5 mg/mL and was administered through the catheter in the right jugular vein using a standard infusion pump (Ohmeda 9000 Syringe Pump<sup>®</sup>). T0 was defined as the end of the injection of saline or enoximone. After T0, data were recorded during 120 minutes. Each pony received all treatments in a randomized crossover trial, with a wash-out period of at least 2 weeks between treatments.

Values for inspiratory and expiratory CO<sub>2</sub> and O<sub>2</sub>, HR, SAP, DAP, MAP, RAP and body temperature were recorded at T5, T10, T15, T20, T25, T30, T40, T50, T60, T70, T80, T90, T100, T110 and T120 (time expressed in minutes),  $\dot{Q}_t$  at T5, T10, T20, T40, T60, T80, T100 and T120. In the EC group, LiDCO measurements were not performed at T5. Simultaneous arterial and central venous blood samples were collected at T10, T20, T40, T60, T80, T100 and T120 and analyzed immediately (ABL5<sup>®</sup>, Radiometer).

The ponies recovered in a padded recovery box. The endotracheal tube was removed once the ponies were able to swallow. A recovery score was given (Table 1) and the times to regain sternal recumbency and to standing were recorded.

**Table 1: Scoring system used to grade recovery**

Score	Description
1	1 attempt to stand, no ataxia
2	1 - 2 attempts to stand, some ataxia
3	>2 attempts to stand, but quiet recovery
4	>2 attempts to stand, excitation
5	severe excitation/pony wounded

### Calculations

Stroke volume (SV) was calculated as:

$$SV \text{ (mL/beat)} = \frac{1000 * \dot{Q}t \text{ (L/min)}}{HR \text{ (beats/min)}}$$

Cardiac index and stroke index were expressed in mL/kg/min and mL/kg respectively.

Systemic vascular resistance (SVR) was calculated using the formula:

$$SVR \left( \text{dyne} * \frac{\text{sec}}{\text{cm}^5} \right) = \frac{80 * (MAP \text{ (mm Hg)} - RAP \text{ (mm Hg)})}{\dot{Q}t \text{ (L/min)}}$$

Alveolar oxygen partial pressure ( $PAO_2$ ), blood oxygen content ( $CzO_2$ ),  $DO_2$ , oxygen consumption ( $\dot{V}O_2$ ) and degree of venous admixture ( $\dot{Q}s/\dot{Q}t$ ) were calculated as follows (Lumb 2005):

$$PAO_2 \text{ (kPa)} = PIO_2 - \frac{PaCO_2}{0.8}$$

Where 0.8 = respiratory quotient and  $PIO_2$  is partial pressure of inspired oxygen.

$$CzO_2 \text{ (mL/L)} = [Hb \text{ concentration (g/L)} * 1.39 * SzO_2] + [PzO_2 \text{ (kPa)} * 0.225]$$

Where z = a, v or  $\acute{c}$  for arterial ( $CaO_2$ ), central venous ( $CvO_2$ ) and end-capillary pulmonary oxygen content ( $C\acute{c}O_2$ ) respectively.  $P\acute{c}O_2$  is taken as  $PAO_2$ . Arterial haemoglobin concentration was used to calculate  $CaO_2$  and  $C\acute{c}O_2$ , while venous haemoglobin concentration was used to calculate  $CvO_2$ .

$$DO_2(L/min) = \frac{CaO_2(mL/L) * \dot{Q}_t(L/min)}{1000}$$

$$\dot{V}O_2(L/min) = \frac{C(a-v)O_2(mL/L) * \dot{Q}_t(L/min)}{1000}$$

$$\frac{\dot{Q}_s}{\dot{Q}_t} = \left( \frac{C\dot{c}O_2 - CaO_2}{C\dot{c}O_2 - CvO_2} \right) * 100 \%$$

The alveolar dead space-to-tidal volume ratio ( $V_D/V_T$ ) was calculated as:

$$V_D/V_T = \frac{PaCO_2 - PE'CO_2}{PaCO_2}$$

where  $PE'CO_2$  = end tidal carbon dioxide tension.

### Statistical analysis

The standing values for HR, SAP, DAP, MAP,  $\dot{Q}_t$  and SV were compared to the overall mean during the 120 min period following treatments S and E by a mixed model with treatment as fixed categorical effect and pony as random effect, using a 5 % significance level.

The effects of enoximone and saline were compared using a mixed model with treatment, time and their interaction as fixed categorical effects and pony as random effect, comparing the treatments S and E both globally (at  $\alpha = 0.05$ ) and at 8 timepoints: T0 (= mean of the 3 baseline measurements), T10, T20, T40, T60, T80, T100 and T120 (at Bonferroni-adjusted  $\alpha = 0.00625$ ).

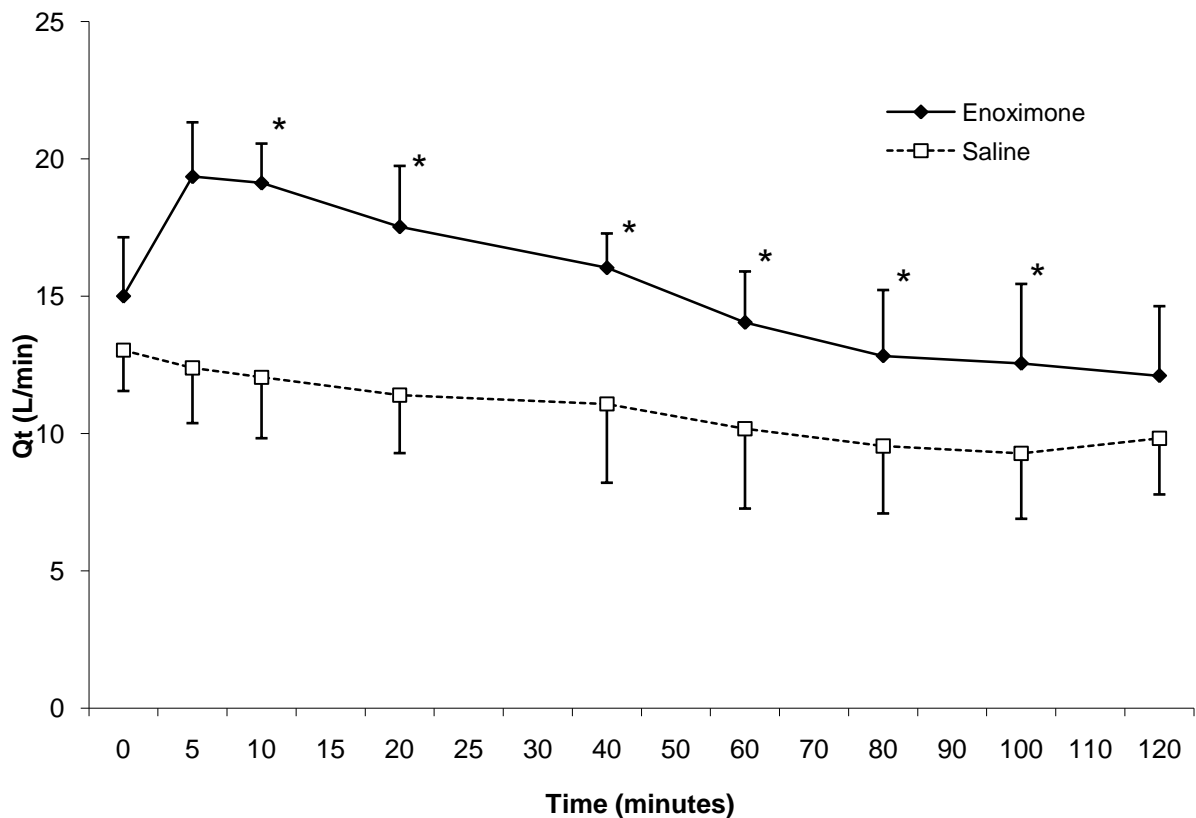
## Results

### Cardiovascular system

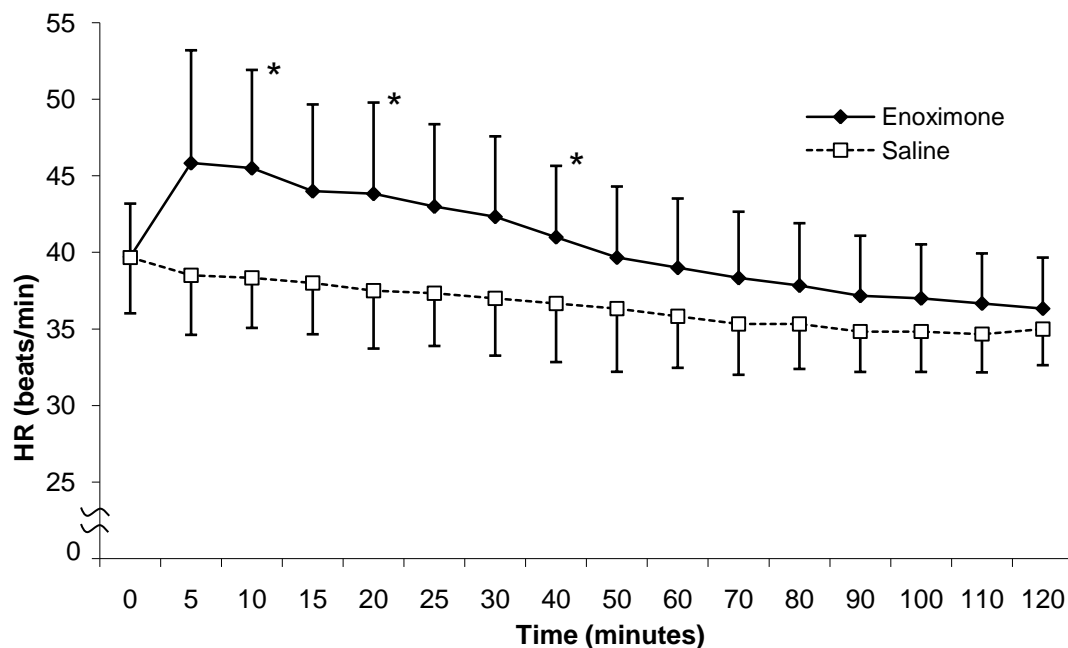
Standing values for  $\dot{Q}_t$ , HR and SV were  $27.7 \pm 7.4$  L/min,  $38 \pm 2$  beats/min and  $731 \pm 162$  mL respectively. Standing values for SAP, DAP and MAP are presented in Table 2. All of these parameters significantly decreased during inhalation anaesthesia, but were not significantly different between groups at T0 (baseline values during anaesthesia).

Compared to saline treatment, administration of enoximone resulted in significant increases in  $\dot{Q}t$  (Fig. 1), HR (Fig. 2), SV (Fig. 3), SAP, DAP and MAP (Table 2). For  $\dot{Q}t$  and SV, this difference was significant up to T100 (except SV at T80). Heart rate was significantly increased for 40 minutes after enoximone administration. As  $\dot{Q}t$  and HR decreased slowly but significantly over time in the saline group, the interaction between treatment and time was significant for both parameters.

In both groups, DAP, MAP and SVR gradually increased over time. RAP was more or less stable throughout the anaesthesia after treatment S. After treatment E however, an initial decrease in RAP (E  $10 \pm 2$  vs. S  $15 \pm 2$  mm Hg at T10) was followed by a gradual increase, although RAP remained significantly lower than in the S group throughout the anaesthesia (120 minutes). The different evolution over time in the two groups resulted in a significant interaction effect between treatment and time for RAP.

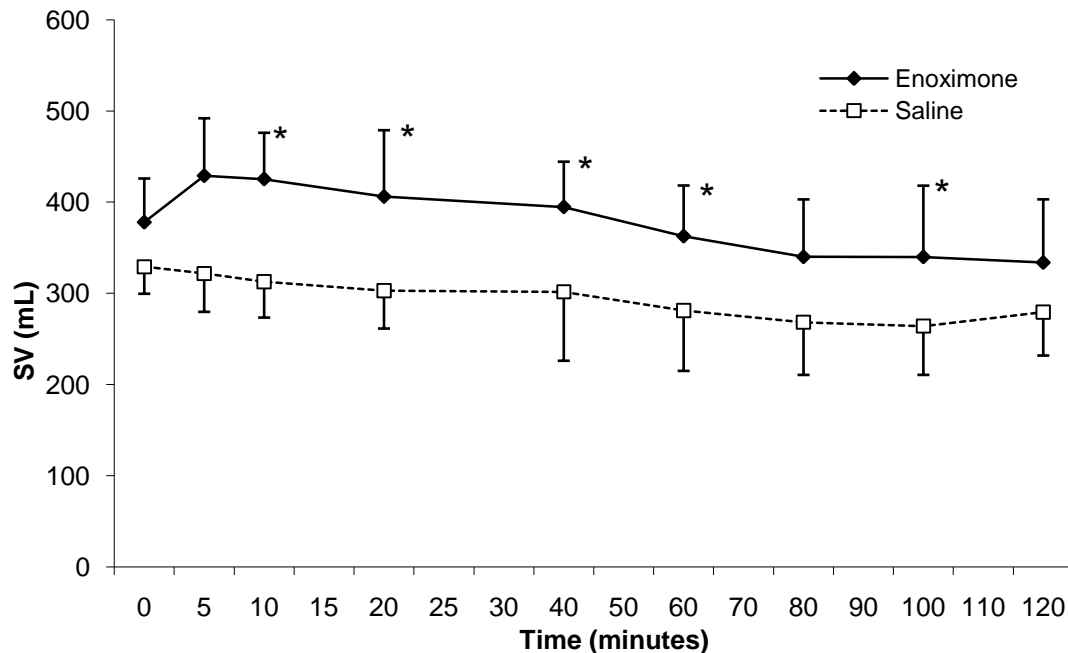


**Fig. 1: Cardiac Output ( $\dot{Q}t$ ) in 6 anaesthetized ponies receiving a bolus of enoximone or saline. Values are displayed as mean  $\pm$  SD. Statistical analysis was performed at T10, T20, T40, T60, T80, T100 and T120. \* indicates a significant difference between the 2 treatments ( $P < 0.00625$ )**



**Fig. 2: Heart Rate (HR) in 6 anaesthetized ponies after a bolus of enoximone or saline.** Values are displayed as mean  $\pm$  SD. Statistical analysis was performed at T10, T20, T40, T60, T80, T100 and T120.

\* indicates a significant difference between treatments ( $P < 0.00625$ )



**Fig. 3: Stroke Volume (SV) in 6 anaesthetized ponies after a bolus of enoximone or saline.** Values are displayed as mean  $\pm$  SD. Statistical analysis was performed at T10, T20, T40, T60, T80, T100 and T120.

\* indicates a significant difference between treatments ( $P < 0.00625$ )

**Table 2: Systolic (SAP), diastolic (DAP), mean arterial (MAP) and right atrial (RAP) pressures and systemic vascular resistance (SVR) in 6 anaesthetized ponies receiving a bolus of enoximone (E) or saline (S).**

Variable	Unit	Standing Values	Trt	Time after treatment (min)								Overall
				T0	T10	T20	T40	T60	T80	T100	T120	
SAP	mm Hg	143 ± 16	E	83 ± 7	86 ± 14	84 ± 12	84 ± 11	88 ± 11	89 ± 10	87 ± 10	85 ± 10	86 ± 5
			S	79 ± 8	78 ± 7	81 ± 9	85 ± 10	84 ± 13	82 ± 12	82 ± 11	83 ± 6	82 ± 5
DAP	mm Hg	90 ± 11	E	51 ± 6	54 ± 14	54 ± 14	56 ± 15	60 ± 14	62 ± 12	61 ± 9	60 ± 10	57 ± 4
			S	49 ± 5	49 ± 3	53 ± 4	57 ± 7	57 ± 8	57 ± 7	57 ± 6	57 ± 3	55 ± 4
MAP	mm Hg	114 ± 11	E	63 ± 6	65 ± 14	65 ± 14	67 ± 14	72 ± 13	73 ± 11	71 ± 9	69 ± 9	68 ± 4
			S	60 ± 6	60 ± 4	63 ± 7	68 ± 9	67 ± 11	66 ± 10	65 ± 12	67 ± 4	65 ± 4
RAP	mm Hg		E	15 ± 2	10 ± 2	10 ± 2	11 ± 3	11 ± 2	12 ± 3	13 ± 3	13 ± 3	11 ± 1
			S	15 ± 2	15 ± 2 §	15 ± 2 §	15 ± 2 §	15 ± 2 §	15 ± 2 §	15 ± 2 §	15 ± 2 §	15 ± 1 *
SVR	dyne.sec/cm <sup>5</sup>		E	261 ± 63	232 ± 66	257 ± 85	282 ± 77	352 ± 90	394 ± 114	400 ± 143	395 ± 143	318 ± 33
			S	275 ± 49	307 ± 77	344 ± 83	406 ± 133	429 ± 111	444 ± 97	436 ± 99	440 ± 126	386 ± 33

Values at individual timepoints are represented as mean ± SD (SD calculated for each treatment group separately).

Overall values are represented as mean ± SE (SE calculated assuming homogeneity of variances).

\* significant difference between E and S for the overall comparison (P<0.05)

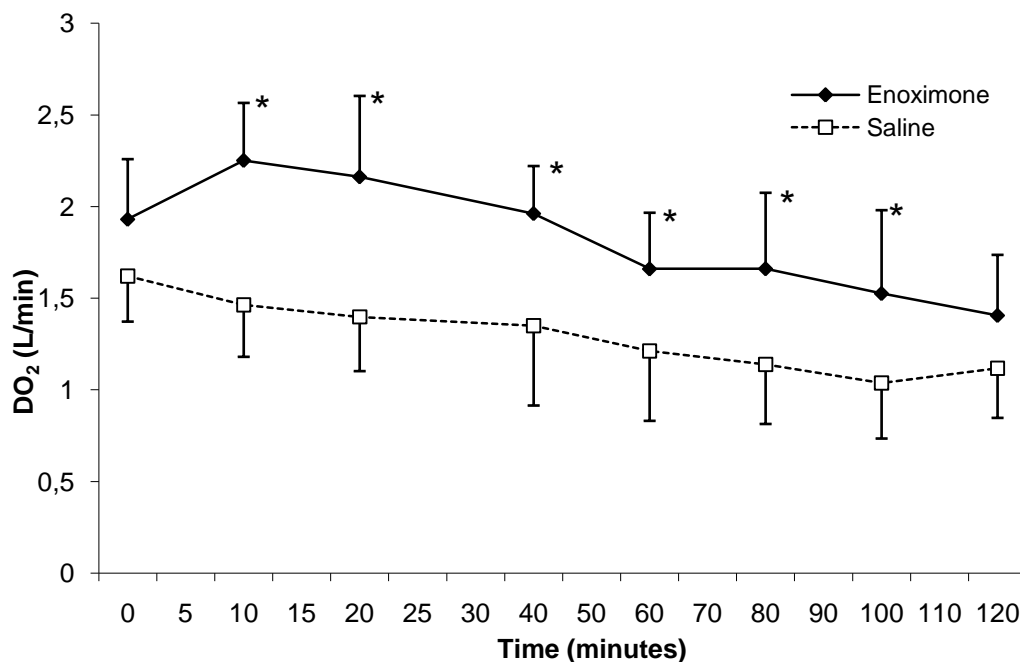
§ significant difference between E and S at individual timepoints (P<0.00625)

## Enoximone in ponies

### Blood gas analysis, packed cell volume and body temperature

Baseline values during anaesthesia were not significantly different between groups for any of the parameters. After enoximone treatment, no significant differences were found for  $t\text{CO}_2$ , ABE and SBE.  $\text{SvO}_2$ ,  $\text{CvO}_2$  and body temperature significantly decreased over time (Tables 3 & 4). Administration of enoximone induced no significant differences in overall blood gas results, PCV or body temperature compared to saline treatment. A significant interaction between treatment and time was detected for  $\text{SaO}_2$ : in the S group,  $\text{SaO}_2$  decreased over time, while in the E group,  $\text{SaO}_2$  was initially lower, but increased over time and became slightly higher than in the S group from T60 onwards. The differences in  $\text{SaO}_2$  were however not statistically significant between the 2 groups (data not shown).

Analysis of the individual differences at selected timepoints (T10, T20, T40, T60, T80, T100 and T120) revealed that after enoximone administration venous PCV was significantly higher at T40,  $\text{CvO}_2$  at T40 and T60,  $\text{SvO}_2$  at T80 and T120.



**Fig. 4: Oxygen delivery ( $\text{DO}_2$ ) in 6 anaesthetized ponies after a bolus of enoximone or saline.** Values are displayed as mean  $\pm$  SD. Statistical analysis was performed at T10, T20, T40, T60, T80, T100 and T120. \* indicates a significant difference between the 2 treatments ( $P < 0.00625$ )



### Venous Admixture, Oxygen Consumption and Oxygen Delivery

No significant differences in baseline values were detected between groups for any of these parameters (Table 4). Oxygen delivery (Fig. 4) significantly decreased over time during the course of the anaesthesia after treatment S, but increased significantly after administration of enoximone, despite significant increases in  $\dot{Q}_s/\dot{Q}_t$  (overall and at T10 and T40). The increase in  $\text{DO}_2$  remained significant until T100.

For  $\dot{V}\text{O}_2$ , the difference between treatments was small ( $0.01 \pm 0.15$  L/min) and not statistically significant.

### Recovery

Recovery scores were comparable in both groups (Table 5). Time for complete recovery (standing up) was  $24 \pm 7$  minutes in the enoximone group, compared to  $26 \pm 9$  minutes in the saline group.

**Table 5: Recovery scores of 6 ponies, receiving either a bolus of enoximone or saline during anaesthesia.**

Pony	Enoximone	Saline
1	2	3
2	4	2
3	2	4
4	2	3
5	4	1
6	2	2

# Enoximone in ponies

**Table 3: Blood gas results, packed cell volume (PCV) and body temperature in 6 anaesthetized ponies receiving a bolus of enoximone (E) or saline (S).**

Variable	Unit	Standing Values	Trt	Time after treatment (minutes)								Overall
				T0	T10	T20	T40	T60	T80	T100	T120	
Body temperature	°C		E	36.3 ± 0.3	35.8 ± 0.6	35.7 ± 0.6	35.5 ± 0.7	35.3 ± 0.8	35.1 ± 0.8	35.0 ± 0.9	34.9 ± 0.9	35.4 ± 0.2
			S	36.1 ± 0.3	35.9 ± 0.3	35.8 ± 0.4	35.5 ± 0.4	35.4 ± 0.4	35.2 ± 0.4	35.2 ± 0.3	35.1 ± 0.3	35.5 ± 0.2
<b>Central venous blood</b>												
pH		7.40 ± 0.02	E	7.41 ± 0.05	7.42 ± 0.05	7.43 ± 0.05	7.44 ± 0.05	7.44 ± 0.04	7.43 ± 0.05	7.43 ± 0.05	7.43 ± 0.06	7.43 ± 0.01
			S	7.41 ± 0.03	7.43 ± 0.03	7.43 ± 0.04	7.43 ± 0.03	7.43 ± 0.03	7.43 ± 0.03	7.41 ± 0.03	7.41 ± 0.04	7.42 ± 0.01
pCO <sub>2</sub>	kPa	6.15 ± 0.21	E	6.85 ± 0.89	6.51 ± 0.93	6.35 ± 0.97	6.29 ± 0.89	6.47 ± 0.52	6.58 ± 0.77	6.53 ± 0.73	6.60 ± 0.80	6.50 ± 0.19
			S	6.82 ± 0.53	6.53 ± 0.15	6.49 ± 0.34	6.47 ± 0.37	6.60 ± 0.50	6.64 ± 0.36	7.00 ± 0.47	7.00 ± 0.52	6.70 ± 0.19
pO <sub>2</sub>	kPa	4.69 ± 0.55	E	4.86 ± 0.72	6.69 ± 5.13	4.78 ± 0.80	4.42 ± 0.76	4.20 ± 0.65	3.93 ± 0.54	3.73 ± 0.70	4.91 ± 2.62	4.70 ± 0.43
			S	4.46 ± 0.66	4.27 ± 0.90	6.15 ± 5.89	3.71 ± 0.75	3.22 ± 0.73	3.18 ± 0.75	3.13 ± 0.59	3.18 ± 0.47	3.80 ± 0.43
SBC	mmol/L	26.5 ± 1.8	E	29 ± 3	29 ± 2	29 ± 2	30 ± 2	30 ± 2	30 ± 2	30 ± 2	30 ± 2	30 ± 1
			S	29 ± 2	30 ± 3	30 ± 3	29 ± 2	29 ± 2	29 ± 2	29 ± 1	29 ± 2	29 ± 1
PCV	L/L	31.0 ± 2.4	E	0.27 ± 0.04	0.26 ± 0.05	0.26 ± 0.04	0.28 ± 0.05	0.26 ± 0.03	0.24 ± 0.02	0.24 ± 0.04	0.24 ± 0.02	0.25 ± 0.01
			S	0.25 ± 0.02	0.25 ± 0.02	0.25 ± 0.03	0.24 ± 0.04§	0.25 ± 0.03	0.24 ± 0.04	0.24 ± 0.04	0.24 ± 0.04	0.24 ± 0.01
<b>Arterial blood</b>												
pH		7.42 ± 0.03	E	7.45 ± 0.05	7.46 ± 0.06	7.47 ± 0.05	7.48 ± 0.05	7.47 ± 0.04	7.47 ± 0.04	7.48 ± 0.05	7.47 ± 0.05	7.47 ± 0.01
			S	7.45 ± 0.03	7.49 ± 0.04	7.48 ± 0.05	7.50 ± 0.04	7.49 ± 0.05	7.49 ± 0.05	7.48 ± 0.04	7.47 ± 0.05	7.49 ± 0.01
pCO <sub>2</sub>	kPa	5.47 ± 0.74	E	5.93 ± 0.68	5.87 ± 0.73	5.71 ± 0.69	5.53 ± 0.72	5.80 ± 0.52	5.71 ± 0.44	5.64 ± 0.49	5.69 ± 0.54	5.70 ± 0.34
			S	6.01 ± 0.51	5.49 ± 0.52	5.47 ± 0.29	5.22 ± 0.58	5.33 ± 0.61	5.42 ± 0.60	5.71 ± 0.44	5.87 ± 0.70	5.50 ± 0.34
pO <sub>2</sub>	kPa	12.62 ± 1.21	E	25.51 ± 13.85	18.62 ± 14.54	24.00 ± 19.74	24.62 ± 18.21	26.71 ± 17.66	25.69 ± 14.67	20.64 ± 7.49	20.80 ± 12.10	23.00 ± 4.98
			S	31.86 ± 21.29	30.04 ± 19.66	33.44 ± 15.58	32.13 ± 13.53	29.49 ± 18.85	28.09 ± 18.69	24.53 ± 15.76	23.60 ± 17.33	28.80 ± 4.98
SBC	mmol/L	26.0 ± 3.5	E	30 ± 2	30 ± 3	30 ± 3	30 ± 2	31 ± 2	30 ± 2	31 ± 2	31 ± 2	30 ± 1
			S	30 ± 3	31 ± 3	31 ± 3	30 ± 2	31 ± 1	31 ± 2	31 ± 2	31 ± 1	31 ± 1
PCV	L/L	0.312 ± 0.019	E	0.27 ± 0.03	0.25 ± 0.05	0.26 ± 0.04	0.26 ± 0.03	0.24 ± 0.03	0.27 ± 0.04	0.25 ± 0.03	0.24 ± 0.02	0.25 ± 0.01
			S	0.25 ± 0.02	0.25 ± 0.03	0.25 ± 0.04	0.24 ± 0.03	0.25 ± 0.03	0.25 ± 0.03	0.23 ± 0.04	0.24 ± 0.04	0.24 ± 0.01

Values at individual timepoints are represented as mean ± SD (SD calculated for each treatment group separately).

Overall values are represented as mean ± SE (SE calculated assuming homogeneity of variances).

No significant differences were found between E and S for the overall comparison (P<0.05)

§ significant difference between E and S at individual timepoints (P<0.00625)

**Table 4: Arterial (CaO<sub>2</sub>), central venous (CvO<sub>2</sub>) and end-capillary pulmonary oxygen content (C $\dot{c}$ O<sub>2</sub>), venous admixture, oxygen delivery (DO<sub>2</sub>) and oxygen consumption ( $\dot{V}$ O<sub>2</sub>) in 6 anaesthetized ponies receiving a bolus of enoximone (E) or saline (S).**

Variable	Unit	Standing values	Trt	Time after treatment (min)								Overall
				T0	T10	T20	T40	T60	T80	T100	T120	
CaO <sub>2</sub>	mL/ L	145.3 ± 8.7	E	128 ± 7	118 ± 12	122 ± 10	122 ± 9	118 ± 9	129 ± 19	121 ± 13	116 ± 5	121 ± 4
			S	124 ± 12	122 ± 14	123 ± 18	120 ± 14	118 ± 8	119 ± 16	111 ± 10	113 ± 9	118 ± 4
CvO <sub>2</sub>	mL/ L		E	90 ± 11	90 ± 18	90 ± 10	93 ± 13	82 ± 6	72.1 ± 11	70 ± 16	76 ± 12	82 ± 5
			S	81 ± 13	78 ± 14	79 ± 24	66 ± 19§	59 ± 18§	55.9 ± 18	54 ± 14	55 ± 9	64 ± 5
C $\dot{c}$ O <sub>2</sub>	mL/L		E	145 ± 8	136 ± 14	140 ± 11	139 ± 10	134 ± 11	146 ± 20	139 ± 13	134 ± 5	138 ± 4
			S	140 ± 10	138 ± 14	138 ± 18	136 ± 15	134 ± 8	135 ± 15	129 ± 12	131 ± 11	134 ± 4
Venous admixture	%		E	32 ± 7	47 ± 24	35 ± 8	43 ± 19	32 ± 5	24 ± 7	28 ± 8	35 ± 16	35 ± 2
			S	26 ± 7	28 ± 6§	33 ± 20	23 ± 4§	23 ± 6	22 ± 7	23 ± 3	23 ± 3	25 ± 2*
DO <sub>2</sub>	L/min	4.13 ± 1.27	E	1.93 ± 0.33	2.25 ± 0.31	2.16 ± 0.44	1.96 ± 0.26	1.66 ± 0.31	1.66 ± 0.41	1.53 ± 0.45	1.41 ± 0.33	1.80 ± 0.31
			S	1.62 ± 0.25	1.46 ± 0.28§	1.40 ± 0.30§	1.35 ± 0.44§	1.21 ± 0.38§	1.14 ± 0.33§	1.04 ± 0.30§	1.12 ± 0.27	1.20 ± 0.31*
$\dot{V}$ O <sub>2</sub>	L/min	1.31 ± 0.50	E	0.57 ± 0.23	0.51 ± 0.30	0.57 ± 0.18	0.46 ± 0.26	0.51 ± 0.19	0.73 ± 0.31	0.61 ± 0.22	0.51 ± 0.25	0.56 ± 0.13
			S	0.57 ± 0.12	0.52 ± 0.17	0.48 ± 0.27	0.60 ± 0.21	0.58 ± 0.19	0.58 ± 0.12	0.51 ± 0.08	0.57 ± 0.13	0.55 ± 0.13

Values at individual timepoints are represented as mean ± SD (SD calculated for each treatment group separately).

Overall values are represented as mean ± SE (SE calculated assuming homogeneity of variances).

\* significant difference between E and S for the overall comparison (P<0.05)

§ significant difference between E and S at individual timepoints (P<0.00625)

### Discussion

Inhalation anaesthesia produces a dose-related cardiovascular depression in horses (Steffey & Howland 1980). In the present study, comparison of the values in the standing, unsedated ponies with the baseline values during inhalation anaesthesia, revealed clear and significant decreases in SAP, DAP, MAP,  $\dot{Q}_t$  and SV. During the further course of the anaesthesia in the saline group, DAP, MAP and SVR increased slowly, while HR,  $\dot{Q}_t$ , SV and  $DO_2$  gradually decreased. The cellular mechanisms responsible for the negative effects of volatile anaesthetics on cardiac contractility are generally attributed to alterations in intracellular calcium homeostasis in the myocardium (Pagel et al. 1993). These alterations include reductions in the influx of calcium through slow channels (Komai & Rusy 1987, Rusy & Komai 1987), impaired calcium uptake and release by the sarcoplasmic reticulum (Casella et al. 1987, Housmans & Murat 1988) and decreased calcium sensitivity of the myofilaments (Rusy & Komai 1987, Housmans & Murat 1988).

The drugs most commonly used for inotropic support in horses are the  $\beta$ -adrenergic sympathomimetic agents (e.g. dobutamine). When these agents bind to the  $\beta_1$  receptor, the G-protein coupled to this receptor splits and stimulates adenylylcyclase, the enzyme responsible for the synthesis of cAMP. An increase in cAMP concentration in the cardiac muscle activates a cAMP-dependent protein kinase, which phosphorylates the L-type calcium channels, leading to an increase in the mean open probability of individual channels (Hove-Madsen et al. 1996). The subsequent increase in intracellular calcium levels in turn causes calcium-induced calcium release from the sarcoplasmic reticulum (Fabiato 1983), which leads to an increase in the contractile forces (Vernon et al. 1991). Furthermore, cAMP augments calcium-ATPase activity in the sarcoplasmic reticulum, promoting increased calcium storage during diastole (Muir 1995) and facilitating relaxation of the heart (Vernon et al. 1991).

Another class of drugs, the PDE inhibitors, increase the intracellular levels of cAMP and/or cGMP in different tissues through inhibition of their breakdown by phosphodiesterase enzymes (Hall 1993). At least five different phosphodiesterase isoenzymes have been described, with each family containing at least 2 subfamilies. Selective inhibition of these isoenzymes produces partially tissue specific effects. This leads to different clinical applications for different isoenzyme selective PDE inhibitors, including stimulation of

myocardial contractility, vasodilation, inhibition of platelet aggregation, bronchodilation and the use as anti-inflammatory drugs or antidepressants (Hall 1993).

Enoximone is a selective inhibitor of the type III PDE isoenzyme (Vernon et al. 1991), which is principally present in the myocardium, smooth muscles and platelets and breaks down both cAMP and cGMP (Calvey & Williams 2001, Hall 1993). In the myocardium enoximone induces inotropic and lusitropic effects, with a significantly lower myocardial oxygen consumption than after dobutamine therapy in man (Lançon et al. 1990). In vascular smooth muscle, cAMP phosphorylates protein kinase and myosin-light-chain kinase and alters ion fluxes, resulting in vasodilation (Evans 1989, Calvey & Williams 2001). Because of an increase in platelet cAMP, platelet aggregation is diminished (Calvey & Williams 2001). Possible side-effects of enoximone are usually only seen after long term oral treatment in men and include tachyarrhythmias, hypotension, thrombocytopenia, nausea, dyspepsia, diarrhoea, vomiting, fever, oliguria and limb pain (Vernon et al. 1991, Calvey & Williams 2001). Side effects using a bolus or constant rate infusion during anaesthesia are rare and were not observed in the ponies of the present study. Although adverse effects during recovery have been reported with some sympathomimetics, such as dopexamine in horses (Young et al. 1997, Lee et al. 1998), the recovery scores were comparable in the two treatment groups.

Enoximone's principal effects are positive inotropism and vasodilation (Dage and Okerholm 1990, Vernon et al. 1991, Hall 1993). In the present study, a bolus of 0.5 mg/kg enoximone significantly augmented  $\dot{Q}_t$  for a period of 100 minutes in healthy ponies during isoflurane anaesthesia. This increase in  $\dot{Q}_t$  is in agreement with the reported effects of enoximone in dogs (Dage et al. 1982) and milrinone in halothane anaesthetized horses (Muir 1995). Cardiac output is determined by HR and SV, which both increased after the administration of enoximone (HR until T40, SV until T100).

Mild and transient chronotropic effects have also been reported in dogs (Dage et al. 1982) and humans (Amin et al. 1985, Installe et al. 1987) after enoximone administration and can be explained by the consistent electrophysiological changes with this drug. Indeed, this PDE inhibitor shortens basic sinus cycle length, sinus node recovery time and sinoatrial conduction time and decreases Wenckebach cycle length and atrioventricular and atrial refractoriness, leading to positive chronotropic and dromotropic effects. Despite these changes during bolus administration, enoximone did not appear to be arrhythmogenic (Pop et

## Enoximone in ponies

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al. 1986). Only chronic, long-term oral administration in humans has been associated with tachyarrhythmias (Calvey & Williams 2001). In the present study, no arrhythmias were observed in our ponies and the maximal difference in mean HR between treatments occurred 5 minutes after administration of the bolus ( $7 \pm 1$  beats per minute). Heart rate remained below 50 beats per minute in all ponies, except in 1 animal where HR temporarily increased from 45 (T0) to 59 beats per minute at T5. After T5, the difference in HR between the two groups gradually decreased and was no longer significant from T40 onwards.

In the present study, enoximone significantly increased SV for 100 minutes. The three parameters which determine SV are preload, contractility and afterload, which are all influenced by enoximone in man (Vernon et al. 1991). Muir (1995) observed a reduction in mean right atrial and pulmonary artery pressures during and after milrinone infusions in horses. In the present study, a significant decrease in RAP during at least 120 minutes after administration of enoximone to our ponies was also observed, indicating a reduction in preload of the right heart. This finding might be explained by venous pooling, which has been described in man after enoximone treatment (Boldt et al. 1993, Lehtonen et al. 2004). While RAP reflects preload of the right heart, preload of the left heart is reflected by pulmonary capillary wedge pressure, which was reported to decrease after administration of enoximone in man (Vernon et al. 1991). This reduction in left ventricular filling pressure was larger than the one produced by dobutamine (Amin et al. 1985).

Contractility, the second factor which influences SV, was enhanced by the positive inotropic effects of enoximone in both dogs and humans (Installe et al. 1987, Dage & Okerholm 1990, Vernon et al. 1991, Boldt et al. 1992, Hall 1993, Ghio et al. 2003, Lehtonen et al. 2004, Calvey & Williams 2001). Ringe et al. (2003) even stated that in patients with severe prolonged catecholamine and volume refractory endotoxin shock, enoximone could restore myocardial contractility. In the present study, we observed an increase in SV without a decrease in SVR. Although contractility was not measured directly in the present study, it was most likely also enhanced.

The third factor, namely the afterload, was reported to be reduced by enoximone in man (Lehtonen et al. 2004). A frequently used clinical index of left ventricular afterload is SVR (Lang et al. 1986), which decreased after enoximone administration in man because of vasodilation (Vernon et al. 1991, Boldt et al. 1992, Calvey & Williams 2001). Similarly, SVR decreased in response to administration of enoximone in dogs (Dage et al. 1982) and

milrinone in horses (Muir 1995). In the present study, the decrease in SVR after enoximone treatment was not significant. It might be hypothesized that sedation with romifidine attenuated the vasodilating properties of enoximone, since  $\alpha_2$  agonists induce vasoconstriction by binding to postsynaptic  $\alpha_2$  receptors, leading to a reduced synthesis of cAMP in the vascular smooth muscle cells. However, it has been reported that the increase in SVR in standing horses after administration of romifidine at doses of 80 and 120  $\mu\text{g}/\text{kg}$  IV was only significant with the highest dose and no longer than 15 minutes (Freeman et al. 2002). In the present study, a low dose of romifidine (80  $\mu\text{g}/\text{kg}$ ) was used and the time between sedation and administration of enoximone was 105 minutes. It is therefore most unlikely that the pre-anaesthetic use of romifidine was responsible for the lack of a significant effect of enoximone on SVR.

On the other hand, SVR reflects only peripheral vasomotor tone. A better measure of left ventricular afterload is left ventricular end-systolic wall stress ( $\sigma_{\text{es}}$ ), which combines the effects of peripheral loading conditions and left ventricular chamber pressure, dimension and wall thickness (Lang et al. 1986). When afterload is decreased and contractility increased, SVR actually underestimates the decrease in left ventricular  $\sigma_{\text{es}}$  (up to 50% when dobutamine is administered) (Lang et al. 1986). This phenomenon may also have occurred in the present study, as enoximone was reported to cause both arterial vasodilation (Boldt et al. 1993) and increased myocardial contractility (Installe et al. 1987, Dage and Okerholm 1990, Vernon et al. 1991, Boldt et al. 1992, Hall 1993, Ghio et al. 2003, Lehtonen et al. 2004, Calvey & Williams 2001).

Because of its actions as smooth muscle relaxant, enoximone was responsible for a decrease in blood pressure in some studies (Dage et al. 1982, Installe et al. 1987, Boldt et al. 1993, Hall 1993, Schmidt et al. 2001, Calvey & Williams 2001). However, several other authors could not detect significant influences of enoximone on arterial pressure (Vernon et al. 1991, Paulus et al. 1994), even in patients with severe cardiogenic shock (Vincent et al. 1988). In the present study, using normovolemic ponies, arterial pressure even tended to be slightly higher after the enoximone bolus; none of the observed differences in blood pressure were however statistically significant. Nevertheless, in cases of severe hypotension or endotoxaemia with major vasodilation, enoximone should be used with caution until its cardiovascular effects in case of hypovolemia/endotoxaemia are fully investigated. At the same time, more studies are necessary to determine whether horses respond in a similar way as ponies.

## Enoximone in ponies

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In the present study,  $\dot{Q}_s/\dot{Q}_t$  was significantly higher after enoximone treatment (overall and at T10 and T40). In the study of Muir (1995), no data was given about the influence of milrinone infusions on arterial blood gases or the degree of  $\dot{Q}_s/\dot{Q}_t$ . Although Boldt et al. (1992) did not detect any differences in intrapulmonary shunting, increased venous admixture after enoximone administration in man has been reported by other authors (Vincent et al. 1988, Paulus et al. 1994) and was probably related to an increased cardiac index and the inhibition of hypoxic pulmonary vasoconstriction (HPV) (Lynch et al. 1979, Paulus et al. 1994). In the present study,  $\dot{Q}_t$  was indeed significantly higher after enoximone treatment. An inhibition of HPV may also have occurred and could be explained by two factors, namely the administration of enoximone on itself and an induced increase in mixed venous oxygen content ( $C\bar{v}O_2$ ). In man, enoximone reduces pulmonary vascular resistance, indicating vasodilation in the pulmonary circulation, which would counteract HPV. Secondly,  $C\bar{v}O_2$  is a partial determinant of HPV: with increasing  $C\bar{v}O_2$ , the stimulus for HPV decreases (Domino et al. 1983). However, in the present study, the increase in  $\dot{Q}_s/\dot{Q}_t$  after enoximone treatment was attributable to extreme values for  $PvO_2$  at T10 in 1 pony and for venous PCV at T40 in 2 ponies, which explains the large standard deviations for  $PvO_2$ , PCV,  $CvO_2$  and  $\dot{Q}_s/\dot{Q}_t$  at the respective timepoints in tables 3 and 4. These extreme values were the main reason why venous PCV and  $CvO_2$  were also significantly higher at T40. In the authors' opinion, these findings are therefore probably incidental, as in all other ponies, the values were comparable to saline treatment.

Despite the increase in  $\dot{Q}_s/\dot{Q}_t$  after enoximone administration in the present study, no significant decrease in  $CaO_2$  was observed. As  $CvO_2$  was increased,  $\dot{Q}_s/\dot{Q}_t$  could indeed be expected to have less influence on  $CaO_2$ . Also, although  $PaO_2$  was somewhat lower in the E group, mean  $PaO_2$  always remained in the range to fully saturate haemoglobin, which is the main determinant of  $CaO_2$ . Possibly, in cases of severe hypoxemia, where a small reduction in  $PaO_2$  can result in a severe decrease in  $SaO_2$ , the effects of increased  $\dot{Q}_s/\dot{Q}_t$ , if present, might be more pronounced. However, it must be noted that, although they are generally accepted, the equations for calculation of blood oxygen content and degree of  $\dot{Q}_s/\dot{Q}_t$  are based on a few assumptions which can lead to inaccuracy. Firstly, during calculation of oxygen content, standard values are routinely used for the oxygen solubility coefficient and the oxygen-combining capacity of haemoglobin, which may not always be constant under all circumstances and in all subjects. Secondly, the equation for the degree of  $\dot{Q}_s/\dot{Q}_t$  does not



take Thebesian and bronchial venous blood into account (Lumb 2005). It may also be argued that the use of central venous blood (taken from the right atrium) instead of true mixed venous blood led to inaccuracy, but different authors documented that central venous blood collected from the right atrium can replace mixed venous blood to calculate the degree of pulmonary shunt (Tahvanainen et al. 1982, López Escárcega et al. 1985). Finally, while haemoglobin saturation is required for calculation of blood oxygen content, the ABL5 Radiometer<sup>®</sup> does not measure haemoglobin saturation but calculates it, as it is not equipped with a co-oximeter. For all of these reasons, and especially because there was no significant difference in PaO<sub>2</sub> in the present study, the importance of the increase in  $\dot{Q}_s/\dot{Q}_t$  should not be overinterpreted until further studies are performed in hypoxaemic horses.

Because  $\dot{Q}_t$  was increased without changes in CaO<sub>2</sub>, a significant increase in DO<sub>2</sub> during 100 minutes was found, which is in agreement with several reports in man (Teboul et al. 1992, Paulus et al. 1994, Loick et al 1997, Kern et al. 2001). Especially in equine anaesthesia, where hypoxaemia and cardiovascular depression are common clinical findings and can have detrimental effects, improved oxygen delivery is one of the most important goals of the anaesthetist. Furthermore, in humans, enoximone increased organ perfusion and skin capillary blood flow (Boldt et al. 1992), while indications for an improved nutritive microcirculation have been reported (Boldt et al. 1993). During an early stage of sepsis in anaesthetized rats, enoximone prevented mucosal hypoperfusion of the ileum (Schmidt et al. 2001). In fluid-optimized septic shock in man, enoximone also improved hepatosplanchnic function and helped to attenuate the inflammatory response (Kern et al. 2001). This PDE inhibitor additionally seemed to have a beneficial effect on tissue damage and barrier function of the gut, since it diminished the increase in endotoxin concentrations in liver venous blood following cardiopulmonary bypass (Loick et al. 1997). Limb blood flow was also increased in response to a single oral dose of enoximone in man (Vernon et al. 1991). However, before assumptions are made in ponies or horses, the effects of enoximone on peripheral perfusion should be studied in depth in these species.

In conclusion, a single bolus of enoximone in isoflurane anaesthetized ponies induced increases in HR,  $\dot{Q}_t$  and SV without obvious effects on arterial pressure or SVR. Right atrial pressure, a reflection of right heart preload, was significantly reduced. Despite significant increases in  $\dot{Q}_s/\dot{Q}_t$ , oxygen delivery to the tissues was higher. Further studies are needed to determine whether the effects of enoximone are similar in horses as in ponies, to detect

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possible interactions with other drugs and to investigate the effects of enoximone in horses with hypoxaemia, when increased  $\dot{Q}_s/\dot{Q}_t$  may have more importance and in horses with hypovolemia and/or hypotension, when vasodilation might have more pronounced effects on blood pressure.

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## **Cardiorespiratory effects of dobutamine after enoximone in isoflurane anaesthetized ponies**

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**SUMMARY**

The cardiovascular and respiratory effects of dobutamine after a bolus of enoximone were examined in 6 healthy, isoflurane anaesthetized ponies, weighing  $286 \pm 52$  kg and aged  $5.0 \pm 1.6$  years. After sedation with romifidine [80  $\mu$ g/kg intravenously (IV)], anaesthesia was induced with midazolam (0.06 mg/kg IV) and ketamine (2.2 mg/kg IV) and maintained with isoflurane in oxygen. The ponies were ventilated to maintain normocapnia. After 90 minutes (= T0), enoximone alone (0.5 mg/kg IV) (E) or enoximone followed by a constant rate infusion of dobutamine (0.5  $\mu$ g/kg/min) (ED) for 120 minutes were administered. Each pony received both treatments in a crossover trial, with at least 2 weeks between treatments. Heart rate (HR), cardiac output ( $\dot{Q}_t$ ), stroke volume (SV), right atrial (RAP), systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP), blood gases, systemic vascular resistance (SVR), oxygen delivery ( $DO_2$ ) and several respiratory gas exchange variables were obtained before treatment and until T120.

Compared to enoximone alone, ED treatment induced overall increases in HR,  $\dot{Q}_t$ , SV, RAP, SAP, DAP, MAP, packed cell volume (PCV) and  $DO_2$ . The difference was significant from T60 to T120 (except at T80) for HR, throughout the observational period for  $\dot{Q}_t$ , SAP, MAP, PCV and  $DO_2$ , from T40 to T120 for DAP, at T10, T60, T80 and T120 for SV and at T10 and T20 for RAP. Overall values for SVR and dead space ventilation ( $V_D/V_T$ ) were lower after treatment ED compared to treatment E.  $V_D/V_T$  was lower at T20 and from T80 to T120. Venous oxygen saturation was higher after treatment ED than after treatment E from T60 onwards. These results suggest that enoximone and dobutamine have additive cardiovascular effects and reduce  $V_D/V_T$  in isoflurane anaesthetized ponies.

# Enoximone & dobutamine in ponies

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## Introduction

To maintain oxygen delivery ( $DO_2$ ) to the tissues during equine anaesthesia, inotropic drugs are often needed. For this purpose  $\beta$ -adrenergic sympathomimetics are used most frequently in horses. These agents increase the intracellular level of cyclic adenosine monophosphate (cAMP) through stimulation of adenylyl cyclase. As a result, myocardial contractility is enhanced. However, the administration of these drugs increases cardiac work and myocardial oxygen demand (Notterman 1991) and can be accompanied by several side-effects (Swanson et al. 1985, Trim et al. 1985, Gasthuys et al. 1991, Notterman 1991). The phosphodiesterase (PDE) III inhibitors, a second class of inotropic drugs, exert their action through inhibition of the enzymatic hydrolysis of cAMP (Vernon et al. 1991). In horses or ponies, only the effects of milrinone (Muir 1995) and enoximone (Chapter 4.1) have been described.

As  $\beta$ -sympathomimetics and PDE III inhibitors both increase the intracellular concentration of cAMP through independent, additive mechanisms, their combined use has been studied in man. A combination of adrenaline and amrinone produced additive effects on stroke volume (SV) after cardiopulmonary bypass surgery (Royster et al. 1993). Also, enoximone's favourable cardiovascular effects were additive to those produced by dobutamine in patients with class IV heart failure. Larger increases in cardiac index (CI), left ventricular stroke work index and heart rate (HR) were observed, together with more pronounced decreases in right atrial pressure (RAP), pulmonary artery pressure, pulmonary wedge pressure, systemic vascular resistance (SVR) and pulmonary vascular resistance (Gilbert et al. 1995).

In horses, no studies have been performed on the combined use of a PDE III inhibitor with a  $\beta$ -sympathomimetic. Therefore, the objective of the present study was to evaluate the effects on the cardiovascular system and on respiratory gas exchange of a constant rate infusion (CRI) of dobutamine after bolus administration of enoximone in isoflurane anaesthetized ponies.

### Materials & Methods

The experimental protocol has been described in chapter 4.1. For statistical analysis, treatments E and ED were compared using a mixed model with treatment, time and their interaction as fixed categorical effects and pony as random effect. This model was used to analyze the overall difference between the two treatments (at  $\alpha = 0.05$ ) and the difference at 8 selected time points: Baseline, T10, T20, T40, T60, T80, T100 and T120 (at Bonferroni-adjusted  $\alpha = 0.00625$ ).

### Results

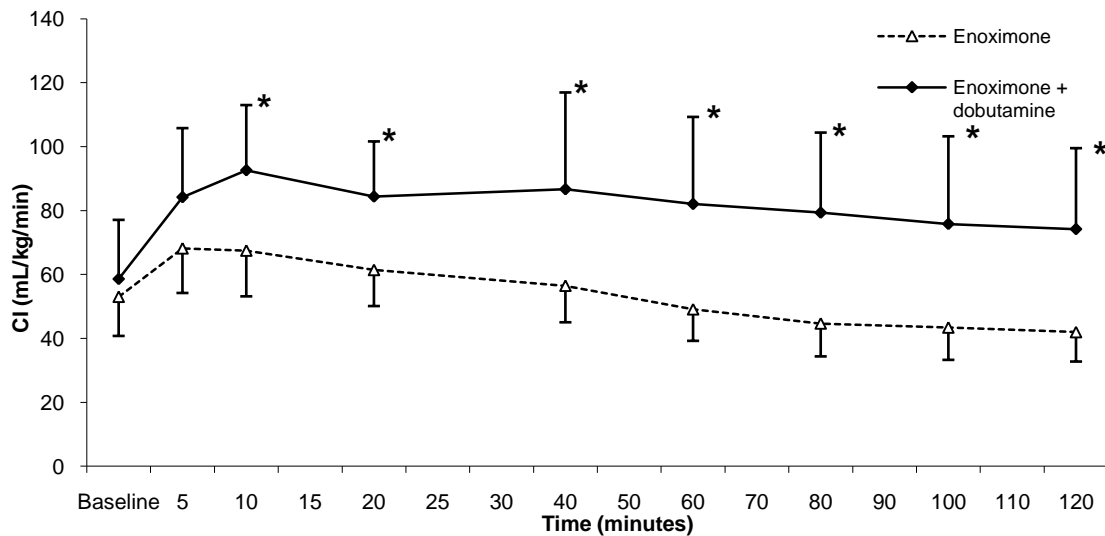
#### Cardiovascular system

Compared to enoximone alone (treatment E), cardiac output ( $\dot{Q}_t$ ) ( $P=0.004$ ) and SV ( $P=0.006$ ) were higher during treatment with enoximone and dobutamine (treatment ED) (Table 1, Fig. 1 & 2). Analysis at the selected time points revealed that the difference was significant throughout the observational time for  $\dot{Q}_t$  and at T10, T60, T80 and T120 for SV. Mean CI was  $54.08 \pm 7.19$  mL/kg/min with enoximone alone versus  $82.40 \pm 7.19$  mL/kg/min when enoximone and dobutamine were combined.

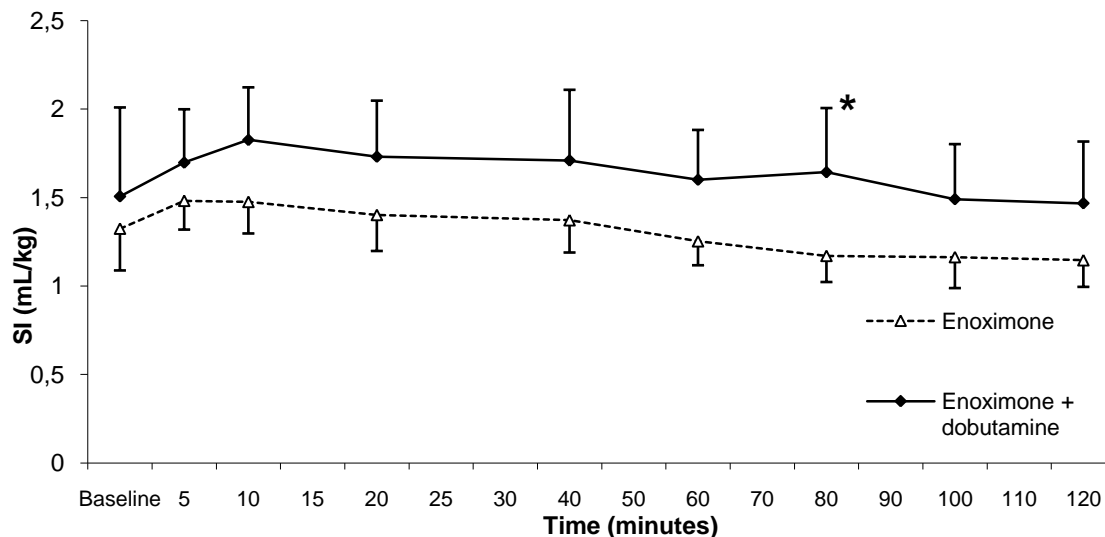
Heart rate (Table 1) increased after administration of enoximone in both groups, but was higher during treatment ED ( $50.3 \pm 3.3$  beats/min) compared to treatment E ( $40.5 \pm 3.3$  beats/min) ( $P=0.026$ ). This difference was significant from T60 onwards (except at T80).

The addition of a CRI of dobutamine also resulted in increases in blood pressure (Table 1) compared to enoximone alone: overall systolic (SAP) ( $P=0.0015$ ), diastolic (DAP) ( $P=0.0018$ ) and mean (MAP) ( $P=0.0007$ ) arterial pressures were higher during treatment ED. As this difference gradually became larger over time, a significant interaction effect between treatment and time was detected. On T10 and T20, RAP was also significantly larger during treatment ED compared to treatment E.

Systemic vascular resistance increased over time during both treatments ( $P<0.0001$ ) (Table 1). Analysis of the overall values revealed a lower SVR during treatment ED ( $ED 318 \pm 65$  vs E  $274 \pm 77$  dynes.sec/cm<sup>5</sup>,  $P=0.0423$ ). However, after Bonferroni correction, no significant differences between the two treatments could be detected at any of the selected time points.



**Fig. 1: Cardiac index (CI) in 6 anaesthetized ponies receiving enoximone alone or enoximone followed by a CRI of dobutamine.**  
 Values are displayed as mean  $\pm$  SD.  
 \* indicates a significant difference between the 2 treatments ( $P < 0.00625$ ).



**Fig. 2: Stroke volume index (SI) in 6 anaesthetized ponies receiving enoximone alone or enoximone followed by a CRI of dobutamine.**  
 Values are displayed as mean  $\pm$  SD.  
 \* indicates a significant difference between the 2 treatments ( $P < 0.00625$ ).

## Body temperature, blood gas analysis and packed cell volume

During the observational period, body temperature gradually decreased over time ( $P < 0.0001$ ) (Table 2). Although the overall values for body temperature were not significantly different between treatments, body temperature decreased more rapidly during treatment ED, leading to an interaction effect between the factors treatment and time ( $P < 0.0001$ ).

**Table 1: Heart rate (HR), systolic (SAP), diastolic (DAP), mean arterial (MAP) and right atrial (RAP) pressures, cardiac output (Qt), stroke volume (SV) and systemic vascular resistance (SVR) in 6 anaesthetized ponies receiving enoximone alone (E) or enoximone followed by a CRI of dobutamine (ED).**

Variable	Unit	Trt	Time after treatment (min)								Overall
			Baseline	T10	T20	T40	T60	T80	T100	T120	
HR	beats/min	E	39 ± 4	46 ± 6	44 ± 6	41 ± 5	39 ± 5	38 ± 4	37 ± 4	36 ± 3	41 ± 3
		ED	39 ± 6	51 ± 5	49 ± 6	50 ± 9	51 ± 12 §	49 ± 14	51 ± 18 §	52 ± 19 §	50 ± 3 *
SAP	mm Hg	E	83 ± 7	86 ± 14	84 ± 12	84 ± 11	88 ± 11	89 ± 10	87 ± 10	85 ± 10	86 ± 5
		ED	80 ± 5	113 ± 8 §	112 ± 6 §	115 ± 13 §	119 ± 19 §	121 ± 22 §	121 ± 23 §	118 ± 23 §	115 ± 5 *
DAP	mm Hg	E	51 ± 6	54 ± 14	54 ± 14	56 ± 15	60 ± 14	62 ± 12	61 ± 9	60 ± 10	57 ± 4
		ED	47 ± 3	62 ± 8	63 ± 8	69 ± 9 §	77 ± 9 §	80 ± 15 §	80 ± 15 §	79 ± 15 §	71 ± 4 *
MAP	mm Hg	E	63 ± 6	65 ± 14	65 ± 14	67 ± 14	72 ± 13	73 ± 11	71 ± 9	69 ± 9	68 ± 4
		ED	59 ± 3	77 ± 7 §	79 ± 7 §	85 ± 9 §	92 ± 12 §	96 ± 17 §	97 ± 17 §	95 ± 17 §	87 ± 4 *
RAP	mm Hg	E	15 ± 2	10 ± 2	10 ± 2	11 ± 3	11 ± 2	12 ± 3	13 ± 3	13 ± 3	11 ± 1
		ED	16 ± 5	14 ± 4 §	14 ± 4 §	14 ± 5	15 ± 6	15 ± 5	15 ± 4	15 ± 5	15 ± 1 *
Qt	L/min	E	15.01 ± 2.15	19.13 ± 1.44	17.53 ± 2.22	16.04 ± 1.26	14.05 ± 1.86	12.83 ± 2.41	12.56 ± 2.90	12.11 ± 2.54	15.45 ± 1.27
		ED	15.39 ± 2.10	25.13 ± 4.95 §	22.89 ± 4.32 §	23.21 ± 6.09 §	21.76 ± 4.32 §	21.18 ± 4.20 §	20.30 ± 5.38 §	19.96 ± 5.34 §	22.12 ± 1.27 *
SV	mL	E	378 ± 48	425 ± 51	406 ± 73	395 ± 50	363 ± 56	340 ± 63	340 ± 78	334 ± 69	379 ± 20
		ED	396 ± 70	494 ± 50 §	466 ± 33	458 ± 46	432 ± 42 §	444 ± 63 §	407 ± 82	403 ± 100 §	445 ± 20 *
SVR	dyne.sec/cm <sup>5</sup>	E	261 ± 63	232 ± 66	257 ± 85	282 ± 77	352 ± 90	394 ± 114	400 ± 143	395 ± 143	318 ± 29
		ED	225 ± 29	206 ± 37	231 ± 37	262 ± 79	296 ± 71	318 ± 98	356 ± 170	355 ± 180	274 ± 29 *

Values at individual timepoints are represented as mean ± SD (SD calculated for each treatment group separately).

Overall values are represented as mean ± SE (SE calculated assuming homogeneity of variances).

\* significant difference between E and ED for the overall comparison (P<0.05)

§ significant difference between E and ED at individual timepoints (P<0.00625)

## Enoximone & dobutamine in ponies

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No differences in arterial oxygen tension ( $\text{PaO}_2$ ) (Table 2) and haemoglobin saturation with oxygen ( $\text{SaO}_2$ ) could be detected between treatments, but an interaction effect between treatment and time was observed. During treatment E,  $\text{PaO}_2$  and  $\text{SaO}_2$  decreased at T10, returned to baseline values at T20 and gradually decreased again after T80. After a similar decrease at T10, a steady increase was observed throughout the remaining anaesthetic period during treatment ED. Also, venous haemoglobin oxygen saturation ( $\text{SvO}_2$ ) was higher during treatment ED ( $P=0.0084$ ). This difference was significant from T60 onwards. At T80, a significant difference in venous oxygen tension ( $\text{PvO}_2$ ) was detected, most likely due to abnormally high values recorded in 2 ponies (15.8 and 17.7 kPa respectively). When these ponies were excluded from analysis, this difference was no longer significant.

Packed cell volume (PCV) was higher during treatment ED ( $P = 0.0018$ ) with an interaction effect between treatment and time ( $P = 0.0348$ ): PCV increased with treatment ED but remained constant with treatment E (Table 2).

### **Respiratory system, oxygen delivery and oxygen consumption**

Overall RR was not different between treatments (E  $11.3 \pm 1.6$  vs ED  $12.5 \pm 2.1$  breaths/min). While no differences in overall venous admixture ( $\dot{Q}_s/\dot{Q}_t$ ) were detected between the 2 treatments, overall alveolar dead space-to-tidal volume ratio ( $V_D/V_T$ ) was lower during treatment ED (ED  $35.3 \pm 1.9$  vs E  $42.6 \pm 1.9$  %;  $P=0.0132$ ) (Fig. 3). This difference was significant at T20 and from T80 onwards. For the alveolar-to-arterial oxygen tension difference ( $P(A-a)\text{O}_2$ ), an interaction effect between treatment and time was observed: it remained stable during treatment E, but gradually decreased over time during treatment ED ( $P=0.0067$ ) (Fig. 4).

Overall and at each selected timepoint, higher values were found during treatment ED for the arterial oxygen content ( $\text{CaO}_2$ ) ( $P=0.0003$ ), central venous oxygen content ( $\text{CvO}_2$ ) ( $P=0.0002$ ) and end-capillary pulmonary oxygen content ( $\text{C}\acute{\text{c}}\text{O}_2$ ) ( $P=0.0008$ ) (Table 3). A significant interaction effect between treatment and time was also detected for all 3 variables: while these values remained stable throughout anaesthesia after treatment E, a gradual increase was observed during treatment ED.

**Table 2: Body temperature, blood gas results and packed cell volume (PCV) in 6 anaesthetized ponies receiving enoximone alone (E) or enoximone followed by a CRI of dobutamine (ED).**

Variable	Unit	Trt	Time after treatment (minutes)								Overall
			Baseline	T10	T20	T40	T60	T80	T100	T120	
Body temperature	°C	E	36.3 ± 0.3	35.8 ± 0.6	35.7 ± 0.6	35.5 ± 0.7	35.3 ± 0.8	35.1 ± 0.8	35.0 ± 0.9	34.9 ± 0.9	35.4 ± 0.3
		ED	36.0 ± 0.4	35.7 ± 0.4	35.5 ± 0.4	35.1 ± 0.5	34.7 ± 0.7	34.5 ± 0.7	34.3 ± 0.8	34.1 ± 0.9	34.9 ± 0.3
<b>Central venous blood</b>											
pH		E	7.41 ± 0.05	7.42 ± 0.05	7.43 ± 0.05	7.44 ± 0.05	7.44 ± 0.04	7.43 ± 0.05	7.43 ± 0.05	7.43 ± 0.06	7.43 ± 0.02
		ED	7.44 ± 0.03	7.42 ± 0.02	7.43 ± 0.03	7.44 ± 0.03	7.45 ± 0.04	7.46 ± 0.03	7.47 ± 0.05	7.47 ± 0.06	7.45 ± 0.02
pCO <sub>2</sub>	kPa	E	6.85 ± 0.89	6.51 ± 0.93	6.35 ± 0.97	6.29 ± 0.89	6.47 ± 0.52	6.58 ± 0.77	6.53 ± 0.73	6.60 ± 0.80	6.50 ± 0.24
		ED	6.30 ± 0.56	6.42 ± 0.32	6.40 ± 0.42	6.04 ± 0.44	6.02 ± 0.54	5.91 ± 0.53	5.84 ± 0.70	5.80 ± 0.80	6.06 ± 0.24
pO <sub>2</sub>	kPa	E	4.86 ± 0.72	6.69 ± 5.13	4.78 ± 0.80	4.42 ± 0.76	4.20 ± 0.65	3.93 ± 0.54	3.73 ± 0.70	4.91 ± 2.62	4.70 ± 0.78
		ED	4.70 ± 1.79	5.51 ± 1.78	5.98 ± 1.92	5.95 ± 2.30	5.95 ± 2.28	8.82 ± 6.22 §	5.95 ± 1.83	5.84 ± 2.02	6.29 ± 0.78
SBC	mmol/L	E	29 ± 3	29 ± 2	29 ± 2	30 ± 2	30 ± 2	30 ± 2	30 ± 2	30 ± 2	30 ± 1
		ED	29 ± 1	29 ± 1	29 ± 1	29 ± 1	30 ± 1	30 ± 1	30 ± 1	30 ± 2	29 ± 1
PCV	L/L	E	0.27 ± 0.04	0.26 ± 0.05	0.26 ± 0.04	0.28 ± 0.05	0.26 ± 0.03	0.24 ± 0.02	0.24 ± 0.04	0.24 ± 0.02	0.25 ± 0.01
		ED	0.27 ± 0.03	0.30 ± 0.04 §	0.31 ± 0.03 §	0.33 ± 0.04	0.33 ± 0.05 §	0.33 ± 0.04 §	0.33 ± 0.04 §	0.33 ± 0.04 §	0.32 ± 0.01 *
<b>Arterial blood</b>											
pH		E	7.45 ± 0.05	7.46 ± 0.06	7.47 ± 0.05	7.48 ± 0.05	7.47 ± 0.04	7.47 ± 0.04	7.48 ± 0.05	7.47 ± 0.05	7.47 ± 0.02
		ED	7.47 ± 0.04	7.44 ± 0.03	7.45 ± 0.03	7.46 ± 0.04	7.47 ± 0.05	7.48 ± 0.04	7.50 ± 0.06	7.51 ± 0.06	7.47 ± 0.02
pCO <sub>2</sub>	kPa	E	5.93 ± 0.68	5.87 ± 0.73	5.71 ± 0.69	5.53 ± 0.72	5.80 ± 0.52	5.71 ± 0.44	5.64 ± 0.49	5.69 ± 0.54	5.70 ± 0.20
		ED	5.53 ± 0.50	5.98 ± 0.37	5.73 ± 0.42	5.51 ± 0.53	4.71 ± 2.12	5.40 ± 0.51	5.22 ± 0.78	5.07 ± 0.75	5.37 ± 0.20
pO <sub>2</sub>	kPa	E	25.51 ± 13.85	18.62 ± 14.54	24.00 ± 19.74	24.62 ± 18.21	26.71 ± 17.66	25.69 ± 14.67	20.64 ± 7.49	20.80 ± 12.10	23.00 ± 5.28
		ED	26.09 ± 18.25	17.93 ± 8.34	25.62 ± 15.14	32.26 ± 15.95	35.26 ± 14.44	37.69 ± 11.87	39.08 ± 12.84	39.26 ± 12.70	32.44 ± 5.28
SBC	mmol/L	E	30 ± 2	30 ± 3	30 ± 3	30 ± 2	31 ± 2	30 ± 2	31 ± 2	31 ± 2	30 ± 1
		ED	30 ± 2	30 ± 1	29 ± 1	29 ± 2	30 ± 1	30 ± 1	30 ± 1	30 ± 2	30 ± 1
PCV	L/L	E	0.27 ± 0.03	0.25 ± 0.05	0.26 ± 0.04	0.26 ± 0.03	0.24 ± 0.03	0.27 ± 0.04	0.25 ± 0.03	0.24 ± 0.02	0.25 ± 0.01
		ED	0.27 ± 0.03	0.30 ± 0.03	0.31 ± 0.03 §	0.33 ± 0.04 §	0.33 ± 0.05 §	0.32 ± 0.04 §	0.33 ± 0.04 §	0.32 ± 0.04 §	0.32 ± 0.01 *

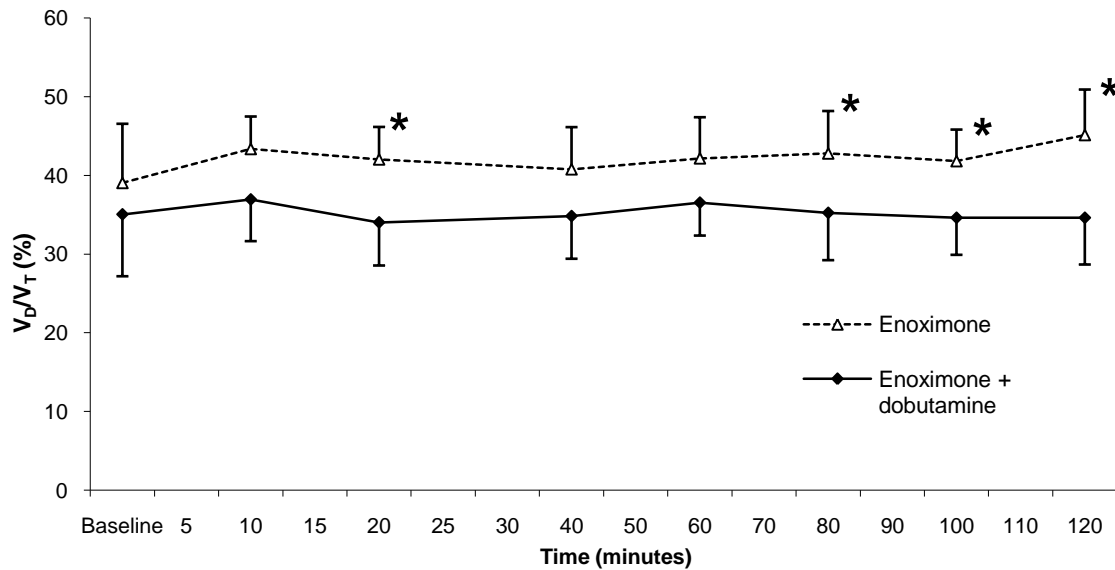
Values at individual timepoints are represented as mean ± SD (SD calculated for each treatment group separately).

Overall values are represented as mean ± SE (SE calculated assuming homogeneity of variances).

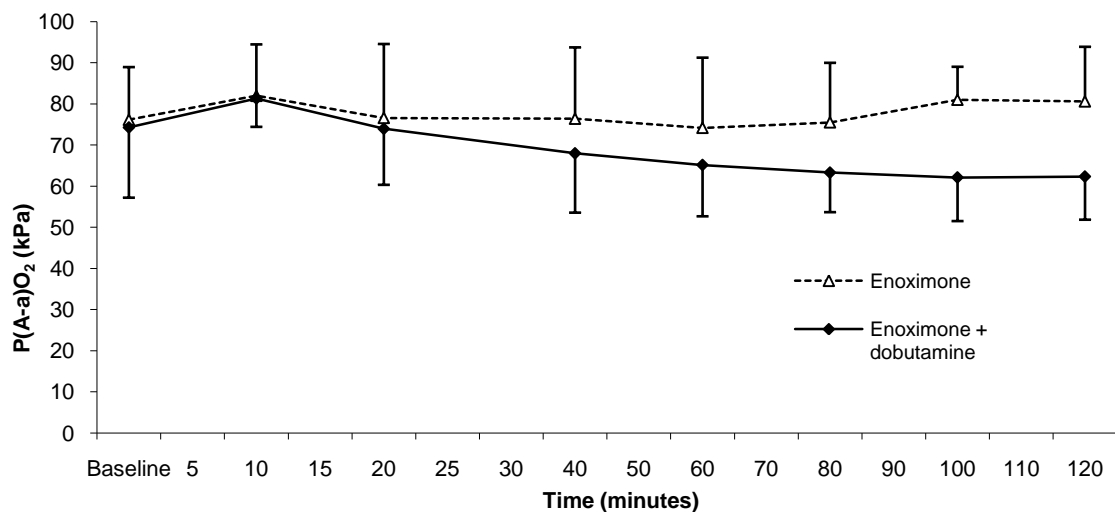
\* significant difference between E and ED for the overall comparison (P<0.05)

§ significant difference between E and ED at individual timepoints (P<0.00625)

## Enoximone & dobutamine in ponies



**Fig. 3:** Alveolar dead space-to-tidal volume ratio ( $V_D/V_T$ ) in 6 anaesthetized ponies receiving enoximone alone or enoximone followed by a CRI of dobutamine. Values are displayed as mean  $\pm$  SD. \* indicates a significant difference between the 2 treatments ( $P < 0.00625$ )



**Fig. 4:** Alveolar - arterial oxygen tension difference [ $P(A-a)O_2$ ] in 6 anaesthetized ponies receiving enoximone alone or enoximone followed by a CRI of dobutamine. Values are displayed as mean  $\pm$  SD.

Compared to enoximone alone, overall  $\dot{V}O_2$  was higher with treatment ED ( $P=0.0011$ ) (Table 3). This difference was significant at each selected timepoint during the observational period. No difference in overall oxygen consumption ( $\dot{V}O_2$ ) could be detected between the 2 treatments (Table 3).



**Table 3: Arterial ( $\text{CaO}_2$ ), central venous ( $\text{CvO}_2$ ) and end-capillary pulmonary oxygen content ( $\text{C}\acute{\text{c}}\text{O}_2$ ), degree of venous admixture ( $\dot{\text{Q}}\text{s}/\dot{\text{Q}}\text{t}$ ), oxygen delivery ( $\text{DO}_2$ ) and oxygen consumption ( $\dot{\text{V}}\text{O}_2$ ) in 6 anaesthetized ponies receiving enoximone alone (E) or enoximone followed by a CRI of dobutamine (ED).**

Variable	Unit	Trt	Time after treatment (min)								Overall
			Baseline	T10	T20	T40	T60	T80	T100	T120	
$\text{CaO}_2$	mL/L	E	128 ± 7	118 ± 12	122 ± 10	122 ± 9	118 ± 9	129 ± 19	121 ± 13	116 ± 5	121 ± 5
		ED	130 ± 13	140 ± 9 §	150 ± 10 §	160 ± 15 §	165 ± 23 §	161 ± 16 §	162 ± 17 §	161 ± 18 §	157 ± 5 *
$\text{CvO}_2$	mL/L	E	90 ± 11	90 ± 18	90 ± 10	93 ± 13	82 ± 6	72 ± 11	70 ± 16	76 ± 12	82 ± 5
		ED	85 ± 15	112 ± 17 §	118 ± 12 §	126 ± 14 §	128 ± 17 §	134 ± 15 §	131 ± 16 §	128 ± 19 §	125 ± 5 *
$\text{C}\acute{\text{c}}\text{O}_2$	mL/L	E	145 ± 8	136 ± 14	140 ± 11	139 ± 10	134 ± 11	146 ± 20	139 ± 13	134 ± 5	138 ± 5
		ED	147 ± 15	158 ± 9 §	166 ± 10 §	175 ± 16 §	180 ± 23 §	175 ± 17 §	176 ± 18 §	175 ± 19 §	172 ± 5 *
Venous admixture	%	E	32 ± 7	47 ± 24	35 ± 8	43 ± 19	32 ± 5	24 ± 7	28 ± 8	35 ± 16	35 ± 3
		ED	29 ± 9	44 ± 15	36 ± 10	34 ± 13	31 ± 11	41 ± 18	32 ± 9	33 ± 14	36 ± 3
$\text{DO}_2$	L/min	E	1.93 ± 0.33	2.25 ± 0.31	2.16 ± 0.44	1.96 ± 0.26	1.66 ± 0.31	1.66 ± 0.41	1.53 ± 0.45	1.41 ± 0.33	1.80 ± 0.25
		ED	2.00 ± 0.34	3.51 ± 0.80 §	3.43 ± 0.76 §	3.69 ± 0.95 §	3.60 ± 0.95 §	3.39 ± 0.69 §	3.29 ± 0.97 §	3.21 ± 1.01 §	3.45 ± 0.25 *
$\dot{\text{V}}\text{O}_2$	L/min	E	0.57 ± 0.23	0.51 ± 0.30	0.57 ± 0.18	0.46 ± 0.26	0.51 ± 0.19	0.73 ± 0.31	0.61 ± 0.22	0.51 ± 0.25	0.56 ± 0.09
		ED	0.68 ± 0.25	0.70 ± 0.36	0.72 ± 0.26	0.74 ± 0.26	0.79 ± 0.39	0.53 ± 0.33	0.61 ± 0.20	0.63 ± 0.28	0.68 ± 0.09

Values at individual timepoints are represented as mean ± SD (SD calculated for each treatment group separately).

Overall values are represented as mean ± SE (SE calculated assuming homogeneity of variances).

\* significant difference between E and ED for the overall comparison ( $P < 0.05$ )

§ significant difference between E and ED at individual timepoints ( $P < 0.00625$ )

# Enoximone & dobutamine in ponies

## Recovery (Table 4)

The recovery scores were comparable for both treatments, although two ponies showed some excitation during recovery after treatment E, which was not observed after treatment ED. Time to stand up was  $23.7 \pm 7.1$  minutes after treatment E, compared to  $21.3 \pm 5.4$  minutes after treatment ED.

**Table 4: Recovery scores of 6 ponies, receiving either a bolus of enoximone or enoximone followed by dobutamine during anaesthesia.**

Pony	Enoximone	Enoximone + Dobutamine
1	2	3
2	4	3
3	2	2
4	2	2
5	4	2
6	2	3

## Discussion

Compared to enoximone alone, a combination of enoximone and dobutamine increased HR,  $\dot{Q}_t$ , SV, arterial blood pressure and  $DO_2$ . When comparing these results to those found with enoximone in ponies (Chapter 4.1) and with dobutamine in horses (Swanson et al. 1985, Swanson & Muir 1986, Gasthuys et al. 1991, Lee et al. 1998, Young et al. 1998, Rasis et al. 2000), the cardiovascular effects of enoximone and dobutamine appeared to be at least additive, but perhaps even synergistic. Additive effects of PDE III inhibitors and  $\beta$ -adrenergic sympathomimetics have also been reported in man (Royster et al. 1993, Thuillez et al. 1993, Gilbert et al. 1995, Cracowski et al. 1999, Via et al. 2003). Furthermore, the results of the present study indicate that a combination of enoximone and dobutamine may have beneficial effects on respiratory gas exchange, as a reduction in  $V_D/V_T$  was observed.

By increasing the intracellular concentration of cAMP through different pathways, enoximone and dobutamine can have additive or even synergistic effects. In horses, dobutamine was shown to increase  $\dot{Q}_t$  at dosages of  $1.25 \mu\text{g}/\text{kg}/\text{min}$  or higher (Swanson et al. 1985, Swanson & Muir 1986, Gasthuys et al. 1991, Lee et al. 1998, Young et al. 1998). However, infusion rates up to  $1 \mu\text{g}/\text{kg}/\text{min}$  did not induce significant changes in  $\dot{Q}_t$  in several studies (Swanson & Muir 1986, Lee et al. 1998, Rasis et al. 2000). In the present study, a

dobutamine CRI of only 0.5  $\mu\text{g}/\text{kg}/\text{min}$  significantly increased CI from  $54.08 \pm 7.19$  to  $82.40 \pm 7.19$  mL/kg/min. In literature, such an increase was only reported with higher doses of dobutamine (Swanson et al. 1985, Gasthuys et al. 1991). It can be concluded that enoximone and dobutamine may have synergistic effects on  $\dot{Q}_t$  in isoflurane anaesthetized ponies. Furthermore, the difference between treatments E and ED was fairly constant throughout the observational period, indicating that a single bolus of enoximone potentiated the effects of dobutamine during at least 2 hours. This is in agreement with the results of chapter 4.1, where enoximone significantly increased  $\dot{Q}_t$  during 100 minutes.

The increase in  $\dot{Q}_t$  found in our ponies was due to increases in both SV and HR. Dobutamine was reported to increase SV at doses of 1  $\mu\text{g}/\text{kg}/\text{min}$  or higher (Gasthuys et al. 1991, Lee et al. 1998) but not at a low dose of 0.5  $\mu\text{g}/\text{kg}/\text{min}$  (Raisis et al. 2000). Again this indicates that enoximone increases the effects of dobutamine in isoflurane anaesthetized ponies, as was reported in man for combinations of PDE III inhibitors and  $\beta$ -adrenergic sympathomimetics (Royster et al. 1993, Gilbert et al. 1995). An increase in SV can result from an increase in preload, a decrease in afterload and/or an increase in contractility. Although RAP, which reflects preload, increased during administration of dobutamine, this difference was only significant during the first 20 minutes. Systemic vascular resistance, which reflects afterload, was significantly lower during treatment ED when overall data were analyzed. However, this difference was small and could not be confirmed statistically when analyzing the data at specific time points. These findings indicate that in the present study, dobutamine increased SV mainly by increasing contractility.

Heart rate, a second determinant of  $\dot{Q}_t$ , was also increased during treatment ED. The difference between the 2 treatments became larger over time, but was only significant from T60 onwards. In chapter 4.1 it was shown that a bolus of 0.5 mg/kg enoximone increased HR during 40 minutes in isoflurane anaesthetized ponies. During this time period, dobutamine did not induce further increases in HR in the present study, although human patients with class IV heart failure receiving enoximone and dobutamine had a higher increase in HR than patients receiving either of the drugs alone (Gilbert et al. 1995). The reason for this different response is not clear: the effects of dobutamine on HR reported in horses vary largely in literature, while no clear correlation seems to exist with the administered dose of dobutamine. Indeed, the influence of dobutamine on HR in anaesthetized horses varied between no effects with doses between 0.5 and 10  $\mu\text{g}/\text{kg}/\text{min}$  (Swanson et al. 1985, Gasthuys et al. 1991, Lee et

## Enoximone & dobutamine in ponies

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al. 1998, Raisis et al. 2000), decreases with doses between 1.5 and 5  $\mu\text{g}/\text{kg}/\text{min}$  (Swanson et al. 1985, Donaldson 1988) and increases with doses between 2.5 and 10  $\mu\text{g}/\text{kg}/\text{min}$  (Gasthuys et al. 1991, Lee et al. 1998). In the present study, a low dose of dobutamine only increased HR after the effects of enoximone on HR had waned off. As the time between sedation and administration of enoximone was 105 minutes, it is unlikely that romifidine influenced HR during the observational period. After a similar time period and compared to baseline, no differences in HR were reported after romifidine administration (Freeman et al. 2002). Alternatively, the increase in blood pressure during dobutamine administration may have elicited a vagal response, preventing a further increase in HR (Alexander & De Cuir 1963). Also, the influence of the infusion of dobutamine might have been delayed, similar to the findings of Young et al. (1998), where an increase in HR was not observed until 60 minutes after initiating an infusion of dobutamine at 4  $\mu\text{g}/\text{kg}/\text{min}$ . Despite the increase in HR and similar to the human studies in patients with class IV heart failure (Gilbert et al. 1995), no arrhythmias occurred during the combined use of enoximone and dobutamine in the ponies of the present study.

Although enoximone did not induce any changes in blood pressure in healthy, isoflurane anaesthetized ponies (Chapter 4.1), it has been reported that the use of PDE inhibitors can be accompanied by a sudden decrease of the arterial blood pressure (Kulka & Tryba 1993). In those cases, excessive vasodilation had to be counteracted by catecholamine  $\alpha$ -stimulation (Via et al. 2003). Results of the present study indicate that an infusion of dobutamine may be useful in such cases, as arterial blood pressure was always higher during treatment ED. Indeed, dobutamine is well known to increase arterial pressure in anaesthetized horses (Swanson et al. 1985, Gasthuys et al. 1991, Hellyer et al. 1998, Raisis et al. 2000). However, further studies are necessary in hypovolaemic horses, as the effects of dobutamine may be limited in those cases.

Dobutamine has been reported to reduce total peripheral and pulmonary resistances, suggesting vasodilation of the peripheral and pulmonary vascular beds (Gasthuys et al. 1991, Thuillez et al. 1993). Furthermore, combining dobutamine and enoximone potentiates the systemic and brachial vasodilator effects of each drug in man (Thuillez et al. 1993, Gilbert et al. 1995, Cracowski et al. 1999). Yet, in the present study, the overall difference in SVR, although statistically significant, was quite small ( $317.6 \pm 29.3$  vs  $274.0 \pm 29.3$  dynes. $\text{sec}/\text{cm}^5$ ). Also, after Bonferroni correction, the differences were not significant at any of the selected timepoints. Apparently, both drugs appeared to reduce SVR to a lesser extent

in horses than in man: enoximone did not reduce SVR in isoflurane anaesthetized ponies (Chapter 4.1) and reported effects of racemic dobutamine on SVR in horses are only small and often not significant (Swanson et al. 1985, Rasis et al. 2000). This can be explained by the physiologic and pharmacologic antagonisms of the individual stereoisomers of the racemic mixture (Ruffolo et al. 1981). Also, the observed decrease in SVR in the present study may have been attenuated by an increase in PCV, which increases viscosity and thus SVR.

Right atrial pressure was larger during treatment ED compared to enoximone alone. Increases in RAP have indeed been reported with the use of dobutamine in horses (Swanson et al. 1985, Rasis et al. 2000). In the present study, this difference was significant during the first 20 minutes after the administration of enoximone. Dobutamine appeared to attenuate the venous vasodilating effect of enoximone, which has been shown to reduce RAP in isoflurane anaesthetized ponies (Chapter 4.1). This finding is in agreement with reports about the combination of enoximone and dobutamine in man (Gilbert et al. 1995).

During the observational period, general anaesthesia induced a gradual decrease in body temperature over time. An interaction effect between the factors treatment and time was also detected, with a more rapid decrease in body temperature during treatment ED, despite a similar room temperature. The reason for this difference is unclear. To the authors' knowledge, neither enoximone nor dobutamine have been reported to cause a decrease in body temperature. Perhaps a more pronounced vasodilation of the peripheral vasculature occurred during treatment ED. As hypothermia has been shown to reduce the MAC of isoflurane (Vitez et al. 1974, Antognini 1993), it is likely that anaesthetic depth gradually increased in the present study. However, the difference in body temperature between the two treatments was small and not significant and should therefore not have interfered with the comparison of both treatments.

Using a CRI of dobutamine at rates of 1, 3 and 5  $\mu\text{g}/\text{kg}/\text{min}$ , Swanson and Muir (1986) did not detect any differences in the degree of venous admixture,  $V_D/V_T$  or  $P(A-a)O_2$ . Similarly, no difference in the degree of venous admixture was detected between the two treatments in the present study. However, we did observe a decrease in  $V_D/V_T$ , which suggests increased blood flow to adequately ventilated lung regions, possibly due to vasodilation of the pulmonary circulation in these areas. In man, a combination of enoximone and dobutamine reduced pulmonary vascular resistance compared to enoximone treatment alone (Gilbert et al.

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1995). While this reduction in dead space ventilation, which was most pronounced after T80, did not result in differences in  $P(A-a)O_2$  or  $PaO_2$ , an interaction effect between treatment and time was observed for both of these variables: during treatment ED,  $P(A-a)O_2$  gradually became smaller and  $PaO_2$  larger than after enoximone treatment alone.

Partly due to this gradual increase in  $PaO_2$ , but mainly due to the increase in PCV,  $CaO_2$  was higher during treatment ED. Increases in PCV have indeed been described during or after dobutamine administration (Gasthuys et al. 1991, Hellyer et al. 1998, Rasis et al. 2000). The combination of increased  $\dot{Q}_t$  and augmented  $CaO_2$  resulted in a higher oxygen delivery with treatment ED. It should be noted however that increases in microcirculatory PCV may result in increased viscosity, which might reduce the flow in small vessels and limit oxygen delivery to the tissues (Rasis et al. 2000). Also, central indices of left ventricular function, ( $\dot{Q}_t$ , MAP and SVR) do not always predict the effects of agents on regional perfusion (Rasis et al. 2000). Therefore, further studies are needed to investigate the effects of enoximone and dobutamine on intramuscular blood flow.

In conclusion, the results of the present study indicate that a combination of a bolus of enoximone and a CRI of dobutamine produces greater cardiovascular stimulation than enoximone alone, whereby enoximone potentiated the effects of dobutamine on  $\dot{Q}_t$  and SV in isoflurane anaesthetized ponies. Although SVR was reduced, blood pressure was always higher during the infusion of dobutamine. Also, a reduction in  $V_D/V_T$  was detected, indicating that the combination of enoximone and dobutamine had beneficial effects on pulmonary perfusion. As the present study was conducted in ponies, further studies are necessary to examine the effects of a combination of enoximone and dobutamine in horses, especially in cases of dehydration and/or hypovolaemia.

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## **Influence of calcium chloride on the cardiorespiratory effects of a bolus of enoximone in isoflurane anaesthetized ponies**

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### SUMMARY

The aim of this study was to examine the influence of calcium chloride ( $\text{CaCl}_2$ ) on the cardiorespiratory effects of enoximone in isoflurane anaesthetized ponies in a prospective, randomized, experimental trial. Six healthy ponies, weighing  $287 \pm 55$  kg, were sedated with romifidine,  $80 \mu\text{g}/\text{kg}$  intravenously (IV). Anaesthesia was induced with midazolam ( $0.06 \text{ mg}/\text{kg}$ ) and ketamine ( $2.2 \text{ mg}/\text{kg}$ ) and maintained with isoflurane in oxygen. The ponies' lungs were ventilated to maintain normocapnia. After 90 minutes, enoximone alone ( $0.5 \text{ mg}/\text{kg}$ ) (treatment E) or enoximone followed by a  $\text{CaCl}_2$  infusion ( $0.5 \text{ mg}/\text{kg}/\text{min}$  over 10 minutes) (treatment EC) was administered. Each pony received both treatments on separate occasions, with a minimal interval of 2 weeks between treatments. Sodium, potassium, ionized and total calcium concentrations, cardiovascular variables and blood gases were measured during 120 minutes after treatment.

Ionized and total calcium concentrations were higher during treatment EC, but the cardiorespiratory effects of enoximone were comparable for both treatments. A small but significant difference in packed cell volume was detected. It can be concluded that calcium chloride does not influence the effects of enoximone in normocalcaemic anaesthetized ponies.

### Introduction

Calcium ions are essential for cardiac membrane depolarization, excitation-contraction coupling and actin-myosin interaction during muscle contraction (Abernethy et al. 1995). Volatile anaesthetics depress myocardial function by altering myocardial cell calcium homeostasis (Pagel et al. 1993) and by decreasing intracellular calcium transients (Bosnjak and Kampine 1986). Calcium influx through slow channels is reduced, resulting in a depression of the rate of upstroke of the slow calcium-mediated action potential (Rusy & Komai 1987). Inhalational agents also depress the maximal uptake of calcium by the sarcoplasmic reticulum (Casella et al. 1987) and may even cause a net loss of calcium from the sarcoplasmic reticulum (Wheeler et al. 1988). Finally, volatile anaesthetics decrease the myofibrillar responsiveness to calcium and/or the calcium sensitivity of the contractile proteins (Housmans & Murat 1988) and induce small but significant decreases in serum ionized and total calcium concentrations in horses (Gasthuys et al. 1985, Grubb et al. 1999).

Enoximone, a phosphodiesterase (PDE) III inhibitor, exerts powerful inotropic and lusitropic effects by increasing the cyclic adenosine monophosphate (cAMP) concentration in cardiac muscle. A cAMP dependent protein kinase is activated, which phosphorylates the L-type calcium channels, facilitating calcium flux across myocardial cell membranes. Intracellular calcium concentrations increase, stimulating a further release of calcium from the sarcoplasmic reticulum and resulting in an increase of the contractile forces (Vernon et al. 1991). In ponies, enoximone induced significant increases in cardiac output ( $\dot{Q}t$ ), stroke volume (SV) and heart rate (HR) (Chapter 4.1).

The inotropic state of the myocardium can also be ameliorated by increasing circulatory calcium concentrations. Calcium attenuated or completely reversed the negative lusitropic actions of halothane and isoflurane (Pagel et al. 1993) and produced positive inotropic effects in cats (Bosnjak and Kampine 1986), dogs (Pagel et al. 1993) and calves (Stanley et al. 1976). Increases in  $\dot{Q}t$  and/or SV were demonstrated in conscious (Grubb et al. 1996) and anaesthetized horses (Grubb et al. 1999), anaesthetized ponies (Gasthuys et al. 1991), hypocalcaemic dogs (Drop and Scheidegger 1980) and humans with cardiac disease (Eriksen et al. 1983).

Because the effects of PDE III inhibitors result from an increased calcium influx in the myocardium, the effects of these drugs may be enhanced when administered simultaneously with calcium. On the other hand, calcium stimulates PDE activity, thereby increasing cAMP

degradation and possibly attenuating the effects of PDE inhibitors (Teo & Wang 1973). Also, calcium overload can induce side effects such as marked shortening of the QT interval, bradyarrhythmias (Drop 1985), impaired diastolic function (Schiffman et al. 2001) and even cardiac arrest (Bergman & Sellers 1953). To the authors' knowledge, no studies have reported the influence of calcium on the effects of enoximone in any species. The aim of the present study was to investigate if a calcium chloride infusion could increase the cardiovascular effects of enoximone in anaesthetized ponies.

### **Materials & Methods**

The general experimental protocol has been described in chapter 4.1. Additionally, blood samples for measurement of serum total calcium (Spotchem SP-4420<sup>®</sup>, A. Menarini Diagnostics, Zaventem, Belgium) and plasma ionized calcium, sodium and potassium (AVL 9180 Electrolyte Analyzer<sup>®</sup>, AVL scientific corporation, Roswell, Georgia, USA 30076) concentrations were collected before sedation (= standing values), at T-10 (= baseline), T30, T60, T90, T120 and T150 (= during recovery, 30 minutes after the end of anaesthesia) during treatments E and EC.

For statistical analysis, a paired samples t-test was performed to analyze the differences between pre-anaesthetic values and baseline values during anaesthesia for plasma sodium, potassium and ionized calcium and serum total calcium levels ( $\alpha = 0.05$ ). The same test was used to compare the pre-anaesthetic levels of these ions to the respective levels during recovery. For all variables, differences between treatments E and EC were compared using a mixed model with treatment, time and their interaction as fixed categorical effects and pony as random effect, comparing the treatments both globally over the entire period after treatment (at  $\alpha = 0.05$ ) and also at specific timepoints: baseline, T30, T60, T90, T120 and T150 for the different ions (at Bonferroni adjusted  $\alpha = 0.0083$ ) and baseline, T10, T20, T40, T60, T80, T100 and T120 for all other variables (at Bonferroni-adjusted  $\alpha = 0.00625$ ).

### **Results**

#### **Sodium, potassium and ionized and total calcium concentrations**

At baseline, ion concentrations were not significantly different between the 2 treatments (Table 1), but baseline Na<sup>+</sup> ( $P = 0.008$ ), ionized ( $P < 0.001$ ) and total Ca<sup>2+</sup> concentrations ( $P <$

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**Table 1: Sodium, potassium and ionized and total calcium concentrations in 6 anaesthetized ponies receiving enoximone (0.5 mg/kg) alone (E), or enoximone (0.5 mg/kg) followed by a calcium chloride infusion (0.5 mg/kg/min during 10 minutes) (EC).**

Ion	Unit	Standing	Trt	Time after enoximone treatment (minutes), CaCl <sub>2</sub> infused from T5 to T15 during treatment EC						Overall
				Baseline	T30	T60	T90	T120	Recovery	
Sodium	mmol/L	137 ± 1	E	133 ± 1 £	132 ± 1	133 ± 1	131 ± 1	132 ± 1	132 ± 1	132 ± 1
			EC	130 ± 1 £	130 ± 1	135 ± 1	132 ± 1	132 ± 1	133 ± 1	132 ± 1
Potassium	mmol/L	3.8 ± 0.1	E	3.8 ± 0.2	3.9 ± 0.2	3.8 ± 0.2	4.2 ± 0.2	4.1 ± 0.2	4.2 ± 0.2	4.0 ± 0.2
			EC	4.2 ± 0.2	4.0 ± 0.2	4.2 ± 0.2	4.2 ± 0.2	4.1 ± 0.2	4.3 ± 0.2	4.2 ± 0.2
Ionized calcium	mmol/L	1.49 ± 0.03	E	1.37 ± 0.01 £	1.29 ± 0.01	1.29 ± 0.01	1.26 ± 0.01	1.26 ± 0.01	1.26 ± 0.01 £	1.27 ± 0.01
			EC	1.41 ± 0.01 £	1.49 ± 0.01 §	1.43 ± 0.01 §	1.42 ± 0.01 §	1.40 ± 0.01 §	1.40 ± 0.01 £	1.43 ± 0.01 *
Total calcium	mmol/L	3.00 ± 0.03	E	2.71 ± 0.03 £	2.63 ± 0.03	2.59 ± 0.03	2.58 ± 0.03	2.58 ± 0.03	2.56 ± 0.03 £	2.59 ± 0.03
			EC	2.56 ± 0.03 £	2.72 ± 0.03	2.69 ± 0.03	2.71 ± 0.03	2.69 ± 0.03	2.78 ± 0.03 £	2.70 ± 0.03 *

Data are represented as mean ± SD (SD calculated assuming homogeneity of variances).

\* significant difference between E and EC for the overall comparison (P<0.05)

§ significant difference between E and EC at individual timepoints (P<0.0083)

£ baseline value and/or value during recovery significantly different from standing value ( $\alpha = 0.05$ ).

0.001) were lower than their respective standing values, with a significantly higher ionized/total  $\text{Ca}^{2+}$  ratio ( $P = 0.037$ ). Ionized  $\text{Ca}^{2+}$  concentration decreased over time in both groups ( $P = 0.003$ ), but was significantly higher throughout the anaesthesia after treatment EC compared to treatment E. Overall, total  $\text{Ca}^{2+}$  concentration was also significantly higher during treatment EC than during treatment E ( $P = 0.042$ ), but this difference was quite small and not significant at the different time points separately. As a result, the ratio ionized/total  $\text{Ca}^{2+}$  was higher during treatment EC ( $P < 0.001$ ). No differences in  $\text{Na}^+$  and  $\text{K}^+$  concentrations were found between treatments.

During recovery,  $\text{Na}^+$  and  $\text{K}^+$  concentrations were not different from standing values and comparable for both treatments. Ionized and total  $\text{Ca}^{2+}$  concentrations were still lower than before anaesthesia ( $P < 0.001$ ), but not different between the 2 treatments.

### **Cardiovascular system**

The cardiovascular effects of treatment EC were not significantly different from those previously reported for treatment E at any of the selected timepoints for any of the measured variables (Table 2). Diastolic (DAP) and mean (MAP) arterial pressure gradually increased over time ( $P < 0.0001$ ). Systemic vascular resistance (SVR) and right atrial pressure (RAP) initially decreased after enoximone treatment, but increased significantly over time ( $P < 0.0001$ ) during the remaining anaesthetic period.

### **Body temperature, respiratory gas exchange, packed cell volume**

Body temperature gradually decreased over time ( $P < 0.0001$ ), but was not different between the two treatments. Arterial and central venous blood gas results (Table 3) and parameters derived from these values (Table 4) were comparable for both treatments. Arterial pH gradually increased over time ( $P = 0.0048$ ), while central venous oxygen content ( $\text{CvO}_2$ ) ( $P < 0.0001$ ) and haemoglobin saturation ( $\text{SvO}_2$ ) ( $P = 0.0002$ ) slowly, but significantly decreased over time. Overall, packed cell volume (PCV) was higher during treatment EC than during treatment E, both in arterial ( $P = 0.0345$ ) and central venous ( $P = 0.0184$ ) blood.

### **Recovery**

The recovery scores after both treatments are represented in table 5. Time to stand up was  $23.7 \pm 7.1$  minutes after treatment E, compared to  $30.3 \pm 7.1$  minutes after treatment EC.

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**Table 2: Systolic (SAP), diastolic (DAP), mean arterial (MAP) and right atrial (RAP) pressures, heart rate (HR), cardiac index (CI), stroke volume index (SI) and systemic vascular resistance (SVR) in 6 anaesthetized ponies receiving enoximone (0.5 mg/kg) alone (E), or enoximone (0.5 mg/kg) followed by a calcium chloride infusion (0.5 mg/kg/min during 10 minutes) (EC).**

Variable	Unit	Trt	Time after enoximone treatment (min), CaCl <sub>2</sub> infused from T5 to T15 during treatment EC								Overall
			Baseline	T10	T20	T40	T60	T80	T100	T120	
SAP <sup>§</sup>	mm Hg	E	83 ± 7	86 ± 14	84 ± 12	84 ± 11	88 ± 11	89 ± 10	87 ± 10	85 ± 10	86 ± 3
		EC	80 ± 5	84 ± 5	84 ± 5	82 ± 7	82 ± 7	83 ± 7	85 ± 7	86 ± 8	84 ± 3
DAP <sup>§,#</sup>	mm Hg	E	51 ± 6	54 ± 14	54 ± 14	56 ± 15	60 ± 14	62 ± 12	61 ± 9	60 ± 10	57 ± 4
		EC	48 ± 4	49 ± 8	51 ± 6	52 ± 9	54 ± 8	55 ± 10	57 ± 8	59 ± 8	53 ± 4
MAP <sup>§,#</sup>	mm Hg	E	63 ± 6	65 ± 14	65 ± 14	67 ± 14	72 ± 13	73 ± 11	71 ± 9	69 ± 9	68 ± 4
		EC	60 ± 4	61 ± 7	62 ± 6	62 ± 8	63 ± 8	65 ± 9	67 ± 9	69 ± 9	64 ± 4
RAP <sup>#</sup>	mm Hg	E	15 ± 2	10 ± 2	10 ± 2	11 ± 3	11 ± 2	12 ± 3	13 ± 3	13 ± 3	11 ± 2
		EC	18 ± 5	14 ± 6	15 ± 6	16 ± 6	17 ± 6	17 ± 7	17 ± 6	18 ± 5	16 ± 2
HR <sup>§,#</sup>	beats/min	E	40 ± 4	46 ± 6	44 ± 6	41 ± 5	39 ± 5	38 ± 4	37 ± 4	36 ± 3	41 ± 2
		EC	39 ± 2	46 ± 4	44 ± 3	42 ± 4	40 ± 3	41 ± 4	40 ± 3	40 ± 4	42 ± 2
CI <sup>§,#</sup>	mL/kg/min	E	53.0 ± 12.2	67.5 ± 14.3	61.4 ± 11.2	56.5 ± 11.4	49.1 ± 9.8	44.7 ± 10.3	43.4 ± 10.1	42.0 ± 9.2	54.1 ± 5.8
		EC	53.3 ± 17.3	66.0 ± 19.9	58.8 ± 21.5	56.0 ± 20.3	52.6 ± 18.9	50.0 ± 16.7	49.1 ± 15.9	45.8 ± 16.3	56.9 ± 5.8
SI <sup>§,#</sup>	mL/kg	E	1.3 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.3 ± 0.1	1.2 ± 0.1	1.2 ± 0.2	1.1 ± 0.2	1.3 ± 0.1
		EC	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.5	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.1
SVR <sup>#</sup>	dyne.sec/cm <sup>5</sup>	E	261 ± 63	232 ± 66	257 ± 85	282 ± 77	352 ± 90	394 ± 114	400 ± 143	395 ± 143	318 ± 25
		EC	228 ± 36	208 ± 36	240 ± 70	248 ± 80	268 ± 73	288 ± 67	295 ± 60	328 ± 64	255 ± 25

Values at individual timepoints are represented as mean ± SD (SD calculated for each treatment group separately).

Overall values are represented as mean ± SE (SE calculated assuming homogeneity of variances).

§ significantly lower at baseline compared to the respective standing values ( $\alpha = 0.05$ ).

# significant change over time during anaesthesia ( $\alpha = 0.05$ ).

No significant differences between the 2 treatments were detected for any of the measured variables ( $\alpha = 0.05$ ).



**Table 3: Blood gas results, packed cell volume (PCV) and body temperature in 6 anaesthetized ponies receiving enoximone (0.5 mg/kg) alone (E), or enoximone (0.5 mg/kg) followed by a calcium chloride infusion (0.5 mg/kg/min during 10 minutes) (EC).**

Variable	Unit	Trt	Time after enoximone treatment (minutes), CaCl <sub>2</sub> infused from T5 to T15 during treatment EC								Overall
			Baseline	T10	T20	T40	T60	T80	T100	T120	
Body temperature #	°C	E	36.3 ± 0.3	35.8 ± 0.6	35.7 ± 0.6	35.5 ± 0.7	35.3 ± 0.8	35.1 ± 0.8	35.0 ± 0.9	34.9 ± 0.9	35.4 ± 0.2
		EC	36.0 ± 0.3	35.6 ± 0.2	35.5 ± 0.2	35.4 ± 0.2	35.2 ± 0.2	35.2 ± 0.2	35.0 ± 0.3	35.0 ± 0.4	35.5 ± 0.2
<b>Central venous blood</b>											
pH		E	7.41 ± 0.05	7.42 ± 0.05	7.43 ± 0.05	7.44 ± 0.05	7.44 ± 0.04	7.43 ± 0.05	7.43 ± 0.05	7.43 ± 0.06	7.43 ± 0.02
		EC	7.42 ± 0.03	7.43 ± 0.05	7.43 ± 0.05	7.45 ± 0.04	7.44 ± 0.05	7.46 ± 0.04	7.45 ± 0.05	7.45 ± 0.06	7.44 ± 0.02
pCO <sub>2</sub>	kPa	E	6.85 ± 0.89	6.51 ± 0.93	6.35 ± 0.97	6.29 ± 0.89	6.47 ± 0.52	6.58 ± 0.77	6.53 ± 0.73	6.60 ± 0.80	6.50 ± 0.19
		EC	6.84 ± 0.48	6.73 ± 0.95	6.67 ± 0.88	6.35 ± 0.96	6.64 ± 1.14	6.27 ± 1.07	6.49 ± 1.01	6.40 ± 1.18	6.51 ± 0.19
pO <sub>2</sub>	kPa	E	4.86 ± 0.72	6.69 ± 5.13	4.78 ± 0.80	4.42 ± 0.76	4.20 ± 0.65	3.93 ± 0.54	3.73 ± 0.70	4.91 ± 2.62	4.70 ± 0.43
		EC	4.44 ± 0.80	4.73 ± 1.30	4.69 ± 1.09	4.38 ± 1.40	4.20 ± 1.35	4.11 ± 1.53	3.96 ± 1.47	3.82 ± 1.47	4.27 ± 0.43
SBC	mmol/L	E	29 ± 3	29 ± 2	29 ± 2	30 ± 2	30 ± 2	30 ± 2	30 ± 2	30 ± 2	30 ± 1
		EC	30 ± 2	30 ± 2	30 ± 2	30 ± 2	30 ± 2	31 ± 2	31 ± 2	31 ± 2	30 ± 1
PCV	L/L	E	0.27 ± 0.04	0.26 ± 0.05	0.26 ± 0.04	0.28 ± 0.05	0.26 ± 0.03	0.24 ± 0.02	0.24 ± 0.04	0.24 ± 0.02	0.25 ± 0.01
		EC	0.28 ± 0.02	0.27 ± 0.03	0.27 ± 0.03	0.27 ± 0.04	0.27 ± 0.04	0.27 ± 0.04	0.27 ± 0.05	0.27 ± 0.04	0.27 ± 0.01 *
<b>Arterial blood</b>											
pH #		E	7.45 ± 0.05	7.46 ± 0.06	7.47 ± 0.05	7.48 ± 0.05	7.47 ± 0.04	7.47 ± 0.04	7.48 ± 0.05	7.47 ± 0.05	7.47 ± 0.02
		EC	7.46 ± 0.03	7.45 ± 0.05	7.46 ± 0.05	7.49 ± 0.04	7.49 ± 0.04	7.50 ± 0.04	7.50 ± 0.06	7.50 ± 0.06	7.48 ± 0.02
pCO <sub>2</sub>	kPa	E	5.93 ± 0.68	5.87 ± 0.73	5.71 ± 0.69	5.53 ± 0.72	5.80 ± 0.52	5.71 ± 0.44	5.64 ± 0.49	5.69 ± 0.54	5.70 ± 0.34
		EC	6.15 ± 0.46	6.15 ± 0.79	5.95 ± 0.80	5.60 ± 0.67	5.60 ± 0.57	5.49 ± 0.66	5.47 ± 0.73	5.44 ± 0.83	5.60 ± 0.34
pO <sub>2</sub>	kPa	E	25.51 ± 13.85	18.62 ± 14.54	24.00 ± 19.74	24.62 ± 18.21	26.71 ± 17.66	25.69 ± 14.67	20.64 ± 7.49	20.80 ± 12.10	23.00 ± 5.47
		EC	15.09 ± 13.55	13.38 ± 12.97	13.55 ± 8.44	13.69 ± 12.34	14.58 ± 15.11	13.95 ± 15.23	15.64 ± 16.46	16.73 ± 17.20	14.50 ± 5.47
SBC	mmol/L	E	30 ± 2	30 ± 3	30 ± 3	30 ± 2	31 ± 2	30 ± 2	31 ± 2	31 ± 2	30 ± 1
		EC	31 ± 2	31 ± 2	31 ± 2	31 ± 2	31 ± 2	32 ± 2	31 ± 2	31 ± 2	31 ± 1
PCV	L/L	E	0.27 ± 0.03	0.25 ± 0.05	0.26 ± 0.04	0.26 ± 0.03	0.24 ± 0.03	0.27 ± 0.04	0.25 ± 0.03	0.24 ± 0.02	0.25 ± 0.01
		EC	0.27 ± 0.02	0.27 ± 0.03	0.26 ± 0.04	0.27 ± 0.03	0.27 ± 0.04	0.27 ± 0.04	0.28 ± 0.04	0.27 ± 0.05	0.27 ± 0.01 *

Values at individual timepoints are represented as mean ± SD (SD calculated for each treatment group separately).

Overall values are represented as mean ± SE (SE calculated assuming homogeneity of variances).

\* significant difference between E and EC at the 5% global significance level

# significant change over time during anaesthesia ( $\alpha = 0.05$ ).

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**Table 4: Arterial (CaO<sub>2</sub>), central venous (CvO<sub>2</sub>) and end-capillary pulmonary oxygen content (C<sub>c</sub>O<sub>2</sub>), degree of venous admixture, alveolar dead space-to-tidal volume ratio (V<sub>D</sub>/V<sub>T</sub>), alveolar-arterial O<sub>2</sub> tension difference, oxygen delivery (DO<sub>2</sub>) and oxygen consumption (V̇O<sub>2</sub>) in 6 anaesthetized ponies receiving enoximone (0.5 mg/kg) alone (E), or enoximone (0.5 mg/kg) followed by a calcium chloride infusion (0.5 mg/kg/min during 10 minutes) (EC).**

Variable	Unit	Trt	Time after enoximone treatment (minutes), CaCl <sub>2</sub> infused from T5 to T15 during treatment EC								Overall
			Baseline	T10	T20	T40	T60	T80	T100	T120	
CaO <sub>2</sub>	mL/L	E	128 ± 7	118 ± 12	122 ± 10	122 ± 9	118 ± 9	129 ± 19	121 ± 13	116 ± 5	121 ± 4
		EC	124 ± 11	117 ± 18	120 ± 21	117 ± 11	115 ± 4	117 ± 15	124 ± 8	118 ± 12	118 ± 4
CvO <sub>2</sub> #	mL/L	E	90 ± 11	90 ± 18	90 ± 10	93 ± 13	82 ± 6	72 ± 11	70 ± 16	76 ± 12	82 ± 7
		EC	88 ± 15	90 ± 20	91 ± 19	84 ± 23	76 ± 22	80 ± 31	76 ± 30	72 ± 23	81.3 ± 7
C <sub>c</sub> O <sub>2</sub>	m/ L	E	145 ± 8	136 ± 14	140 ± 11	139 ± 10	134 ± 11	146 ± 20	139 ± 13	134 ± 5	138 ± 4
		EC	143 ± 11	137 ± 18	140 ± 20	137 ± 10	135 ± 4	136 ± 15	143 ± 9	137 ± 12	138.0 ± 4
Venous admixture	%	E	32 ± 7	47 ± 24	35 ± 8	43 ± 19	32 ± 5	24 ± 7	28 ± 8	35 ± 16	35 ± 3
		EC	29 ± 9	44 ± 15	36 ± 1	34 ± 13	31 ± 11	41 ± 18	32 ± 9	33 ± 14	38 ± 3
V <sub>D</sub> /V <sub>T</sub>	%	E	39 ± 8	43 ± 4	42 ± 4	41 ± 5	42 ± 5	43 ± 5	42 ± 4	45 ± 6	43 ± 2
		EC	40 ± 7	41 ± 6	40 ± 7	41 ± 6	42 ± 7	41 ± 6	41 ± 7	41 ± 7	41 ± 2
P(A-a)O <sub>2</sub>	kPa	E	76.14 ± 12.79	81.98 ± 12.46	76.60 ± 17.94	76.39 ± 17.32	74.17 ± 17.05	75.50 ± 14.46	81.02 ± 7.98	80.62 ± 13.24	78.04 ± 4.75
		EC	84.43 ± 11.76	86.86 ± 10.85	87.53 ± 6.19	87.64 ± 10.86	86.75 ± 14.01	87.51 ± 13.94	86.25 ± 14.74	85.38 ± 15.27	86.84 ± 4.75
DO <sub>2</sub> #	L/min	E	1.93 ± 0.33	2.25 ± 0.31	2.16 ± 0.44	1.96 ± 0.26	1.66 ± 0.31	1.66 ± 0.41	1.53 ± 0.45	1.41 ± 0.33	1.80 ± 0.18
		EC	1.84 ± 0.39	2.20 ± 0.63	2.01 ± 0.75	1.87 ± 0.67	1.70 ± 0.45	1.68 ± 0.65	1.76 ± 0.59	1.54 ± 0.51	1.82 ± 0.18
V̇O <sub>2</sub>	L/min	E	0.57 ± 0.23	0.51 ± 0.30	0.57 ± 0.18	0.46 ± 0.26	0.51 ± 0.19	0.73 ± 0.31	0.61 ± 0.22	0.51 ± 0.25	0.56 ± 0.06
		EC	0.51 ± 0.07	0.51 ± 0.19	0.48 ± 0.27	0.50 ± 0.12	0.50 ± 0.21	0.47 ± 0.24	0.62 ± 0.24	0.55 ± 0.18	0.52 ± 0.06

Values at individual timepoints are represented as mean ± SD (SD calculated for each treatment group separately).

Overall values are represented as mean ± SE (SE calculated assuming homogeneity of variances).

# significantly changing over time during anaesthesia ( $\alpha = 0.05$ ).

No significant differences between the 2 treatments were detected for any of the measured variables ( $\alpha = 0.05$ ).

**Table 5: Recovery scores of 6 ponies, receiving either a bolus of enoximone or enoximone followed by a calcium chloride infusion during anaesthesia.**

Pony	Enoximone	Enoximone + calcium
1	2	3
2	4	1
3	2	1
4	2	1
5	4	1
6	2	1

## Discussion

In the present study,  $\text{Na}^+$ , ionized and total  $\text{Ca}^{2+}$  concentrations were significantly lower at baseline compared to the respective preanaesthetic values. Although this may reflect fluid shifts, with some plasma dilution as a result, the changes in ionized and total calcium concentrations were greater than the difference in  $\text{Na}^+$  concentration. Most likely, isoflurane additionally reduced calcium concentrations, since volatile anaesthetics reduced blood calcium concentrations in ponies (Gasthuys et al. 1985) and horses (Grubb et al. 1999, Boscan et al. 2007), while no changes in  $\text{Na}^+$  concentrations were reported after induction of anaesthesia in horses (Tevik et al. 1968, Gasthuys et al. 1986, Boscan et al. 2007). As enoximone exerts its effects by increasing calcium entry into the myocardial cells (Vernon et al. 1991) and peak effects were observed 5 minutes after administration in ponies (Chapter 4.1),  $\text{CaCl}_2$  was administered from 5 to 15 minutes after the injection of enoximone, to maximize possible combined effects. Nonetheless, cardiovascular function and respiratory gas exchange were comparable with both treatments, despite a significant increase in the ionized calcium concentration after  $\text{CaCl}_2$  administration.

The absence of any effects of calcium administration on cardiovascular performance is in contrast with other studies in ponies (Gasthuys et al. 1991) and horses (Grubb et al. 1996, Grubb et al. 1999), where significant cardiovascular effects were reported after administration of calcium in doses comparable to or lower than the dose used in the present study. However, in dogs and humans, calcium administration has not always been found to increase  $\dot{Q}_t$  (Marone et al. 1981, Butterworth et al. 1992, Royster et al. 1992). Furthermore, the effects of  $\text{CaCl}_2$  may in fact be limited when administered in combination with enoximone, since  $\text{CaCl}_2$  also had no influence on the haemodynamic responses to other inotropic drugs, such as amrinone (Butterworth et al. 1992) and adrenaline (Royster et al. 1992). Apparently, when

## Enoximone & calcium in ponies

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intracellular calcium concentrations increase above a certain value, a negative feedback mechanism becomes active in the myocardium. In some cases, the inotropic effects of PDE III inhibitors were actually reduced when calcium was administered (Goyal & McNeill 1986), which would be due to a reduced activity of adenylyl cyclase (Drummond & Duncan 1970, Abernethy et al. 1995) and an increased PDE activity (Teo & Wang 1973) when calcium concentrations increase in the myocardium. Finally, all ponies in the present study were normocalcaemic before anaesthesia. Drop and Scheidegger (1980) reported increases in  $\dot{Q}t$  and SV after calcium administration in hypocalcaemic, but not in normocalcaemic dogs.

In the present study, HR was not influenced by the infusion of  $\text{CaCl}_2$ , although calcium administration decreased HR in halothane anaesthetized ponies (Gasthuys et al. 1991) and horses (Grubb et al. 1999). Possibly, bradycardia in response to calcium is more likely during halothane anaesthesia, since HR was also not influenced by calcium during isoflurane anaesthesia in horses (Grubb et al. 1999) or neuroleptanaesthesia in humans (Eriksen et al. 1983). Furthermore, the effects of calcium on HR may have been attenuated by the positive chronotropic effects of enoximone in ponies (Chapter 4.1).

Arterial blood pressure was also not affected by  $\text{CaCl}_2$  in our ponies. Although calcium gluconate infusion did not influence arterial pressure in conscious horses (Grubb et al. 1996), significant increases were reported in anaesthetized ponies (Gasthuys et al. 1991), horses (Grubb et al. 1999), dogs (Drop & Scheidegger 1980) and humans (Marone et al. 1981, Eriksen et al. 1983), mainly due to an increase in SVR. Calcium induces vasoconstriction by binding to calmodulin and activating myosin light chain kinase, which then phosphorylates myosin, initiating smooth muscle contraction. Calcium would further enhance smooth muscle contraction by binding directly to myosin and by activating protein kinase C, which phosphorylates myosin at a different site than myosin light chain kinase (Adelstein & Sellers 1987).

In the present study, after administration of enoximone, infusion of  $\text{CaCl}_2$  did not increase SVR. The fact that enoximone promotes vasodilation through an increase in the cAMP level in vascular smooth muscle cells (Vernon et al. 1991) may interfere with the contractile response of smooth muscle cells to calcium in several ways. Firstly, cAMP decreases myoplasmic calcium concentrations (Itoh et al. 1993) by inhibiting calcium influx in vascular smooth muscle cells (Ishikawa et al. 1993) and by enhancing calcium pump activity by phosphorylation of phospholamban (Kimura et al. 1991). Secondly, when intracellular cAMP

levels rise, a cAMP-dependent protein kinase catalyzes the phosphorylation of myosin kinase. This decreases the activity of myosin kinase by interfering with the binding of calcium-calmodulin (Adelstein et al. 1982). Finally, enoximone might also cause vasorelaxation through a decrease in calcium sensitivity of contractile elements (Itoh et al. 1993). In conclusion, enoximone may blunt the effects of calcium on the peripheral vasculature by decreasing intracellular calcium concentrations, lowering the activity of myosin light chain kinase and diminishing the calcium sensitivity of contractile elements.

Packed cell volume was not influenced by calcium administration in ponies (Gasthuys et al. 1991) and horses (Grubb et al. 1996). However, in the present study, PCV was higher during treatment EC. This is in agreement with the results of Marone et al. (1981) in humans, who found a significant increase in PCV after administration of calcium gluconate. As in several similar studies (Gasthuys et al. 1991, Grubb et al. 1996), blood gases were not influenced by calcium administration in the present study.

Future studies are justified to determine whether the results of the present study in ponies also apply in horses and whether  $\text{CaCl}_2$  can increase the effects of enoximone in cases of hypocalcaemia and/or endotoxaemia. It might also be hypothesized that  $\text{CaCl}_2$  would produce clearer effects when administered during a constant rate infusion of enoximone. However, a bolus of enoximone produced long lasting effects in anaesthetized ponies, with increases in HR for 40 minutes and  $\dot{Q}_t$  and SV for 100 minutes (Chapter 4.1). Since  $\text{CaCl}_2$ , infused shortly after administration of enoximone, did not induce any significant changes in the present study, it is unlikely that clearer effects would be observed during a constant rate infusion of enoximone. Furthermore, pharmacokinetic data on enoximone in ponies or horses, required to determine a suitable constant rate, are not available up to now. Finally, in the authors' opinion, it is unlikely that different results would be obtained when using calcium gluconate instead of  $\text{CaCl}_2$ , since it has been demonstrated that equal elemental calcium doses of calcium gluconate and  $\text{CaCl}_2$ , injected over the same time period, were equivalent in their ability to raise calcium concentrations during normocalcaemic situations and produced equivalent cardiovascular effects in children and dogs (Cote et al. 1987).

In conclusion, the previously reported positive cardiovascular effects of a bolus of 0.5 mg/kg enoximone were not affected by a  $\text{CaCl}_2$  infusion in the present study in ponies.

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## **Cardiorespiratory effects of enoximone in anaesthetized colic horses**

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## SUMMARY

The aim of this study was to examine whether enoximone improves cardiovascular function and reduces dobutamine requirement in anaesthetized colic horses. Forty eight adult colic horses were enrolled in this prospective, randomized clinical trial. After sedation [xylazine 0.7 mg/kg intravenously (IV)] and induction [midazolam 0.06 mg/kg IV, ketamine 2.2 mg/kg IV], anaesthesia was maintained with isoflurane in oxygen and a lidocaine constant rate infusion (1.5 mg/kg, 2 mg/kg/h). All horses were ventilated ( $\text{PaCO}_2 < 8.00$  kPa). When hypotension occurred, dobutamine and/or colloids were administered. Ten minutes after skin incision, horses randomly received an IV bolus of enoximone (0.5 mg/kg) or saline. Monitoring included respiratory and arterial blood gases, heart rate (HR), arterial pressure and cardiac index (CI). Systemic vascular resistance (SVR), stroke index (SI) and oxygen delivery index ( $\text{DO}_2\text{I}$ ) were calculated. For each variable, changes between baseline and T10 within each treatment group and/or colic type (small intestines (SMA), large intestines (LAR) or mixed (MIX)) were analyzed and compared between treatments in a fixed effects model. Differences between treatments until T30 were investigated using a mixed model ( $\alpha=0.05$ ).

Ten minutes after enoximone treatment, CI ( $P=0.0010$ ), HR ( $P=0.0033$ ) and  $\text{DO}_2\text{I}$  ( $P=0.0007$ ) were higher and SVR lower ( $P=0.0043$ ) than at baseline. The changes in CI, HR and SVR were significantly different from those after saline treatment. During the first 30 minutes after enoximone treatment,  $\text{DO}_2\text{I}$  ( $P=0.0224$ ) and HR ( $P=0.0003$ ) were higher than after saline administration. Because the difference in HR between treatments was much clearer in LAR colic cases, an interaction was detected between treatment and colic type in both analyses ( $P=0.0076$ ;  $P=0.0038$  respectively). It is concluded that enoximone produces significant, but short lasting, cardiovascular effects in colic horses.

### Introduction

Emergency abdominal surgery carries a very high risk in horses: during or within 7 days after surgery, 11.7 % of the patients died unexpectedly or were euthanized because of perioperative complications (unrelated to pre-existing disease) (Johnston et al. 2002). Variables which assess cardiovascular status, including heart rate (HR), packed cell volume (PCV), capillary refill time, mucous membrane colour and/or blood pressure, are good prognostic indicators (Parry et al. 1983; Pascoe et al. 1983; Puotunen-Reinert 1986; French et al. 2002; Proudman et al. 2006). Furthermore, most causes of perianaesthetic death, including post-operative problems such as myopathies, were linked with cardiovascular depression (Johnston et al. 2002). Perioperative cardiovascular support is thus crucial to improve outcome of horses anaesthetized for colic surgery.

Despite high-volume fluid therapy, sympathomimetic drugs, such as dobutamine (Donaldson 1988, Dugdale et al. 2007), dopamine (Trim et al. 1991) and ephedrine (McGrath 1984) often remain an essential part of the supportive therapy in these patients. Another class of inotropic drugs are the phosphodiesterase (PDE) III inhibitors, who inhibit enzymatic cAMP breakdown, producing positive inotropic and lusitropic effects, as well as systemic vasodilation (Vernon et al. 1991). In chapter 4.1 it was shown that the PDE III inhibitor enoximone induced significant increases in cardiac output ( $\dot{Q}_t$ ), HR, stroke volume (SV) and oxygen delivery ( $DO_2$ ), without affecting arterial pressure in anaesthetized ponies. When combining this drug with a constant rate infusion (CRI) of dobutamine, further increases in  $\dot{Q}_t$ , SV and  $DO_2$  were observed, together with increases in arterial pressure (chapter 4.2). The results even suggested that enoximone potentiates the effects of dobutamine in ponies. Since the effects of enoximone have not been studied in horses under clinical conditions and because cardiovascular function may be quite compromised in colic horses, the aim of this study was to evaluate the cardiorespiratory effects of enoximone in horses undergoing emergency laparotomy. It was hypothesized that enoximone would increase  $\dot{Q}_t$ , SV, HR and  $DO_2$  and reduce the dobutamine requirement.

### Materials & Methods

#### Patients and anaesthetic protocol

This prospective, randomized, clinical study included 48 horses undergoing emergency colic surgery at the Faculty of Veterinary Medicine of Ghent University. Before surgery, all horses received broad spectrum antibiotics and flunixin meglumine 1.1 mg/kg intravenously (IV) (Finadyne<sup>®</sup>, Schering Plough Animal Health, Heist-Op-Den-Berg, Belgium) intravenously (IV). When indicated based on a physical examination and/or PCV, hypertonic saline (4 mL/kg bwt) or a colloid (2–4 mL/kg bwt Geloplasma<sup>®</sup>, Fresenius Kabi, Schelle, Belgium) was infused before sedation.

Horses which had already been sedated during clinical examination received the same  $\alpha 2$  adrenoreceptor agonist as premedication; the other horses were sedated with xylazine (Xyl-M<sup>®</sup>, VMD, Arendonk, Belgium). Doses varied depending on the condition of the individual horse and prior administration of sedatives, but in general, standard doses (IV) were 0.7 mg/kg for xylazine, 10  $\mu$ g/kg for detomidine (Domosedan<sup>®</sup>, Pfizer Animal Health S.A., Louvain-la-Neuve, Belgium) and 80  $\mu$ g/kg for romifidine (Sedivet<sup>®</sup>, Boehringer Ingelheim, Brussels, Belgium). After sedation, a nasogastric tube was placed to evacuate stomach contents. Anaesthesia was induced using a combination of 0.06 mg/kg midazolam IV (Dormicum, Roche, Brussels, Belgium) and 2.2 mg/kg ketamine IV (Anesketin, Eurovet, Heusden-Zolder, Belgium). After orotracheal intubation (26-30 mm OD, soft rubber tracheal tube, Rüscher AG, Kernlen, Germany), the horse was hoisted onto a padded surgery table, in dorsal recumbency.

General anaesthesia was maintained with isoflurane (Isoflo<sup>®</sup>, Abbott Laboratories Ltd., Queenborough, Kent, United Kingdom) in oxygen, using a large animal anaesthetic unit (Matrx<sup>®</sup>, Matrx medical inc., Orchard Park, New York, USA + Sulla 909V<sup>®</sup>, Dräger, Lübeck, Germany). A bolus of 1.5 mg/kg lidocaine (Laocaïne<sup>®</sup>, Schering-Plough Vétérinaire, Levallois Perret, France) was administered over 10 minutes, followed by a CRI at 2 mg/kg/hour. This CRI was discontinued 30-45 minutes before the end of anaesthesia. Mechanical ventilation (Smith respirator LA 2100<sup>®</sup>, model 2002, Veterinary Technics/BDO-Medipass, Hoogezand, the Netherlands) was applied in all horses to maintain PaCO<sub>2</sub> < 8 kPa, in an assisted, volume controlled, pressure limited mode, delivering a tidal volume (TV) of 10 mL/kg, with a maximal peak inspiratory pressure (PIP) of 20-30 cm H<sub>2</sub>O. When respiration rate (RR) was lower than 4 breaths/minute during more than 3 minutes or if arterial blood gas

## Enoximone in colic horses

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analysis (ABL5<sup>®</sup>, Radiometer, Copenhagen, Denmark) revealed a high PaCO<sub>2</sub> (>8 kPa) or a low PaO<sub>2</sub> (<13 kPa), respirations were both assisted and controlled (RR6-12 breaths/minute). Crystalloids were infused at 10 mL/kg/h. Fluid choice depended on the base excess (BE), using lactated Ringer's solution (Haemofiltration Formula E2<sup>®</sup>, Bieffe Medital, Grosotto, Italy) or saline (NaCl 0.9%, Baxter, Lessines, Belgium) if BE was below or above 5 mEq/L respectively. If BE was below -5 mEq/L and PaCO<sub>2</sub> did not exceed 8 kPa, bicarbonate (Bicarbonate de sodium 8.4 %<sup>®</sup>, B Braun, Melsungen, Belgium) was additionally infused. When mean arterial pressure was lower than 70 mm Hg, dobutamine (Dobutamine Mayne<sup>®</sup>, Mayne Pharma, Brussels, Belgium) was administered at a rate of 0.3-1.5 µg/kg/min. When arterial pressure was unresponsive to dobutamine or when PCV exceeded 0.45 L/L, Geloplasma<sup>®</sup> (4 mL/kg) was infused and a second jugular catheter was placed for additional administration of crystalloids. At the end of anaesthesia, 0.2 mg/kg xylazine was administered IV. The horses recovered spontaneously in a padded recovery box. The recovery time and recovery score, based on a simple grading system, were recorded.

### Monitoring

Anaesthetic gases were monitored using a calibrated multi-gas analyzer (HP M1025B<sup>®</sup>, Hewlett Packard Company, Houston, USA). Cardiovascular monitoring consisted of pulse oximetry, a base-apex electrocardiogram (ECG), invasive blood pressure measurement from the facial artery (HP M1165A<sup>®</sup>, model 56S, Hewlett-Packard, GmbH, Böblingen, Germany) and  $\dot{Q}_t$  measurements using the lithium dilution technique (LiDCO-plus Hemodynamic Monitor, LiDCO Ltd., London, UK). For  $\dot{Q}_t$  measurements, a lithium chloride bolus of 5 µmol/kg was used. The pressure monitoring system was calibrated against a mercury manometer and zeroed at the level of the right atrium before anaesthesia in each horse. Blood samples withdrawn from the arterial catheter were immediately analyzed for pH, partial pressures of oxygen (PaO<sub>2</sub>) and carbon dioxide (PaCO<sub>2</sub>), saturation (SaO<sub>2</sub>), base excess (BE) and bicarbonate level (ABL5<sup>®</sup>, Radiometer, Copenhagen, Denmark). The PCV was obtained by centrifugation.

### Experimental design

Ten minutes after skin incision, baseline measurements (T0) were obtained for inspiratory and expiratory CO<sub>2</sub>, O<sub>2</sub> and isoflurane, pulse saturation (SpO<sub>2</sub>), HR, systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP),  $\dot{Q}_t$  and arterial blood gases. Subsequently, a bolus

of 0.5 mg/kg enoximone 0.5% (Perfan<sup>®</sup>, Myogen GmbH, Bonn, Germany) (treatment E) or an equivalent volume of saline (treatment S) was administered at a rate of 20 mL/min. The random treatment assignment of E and S was stratified for colic type (small intestines (SMA), large intestines (LAR) or a combination of both (MIX)). Cardiac output measurements and arterial blood gas analysis were performed at T10 and T30; all other measurements were performed at T10, T20 and T30.

Stroke volume, systemic vascular resistance (SVR) and  $DO_2$  were calculated according to standard formulae (Muir 2007), with right atrial pressure (RAP) arbitrarily taken as 7 mm Hg. Cardiac index (CI), and oxygen delivery index ( $DO_2I$ ) were expressed in mL/kg/min, stroke index (SI) in mL/kg.

### **Statistical analysis**

To investigate the short term effects of enoximone administration, it was tested whether there was a significant change between baseline and T10 within each treatment group and/or colic type for the different variables, using a mixed model with time as categorical fixed effect and horse as random effect. The difference between T10 and baseline was also used as the response variable in a fixed effects model with colic type, treatment and their interaction as fixed effects, to investigate whether the change between baseline and T10 was different between treatments and/or between colic types. Finally, the effects of enoximone during a period of 30 minutes after treatment were investigated using a mixed model with horse as random effect and colic type, treatment, time and interaction between colic type and treatment as categorical fixed effects.

The need for a colloid or a second jugular catheter for additional fluid administration and the ventilation mode used (assisted or assisted-controlled) were compared between treatments using Fisher's exact tests.

The recovery scores and recovery times for both treatments were compared using the Wilcoxon rank sum test.

For all analyses mentioned, a 5% significance level was used.

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## Results

### Patient data

The study population included 23 mares, 11 stallions and 14 geldings. The horses were between 1 and 24 years old (mean age  $8.3 \pm 5.5$  years), their body weight ranged between 252 and 703 kg (mean weight  $522.7 \pm 97.3$  kg). All horses were Dutch, French or Belgian warmbloods, except for 5 Thoroughbreds, 1 Standardbred, 1 Friesian horse, 2 Haflingers, 1 Belgian Draught horse and 2 Quarter horses. Colic causes are listed in Table 1.

**Table 1: Causes of colic in 48 horses undergoing emergency laparotomy, receiving an intravenous bolus of enoximone (0.5 mg/kg bwt) or an equivalent volume of saline 10 minutes after skin incision. Total numbers are written in bold.**

	Treatment	
	Enoximone	Saline
<b>Small intestines</b>	<b>9</b>	<b>8</b>
<b>Strangulations</b>	<b>6</b>	<b>5</b>
with resection	3	2
no resection necessary	0	2
euthanasia	3	1
<b>Gastro-enteritis</b>	<b>1</b>	<b>1</b>
<b>Impaction ileum</b>	<b>2</b>	<b>2</b>
<b>Large intestines</b>	<b>14</b>	<b>12</b>
<b>Displacement colon</b>	<b>4</b>	<b>2</b>
<b>Impaction</b>	<b>3</b>	<b>3</b>
Large colon	2	3
Small colon	1	0
<b>Torsions/strangulations</b>	<b>3</b>	<b>3</b>
Strangulation colon	0	1
Torsion colon	1	2
Torsion caecum	2	0
<b>Other</b>	<b>4</b>	<b>4</b>
Type 2 caecal impaction	1	1
Nephrosplenic entrapment	2	1
Caecocolic intussusception	1	0
Intramural haematoma colon	0	1
Enterolith	0	1
<b>Mixed disorders</b>	<b>2</b>	<b>3</b>
<b>Generalized tympany</b>	<b>1</b>	<b>1</b>
<b>Colon displacement</b>		
with ileum obstipation	0	1
with ileum strangulation	0	1
<b>Colon impaction</b>		
with strangulation small intestine	1	0
<b>Overall total</b>	<b>25</b>	<b>23</b>



Seven horses were euthanized intraoperatively (Table 2), including 4 horses with strangulation of the small intestines, 2 colonic torsions and 1 horse with impaction of the colon and necrosis of the colon wall. In 3 of these horses, values were only available until T20, all other horses were euthanized after completion of the study period (T30). Three horses within colic type LAR were premedicated with detomidine (2 of group E and 1 of group S) and 1 with romifidine (group E), all other horses were sedated with xylazine.

### Infusions, ventilation and recovery

In groups S and E, a second catheter was placed to administer additional fluids in 7/23 (30%) and 7/25 (28%) horses respectively, while colloids were administered in 6/23 (26%) and 7/25 (28%) horses respectively. Bicarbonate was infused intraoperatively in 2 horses in group E and in 1 horse in group S, while 2 horses in group E were hypocalcaemic and received an infusion with calcium gluconate (Calcii borogluconas<sup>®</sup>, Eurovet) during anaesthesia. Ventilation mode was assisted throughout the 30 minute period after treatment in 7/23 (30%) and 6/25 (24%) horses of groups S and E respectively. In all other horses, ventilation mode was assisted-controlled. Recovery scores and duration (Table 2) were not significantly different between groups. In one horse in group S, with a strangulation of the small intestines, recovery duration was 360 minutes. This value was not included in the calculation of mean recovery duration of group S.

**Table 2: Recovery and euthanasia data in 48 colic horses, receiving an intravenous bolus of enoximone (0.5 mg kg<sup>-1</sup>) or an equivalent volume of saline during anaesthesia. Because 7 horses were euthanized during surgery and recovery lasted 6 hours in 1 horse of the saline group, calculation of the recovery duration is based on data of 40 horses. For the recovery scores, the values represent the number of horses receiving the respective scores.**

	Treatment	
	Enoximone	Saline
<b>Duration of recovery (min)</b>		
mean ± SD	52 ± 20	47 ± 14
<b>Recovery Score</b>		
1	1	3
2	10	7
3	7	9
4	3	0
5	0	1
<b>Peroperative euthanasia</b>	4	3

## Enoximone in colic horses

**Table 3: Systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP), stroke index (SI) and oxygen delivery index (DO<sub>2</sub>I) in 48 anaesthetized colic horses, receiving an intravenous bolus of enoximone (0.5 mg/kg) or an equivalent volume of saline 10 minutes after incision of the skin (=Baseline).**

Variable	Colic type		Time after treatment (min)				
			Baseline	T10	T20	T30	
SAP <sup>d</sup> (mm Hg)	All	S	<b>105 ± 23</b>	<b>105 ± 16</b>	<b>95 ± 16</b>	<b>92 ± 13</b>	
		E	<b>103 ± 26</b>	<b>101 ± 29</b>	<b>100 ± 26</b>	<b>95 ± 22</b>	
	SMA	S	106 ± 21	114 ± 15	102 ± 19	96 ± 15	
		E	107 ± 29	109 ± 26	114 ± 23	105 ± 15	
	LAR	S	106 ± 26	99 ± 16	90 ± 14	90 ± 13	
		E	101 ± 27	96 ± 32	92 ± 26	91 ± 26	
	MIX	S	100 ± 13	106 ± 9	96 ± 12	92 ± 3	
		E	95 ± 0	96 ± 1	98 ± 4	95 ± 5	
	DAP <sup>d</sup> (mm Hg)	All	S	<b>69 ± 18</b>	<b>71 ± 17</b>	<b>61 ± 16</b>	<b>57 ± 15</b>
			E	<b>66 ± 20</b>	<b>64 ± 19</b>	<b>66 ± 19</b>	<b>65 ± 14</b>
		SMA	S	71 ± 16	78 ± 14	70 ± 19	62 ± 18
			E	73 ± 20	74 ± 19	77 ± 21	71 ± 11
LAR		S	69 ± 20	66 ± 20	55 ± 14	54 ± 16	
		E	62 ± 22	59 ± 19	59 ± 17	60 ± 16	
MIX		S	68 ± 19	75 ± 9	65 ± 10	62 ± 10	
		E	66 ± 3	62 ± 11	69 ± 8	69 ± 1	
MAP <sup>b,d</sup> (mm Hg)		All	S	<b>82 ± 18</b>	<b>81 ± 16</b>	<b>73 ± 15</b>	<b>69 ± 14</b>
			E	<b>78 ± 20</b>	<b>77 ± 22</b>	<b>77 ± 21</b>	<b>76 ± 15</b>
		SMA	S	83 ± 16	89 ± 14	80 ± 16	74 ± 15
			E	84 ± 22	86 ± 22	89 ± 22	82 ± 12
	LAR	S	83 ± 21	75 ± 16 *	68 ± 14	67 ± 15	
		E	75 ± 21	71 ± 22	70 ± 19	72 ± 17	
	MIX	S	79 ± 18	87 ± 6	77 ± 11	72 ± 10	
		E	77 ± 1	75 ± 4	80 ± 6	78 ± 2	
	SI (mL/kg)	All	S	<b>1.64 ± 0.56</b>	<b>1.69 ± 0.76</b>		<b>1.64 ± 0.50</b>
			E	<b>1.45 ± 0.51</b>	<b>1.59 ± 0.62</b>		<b>1.61 ± 0.65</b>
		SMA	S	1.50 ± 0.59	1.59 ± 0.73		1.60 ± 0.42
			E	1.52 ± 0.45	1.76 ± 0.64		1.57 ± 0.45
LAR		S	1.76 ± 0.56	1.71 ± 0.83		1.68 ± 0.61	
		E	1.45 ± 0.58	1.49 ± 0.6		1.65 ± 0.76	
MIX		S	1.58 ± 0.54	1.89 ± 0.75		1.58 ± 0.25	
		E	1.18 ± 0.28	1.58 ± 0.92		1.32 ± 0.54	
DO <sub>2</sub> I <sup>c</sup> (mL/kg/min)		All	S	<b>11.19 ± 3.49</b>	<b>11.92 ± 4.03</b>		<b>11.88 ± 4.22</b>
			E	<b>12.06 ± 3.28</b>	<b>13.83 ± 4.27 *</b>		<b>14.27 ± 4.94</b>
		SMA	S	11.46 ± 3.66	12.87 ± 4.26		13.01 ± 4.61
			E	12.76 ± 2.93	15.02 ± 5.23 *		13.77 ± 4.55
	LAR	S	11.77 ± 3.35	11.37 ± 4.18		11.91 ± 4.47	
		E	11.87 ± 3.66	13.32 ± 3.72		14.5 ± 5.38	
	MIX	S	8.15 ± 3.01	11.90 ± 3.89 *		9.50 ± 1.67	
		E	10.29 ± 2.12	12.07 ± 4.09		12.38 ± 5.18	

SMA = small intestines, LAR = large intestines, MIX = mixed disorders

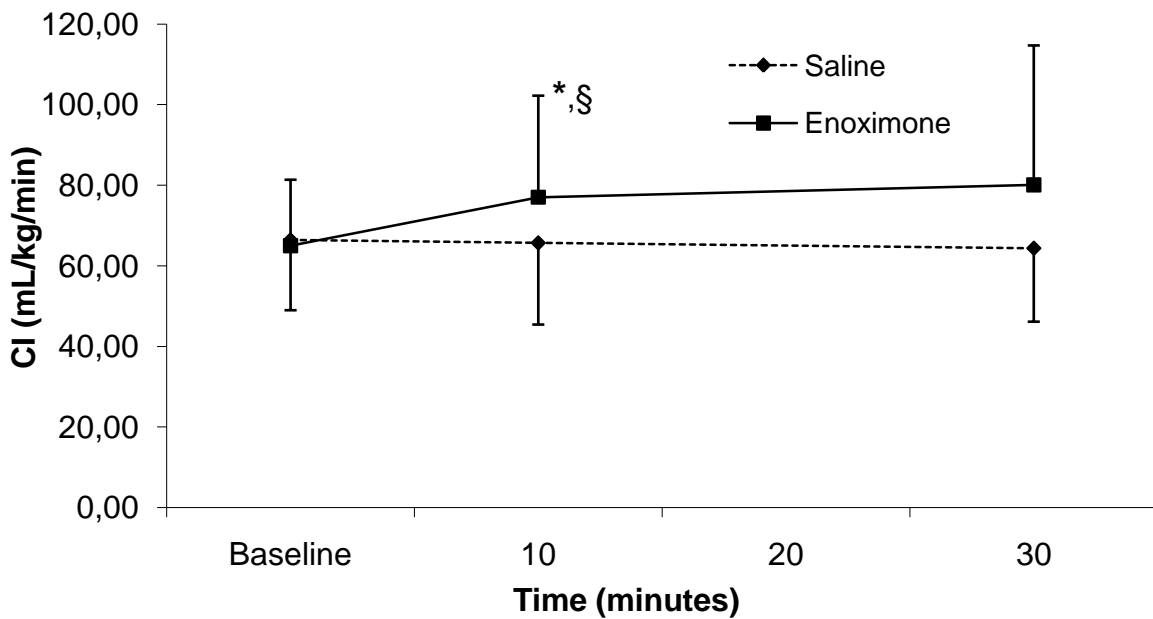
Data are displayed as mean ± SD,  $\alpha = 0.05$  for all analyses

\* Value at T10 significantly different from baseline

<sup>b</sup> Changes between baseline and T10 significantly different between colic types

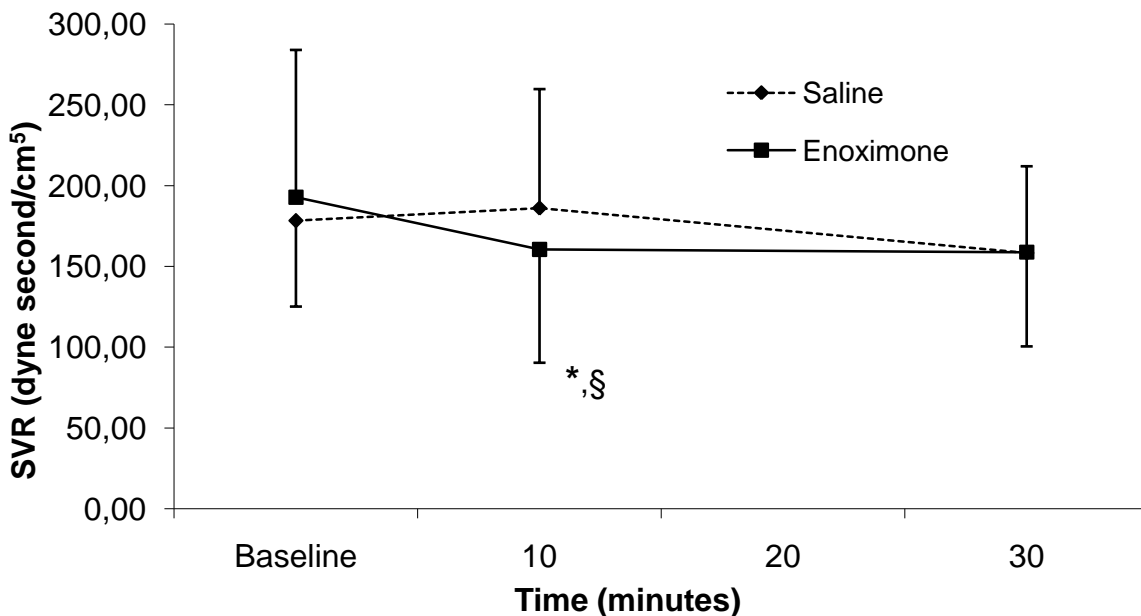
<sup>c</sup> Values from T10 to T30 significantly different between treatments within colic type 'all'

<sup>d</sup> Overall values from T10 to T30 significantly different between colic types



**Figure 1:** Cardiac index (CI) in 48 anaesthetized colic horses, receiving an intravenous bolus of enoximone (0.5 mg/kg) or an equivalent volume of saline 10 minutes after incision of the skin (=T0).

Data are displayed as mean  $\pm$  SD, \* indicates a significant difference between baseline and T10, § indicates that the change between baseline and T10 was significantly different between treatments ( $P < 0.05$ ). No significant difference was found between treatments in overall CI over a 30 minute period after drug administration.



**Figure 2:** Systemic vascular resistance (SVR) in 48 anaesthetized colic horses, receiving an intravenous bolus of enoximone (0.5 mg/kg) or an equivalent volume of saline 10 minutes after incision of the skin (=T0).

Data are displayed as mean  $\pm$  SD, \* indicates a significant difference between baseline and T10, § indicates that the change between baseline and T10 was significantly different between treatments ( $P < 0.05$ ). No significant difference was found between treatments in overall SVR over a 30 minute period after drug administration.

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**Table 4: pH, arterial partial pressures of carbon dioxide (PaCO<sub>2</sub>) and oxygen (PaO<sub>2</sub>), packed cell volume (PCV) and arterial oxygen content (CaO<sub>2</sub>) in 48 anaesthetized colic horses, receiving an intravenous bolus of enoximone (0.5 mg/kg) or an equivalent volume of saline 10 minutes after incision of the skin (=Baseline).**

Variable	Colic type	Treatment	Time after treatment (min)			
			Baseline	T10	T30	
pH	All	S	<b>7.24 ± 0.10</b>	<b>7.25 ± 0.10</b>	<b>7.25 ± 0.09</b>	
		E	<b>7.24 ± 0.10</b>	<b>7.24 ± 0.09</b>	<b>7.27 ± 0.07</b>	
	SMA	S	7.26 ± 0.09	7.25 ± 0.09	7.23 ± 0.09	
		E	7.28 ± 0.07	7.28 ± 0.05	7.29 ± 0.07	
	LAR	S	7.23 ± 0.11	7.24 ± 0.12	7.26 ± 0.10	
		E	7.21 ± 0.11	7.21 ± 0.11	7.25 ± 0.07	
	MIX	S	7.23 ± 0.10	7.25 ± 0.09	7.28 ± 0.06	
		E	7.29 ± 0.02	7.30 ± 0.01	7.30 ± 0.01	
	PaCO <sub>2</sub> <sup>f</sup> (kPa)	All	S	<b>8.40 ± 2.27</b>	<b>8.40 ± 2.13</b>	<b>8.13 ± 1.33</b>
			E	<b>8.40 ± 1.47</b>	<b>8.27 ± 1.60</b>	<b>7.60 ± 0.93</b>
		SMA	S	7.33 ± 0.93	7.73 ± 1.87	8.13 ± 1.20
			E	7.87 ± 0.93	7.87 ± 0.67	7.33 ± 0.53
LAR		S	8.53 ± 1.87	8.27 ± 2.00	8.13 ± 1.07	
		E	8.67 ± 1.73	8.40 ± 2.00	7.60 ± 1.07	
MIX		S	10.40 ± 4.40	10.00 ± 3.20	8.80 ± 2.53	
		E	9.20 ± 1.73	8.40 ± 1.07	8.27 ± 0.13	
PaO <sub>2</sub> <sup>c</sup> (kPa)		All	S	<b>17.46 ± 9.07</b>	<b>20.66 ± 12.93 *</b>	<b>21.60 ± 13.33</b>
			E	<b>24.26 ± 14.00</b>	<b>27.60 ± 16.53 *</b>	<b>30.26 ± 17.20</b>
		SMA	S	19.06 ± 10.53	24.13 ± 16.93	21.20 ± 13.33
			E	26.80 ± 11.47	28.66 ± 13.87	31.20 ± 13.47
	LAR	S	17.60 ± 8.80	19.73 ± 11.2	23.06 ± 15.07	
		E	20.26 ± 14.67	23.46 ± 16.93	26.66 ± 17.86	
	MIX	S	12.13 ± 6.00	16.53 ± 11.73	16.13 ± 4.53	
		E	40.93 ± 2.80	50.79 ± 2.27 *	51.73 ± 0.53	
	PCV <sup>a</sup> (%)	All	S	<b>37 ± 6</b>	<b>39 ± 6 *</b>	<b>39 ± 7</b>
			E	<b>40 ± 8</b>	<b>39 ± 8</b>	<b>38 ± 8</b>
		SMA	S	37 ± 5	39 ± 4	40 ± 8
			E	40 ± 8	39 ± 7	40 ± 7
LAR		S	38 ± 8	40 ± 7	39 ± 7	
		E	40 ± 8	39 ± 10	37 ± 8	
MIX		S	35 ± 4	39 ± 2	39 ± 1	
		E	43 ± 1	43 ± 1	44 ± 1	
CaO <sub>2</sub> <sup>a</sup> (mL/L)		All	S	<b>168.5 ± 28.8</b>	<b>179.8 ± 29.0 *</b>	<b>182.6 ± 31.3</b>
			E	<b>188.6 ± 37.1</b>	<b>185.1 ± 37.5</b>	<b>185.2 ± 35.1</b>
		SMA	S	173.5 ± 28.0	183.9 ± 16.6	189.9 ± 32.0
			E	193.2 ± 39.7	187.0 ± 30.4	192.3 ± 31.1
	LAR	S	168.7 ± 31.5	178.3 ± 37.1	179.0 ± 35.6	
		E	182.3 ± 37.8	179.7 ± 43.1	177.7 ± 36.4	
	MIX	S	154.2 ± 22.9	176.3 ± 18.1 *	182.1 ± 4.5	
		E	212.4 ± 6.0	214.6 ± 7.2	217.2 ± 3.2	

SMA = small intestines, LAR = large intestines, MIX = mixed disorders

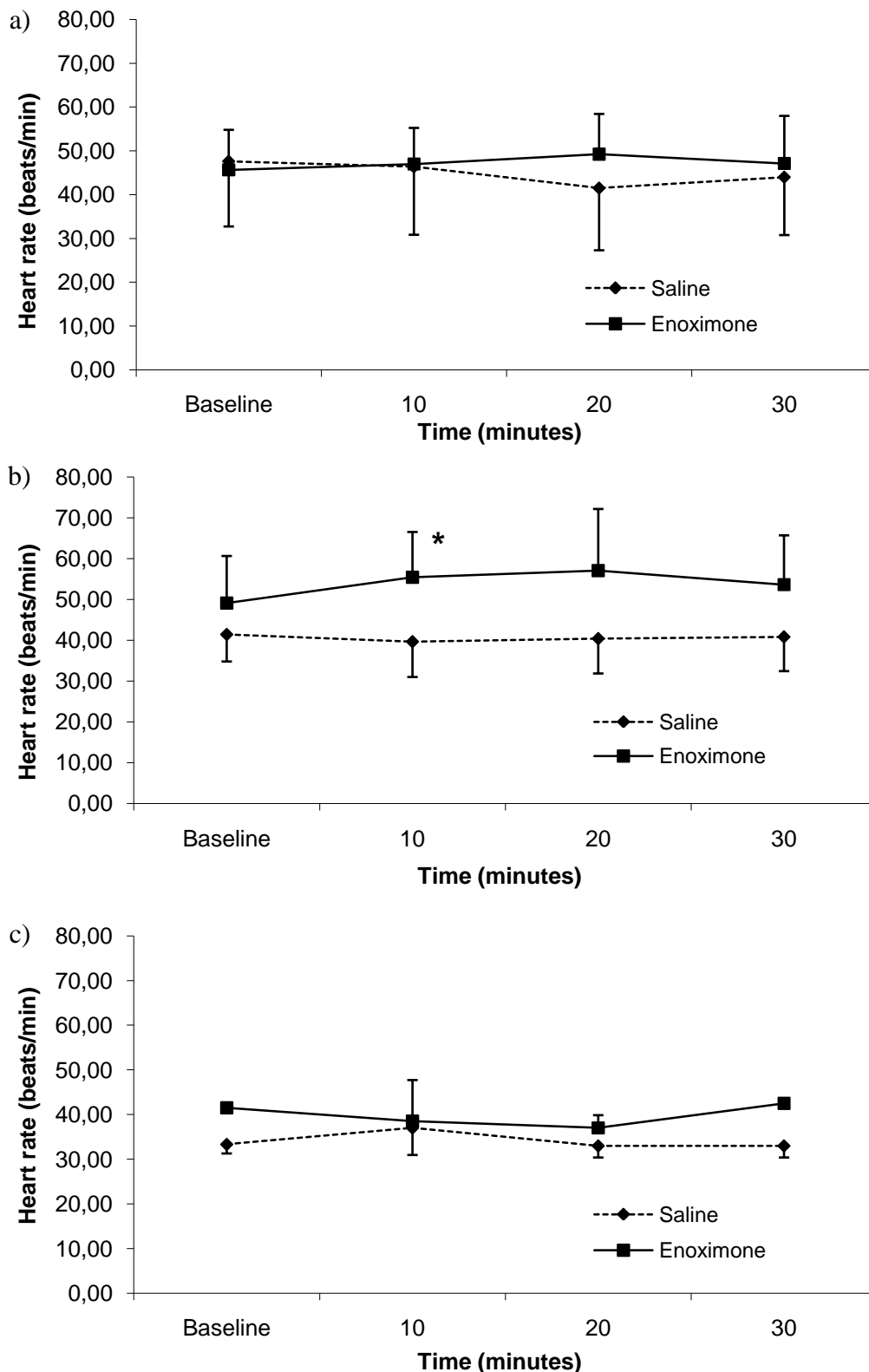
Data are displayed as mean ± SD,  $\alpha = 0.05$  for all analyses

\* Value at T10 significantly different from baseline

<sup>a</sup> Change between baseline and T10 significantly different between treatments within colic type 'all'

<sup>c</sup> Values from T10 to T30 significantly different between treatments within colic type 'all'

<sup>f</sup> Significant interaction between treatment and colic type in comparison of 30 minute period after treatment



**Figure 3:** Heart rate (HR) in 48 anaesthetized colic horses, receiving an intravenous bolus of enoximone (0.5 mg/kg) (E) or an equivalent volume of saline (S) 10 minutes after incision of the skin (=T0). Because a significant interaction was found between treatment and colic type, separate curves are displayed per colic type (curves a, b and c represent colic types 'small intestines', 'large intestines' and 'mixed' respectively). Data are displayed as mean  $\pm$  SD

\* indicates a significant difference between baseline and T10.

## Enoximone in colic horses

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### Comparison between baseline and T10

Irrespective of treatment, significant changes occurred between baseline and T10 in all colic types, but especially in colic type LAR, where HR, DO<sub>2</sub>I, PaO<sub>2</sub> and TV were higher and the end tidal carbon dioxide tension (P<sub>E</sub>'CO<sub>2</sub>), SAP and MAP lower at T10 than at baseline. When comparing the changes between baseline and T10 for the 2 treatments (Tables 3, 4 & 5, Fig. 1, 2 & 3), significant differences were detected for CI (P=0.0133), HR (P=0.0027), SVR (P=0.0080), TV (P=0.0446), PCV (P=0.0078) and CaO<sub>2</sub> (P=0.0317). Indeed, CI (P=0.0010), HR (P=0.0033) and TV (P=0.0405) increased and SVR (P=0.0043) decreased after treatment E, while none of these variables changed after treatment S. Packed cell volume (P=0.0116) and CaO<sub>2</sub> (P=0.0142) both increased after treatment S, but not after treatment E. There was a significant interaction between treatment and colic type (P=0.0076) for HR: a significant difference between E and S was only observed in colic type LAR, with an increase in HR after treatment E compared to treatment S (Fig. 3). A similar interaction effect was found for TV (P=0.0161). Finally, DO<sub>2</sub>I increased (P=0.0007) after treatment E and not after treatment S, but the difference between treatments was not significant.

### Differences between treatments and colic types from T10 to T30

Only PaO<sub>2</sub> (P=0.0016), SaO<sub>2</sub> (P=0.0092) and DO<sub>2</sub>I (P=0.0224) were higher during the first 30 minutes after treatment E than after treatment S (Tables 3 & 4). Although HR was not significantly different between treatments, a significant interaction between treatment and colic type was again detected for HR (P=0.0038), which was always higher after treatment E than after treatment S, but with a much clearer difference in group LAR than in the other groups (Fig. 3). During the first 30 minutes after treatment, significant differences were also detected between the 3 colic types for several variables, which are represented in Tables 3, 4 & 5.

## Discussion

In the present study, DO<sub>2</sub>I, CI and HR increased and SVR decreased 10 minutes after administration of enoximone, but in the overall analysis comparing the first 30 minutes after treatment, only DO<sub>2</sub>I and HR were higher after treatment E, while a clinically relevant difference in HR was only found in colic type LAR. These results do not agree with reports in anaesthetized ponies under standardized experimental conditions, where long lasting cardiovascular effects were observed after a single bolus, with increases in  $\dot{Q}t$  and SV during

**Table 5: Rate of dobutamine infusion, end-tidal isoflurane concentration (FE'Iso) and end-tidal carbon dioxide partial pressure (PE'CO2), tidal volume and peak inspiratory pressure (PIP) in 48 anaesthetized colic horses, receiving a bolus of enoximone (0.5 mg/kg) or an equivalent volume of saline 10 minutes after skin incision (=Baseline).**

Variable	Colic type	Treatment	Time after treatment (min)				
			Baseline	T10	T20	T30	
Dobutamine <sup>d</sup> (µg/kg/min)	All	S	<b>0.41 ± 0.29</b>	<b>0.34 ± 0.30 *</b>	<b>0.35 ± 0.33</b>	<b>0.42 ± 0.33</b>	
		E	<b>0.36 ± 0.23</b>	<b>0.38 ± 0.23</b>	<b>0.42 ± 0.37</b>	<b>0.46 ± 0.40</b>	
	SMA	S	0.31 ± 0.28	0.15 ± 0.30 *	0.15 ± 0.30	0.21 ± 0.31	
		E	0.28 ± 0.23	0.33 ± 0.20	0.27 ± 0.19	0.28 ± 0.19	
	LAR	S	0.44 ± 0.29	0.45 ± 0.28	0.50 ± 0.31	0.57 ± 0.29	
		E	0.38 ± 0.25	0.39 ± 0.27	0.51 ± 0.45	0.55 ± 0.47	
	MIX	S	0.55 ± 0.33	0.40 ± 0.24	0.30 ± 0.27	0.30 ± 0.27	
		E	0.51 ± 0.11	0.51 ± 0.11	0.44 ± 0.21	0.44 ± 0.21	
	FE'Iso <sup>d</sup> (%)	All	S	<b>0.93 ± 0.17</b>	<b>0.95 ± 0.19</b>	<b>1.01 ± 0.20</b>	<b>1.11 ± 0.17</b>
			E	<b>1.00 ± 0.18</b>	<b>0.98 ± 0.19</b>	<b>1.01 ± 0.21</b>	<b>1.06 ± 0.26</b>
SMA		S	1.01 ± 0.20	0.92 ± 0.26	1.02 ± 0.28	1.19 ± 0.24	
		E	0.89 ± 0.17	0.92 ± 0.20	0.94 ± 0.22	1.00 ± 0.25	
LAR		S	0.95 ± 0.16	1.00 ± 0.12	1.04 ± 0.14	1.08 ± 0.12	
		E	1.07 ± 0.18	1.03 ± 0.18	1.06 ± 0.20	1.10 ± 0.26	
MIX		S	0.93 ± 0.21	0.87 ± 0.14	0.88 ± 0.08	1.07 ± 0.16	
		E	0.95 ± 0.14	0.93 ± 0.18	0.90 ± 0.14	0.90 ± 0.14	
PE'CO <sub>2</sub> (kPa)		All	S	<b>5.79 ± 1.11</b>	<b>5.47 ± 0.63 *</b>	<b>5.43 ± 0.71</b>	<b>5.49 ± 0.77</b>
			E	<b>5.99 ± 0.81</b>	<b>5.83 ± 0.80</b>	<b>5.57 ± 0.85</b>	<b>5.48 ± 1.06</b>
	SMA	S	5.49 ± 0.94	5.43 ± 0.87	5.47 ± 0.80	5.65 ± 0.75	
		E	6.01 ± 0.80	6.01 ± 0.73	5.88 ± 0.60	5.77 ± 0.63	
	LAR	S	5.85 ± 0.78	5.47 ± 0.37	5.36 ± 0.54	5.29 ± 0.77	
		E	6.08 ± 0.85	5.77 ± 0.90	5.42 ± 0.99	5.35 ± 1.28	
	MIX	S	6.34 ± 2.50	5.55 ± 0.99	5.64 ± 1.30	5.93 ± 0.82	
		E	5.28 ± 0.07	5.37 ± 0.07	5.42 ± 0.27	5.56 ± 0.07	
	Tidal volume <sup>a,e</sup> (mL/kg)	All	S	<b>7.9 ± 1.8</b>	<b>7.9 ± 1.7</b>	<b>8.3 ± 1.9</b>	<b>9.0 ± 1.5</b>
			E	<b>8.0 ± 3.3</b>	<b>8.8 ± 2.4 *</b>	<b>9.2 ± 1.9</b>	<b>9.0 ± 2.1</b>
SMA		S	8.4 ± 1.7	8.4 ± 1.7	8.2 ± 1.5	8.4 ± 1.4	
		E	9.3 ± 2.6	9.3 ± 2.6	10.1 ± 1.8	9.5 ± 2.6	
LAR		S	8.1 ± 1.7	7.9 ± 1.6	8.6 ± 1.9	9.0 ± 1.5	
		E	7.1 ± 3.6	8.8 ± 2.4 *	9.1 ± 1.8	8.9 ± 1.7	
MIX		S	5.3 ± 0.2	5.9 ± 0.9	7.8 ± 3.0	10.1 ± 1.2	
		E	7.8 ± 3.6	6.9 ± 2.4	6.9 ± 2.4	6.1 ± 1.2	
PIP (cm H <sub>2</sub> O)		All	S	<b>21 ± 3</b>	<b>21 ± 3</b>	<b>21 ± 3</b>	<b>21 ± 3</b>
			E	<b>21 ± 4</b>	<b>22 ± 4</b>	<b>22 ± 4</b>	<b>21 ± 3</b>
	SMA	S	20 ± 0	20 ± 0	20 ± 0	20 ± 0	
		E	20 ± 4	21 ± 3	22 ± 2	22 ± 2	
	LAR	S	20 ± 3	21 ± 3	21 ± 3	21 ± 3	
		E	23 ± 4	23 ± 4	22 ± 5	21 ± 3	
	MIX	S	24 ± 6	24 ± 7	24 ± 7	24 ± 7	
		E	19 ± 1	19 ± 1	19 ± 1	19 ± 1	

SMA = small intestines, LAR = large intestines, MIX = mixed disorders

Data are displayed as mean ± SD,  $\alpha=0.05$  for all analyses

\* Value at T10 significantly different from baseline

<sup>a</sup> Change from baseline at T10 significantly different between treatments within colic type 'all'

<sup>d</sup> Overall values from T10 to T30 significantly different between colic types

<sup>e</sup> Significant interaction between treatment and colic type in analysis of changes between baseline and T10

## Enoximone in colic horses

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100 minutes and increases in HR during 40 minutes (Chapter 4.1). It may therefore be concluded that the effects of enoximone are either less pronounced and of shorter duration in horses with compromised cardiovascular function, or that the effects were masked by the administration of other drugs and by haemodynamic differences between or changes within patients.

Although a stratified treatment assignment was used to attain a more equal distribution in colic types between both treatment groups, a large variability in the cardiovascular status of individual horses in each group was still possible, depending on many factors such as the actual aetiology (Table 1), duration of symptoms, treatments initiated or drugs administered prior to admission/surgery. To minimize the influence of differences between individual horses when analyzing the short term effects of enoximone, the changes between baseline and T10 were calculated and compared between treatments, rather than comparing the absolute values at T10. By using this approach, it became clear that in all colic types, clear and significant changes occurred during this phase of surgery, irrespective of the treatment administered, which may be related to waning of the effects of induction/sedative drugs, increasing effects from fluids/inotropes, and surgical factors such as decompression of the abdomen.

The most pronounced and significant changes occurred in the LAR group, where HR, TV and PaO<sub>2</sub> were higher at T10 than at baseline, while the opposite was observed for P<sub>E</sub>'CO<sub>2</sub>, SAP and MAP. These changes were most likely related to fast surgical decompression of the abdomen by removal of gas from tympanic large intestines and/or by partial exteriorization of intestines. By using a volume controlled, pressure limited mode of ventilation, the set TV was often not delivered in the initial phase of the anaesthesia in tympanic horses, because PIP exceeded the preset pressure limit of the ventilator. In these cases, TV would indeed be expected to increase when pressure on the diaphragm is reduced by surgical decompression of the abdomen. The decrease in P<sub>E</sub>'CO<sub>2</sub> and improvement in arterial oxygenation confirm this hypothesis. Although PaCO<sub>2</sub> was also lower at T10 than at baseline, this difference was not significant. This disagreement between P<sub>E</sub>'CO<sub>2</sub> and PaCO<sub>2</sub> may be statistical coincidence, or may result from an increase in alveolar dead space ventilation due to reduced pulmonary perfusion. Indeed, a second possible effect of reducing intra-abdominal pressure is hypotension, due to decompression of the mesenteric vascular bed and larger abdominal vessels, leading to reductions in venous return (Vos et al. 1995), central venous pressure (Mohapatra 2004) and SVR (Shelly et al. 1987, Mohapatra 2004). In the present study, SAP



and MAP were indeed lower and HR higher at T10 than at baseline in colic type LAR, while no changes in these variables were observed in the other 2 colic types.

Ten minutes after enoximone administration, CI and HR were higher and SVR lower than at baseline. These changes were significantly different from those after saline treatment, where these variables remained constant. Stroke index also tended to increase after enoximone administration, but this difference was not significant ( $P=0.0519$ ). Finally,  $DO_2I$  increased significantly in the enoximone group and not in the saline group, but the change was not significantly different between treatments. The cardiovascular effects of enoximone in this study are in agreement with the inotropic, vasodilating and mild chronotropic effects of enoximone described in humans (Vernon et al. 1991, Lehtonen et al. 2004), dogs (Dage et al. 1982) and ponies (Chapter 4.1). Due to its vasodilating properties, enoximone can induce a decrease in SVR (arterial vasodilation) (Dage et al. 1982, Boldt et al. 1993) and a certain degree of venous pooling (venous vasodilation) (Boldt et al. 1993, Lehtonen et al. 2004). Indeed, RAP was lower after enoximone administration in isoflurane anaesthetized ponies (Chapter 4.1). Because of these combined arterial and venous vasodilating effects, it may be expected that enoximone would induce pronounced arterial hypotension and be contraindicated in patients with low SVR, such as hypovolemic and/or endotoxaemic colic horses during isoflurane anaesthesia. Nevertheless, it was hypothesized that enoximone may still be valuable in colic horses, since this drug was shown to have beneficial effects in humans with endotoxin shock (Ringe et al. 2003) or sepsis (Schmidt et al. 2001) and induced increases in CI without influencing arterial pressure in isoflurane anaesthetized ponies (Chapter 4.1). Similarly, in the present study in colic horses, the effect of enoximone on arterial pressure was not different from the effect of saline. These results and those in ponies indicate that the increase in CI outweighs possible vasodilatory effects of enoximone and/or that enoximone induces less pronounced reductions in SVR in equids compared to humans. It must also be remembered that central venous/right atrial pressure was not measured, but arbitrarily taken as 7 mm Hg, since placement of a central venous catheter was not feasible in these client-owned horses during emergency surgery. This may have biased our calculation of absolute values of SVR, as well as the relative comparison between both treatments. Saline treatment is not expected to affect RAP, but since enoximone has been shown to reduce RAP in ponies (Chapter 4.1), we may have slightly overestimated the reduction in SVR in response to enoximone.

## Enoximone in colic horses

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When analyzing the changes between baseline and T10, a significant interaction effect was observed for HR and TV, indicating that the response to treatment depended on the type of colic. Indeed, compared to the other colic types, the increases in HR and TV 10 minutes after enoximone administration were much more pronounced in the LAR group. As mentioned earlier, TV could only increase when airway resistance decreased and/or compliance increased, since pressure-limited ventilation was used in this study and because the pressure limit was not different between baseline and T10. A higher compliance would most likely result from a decrease in intra-abdominal pressure, which agrees with the observed increase in HR, as described earlier. Since enoximone should not affect intra-abdominal pressure and because TV was already lower at baseline in group E than in group S, it seems likely that, as a coincidence, the initial intra-abdominal pressure of horses in group E was higher and therefore decreased more after surgical decompression of the abdomen. The increase in tidal volume could also have resulted from increased inspiratory effort by the patient during assisted respiration. However, this seems unlikely since no significant changes in PaCO<sub>2</sub>, PaO<sub>2</sub>, end tidal isoflurane concentration or RR were noted between baseline and T10 and because enoximone would not be expected to influence respiratory drive. Finally, it has been shown that combined PDE IV/III inhibitors relax airway smooth muscles and may even be effective for the long-term therapy of asthma (Nicholson et al. 1995). Enoximone, a selective PDE III inhibitor, would also have bronchodilating properties, since this drug reduced lung resistance and increased dynamic lung compliance in spontaneously breathing and artificially ventilated patients with decompensated chronic obstructive pulmonary disease (Leeman et al. 1987). Although bronchodilation would additionally reduce airway resistance, this effect appears less important in the present study since no change in TV was observed after enoximone treatment in the other colic types.

The immediate cardiovascular effects of enoximone in this study (including increases in HR, CI, SI and DO<sub>2</sub>I and a decrease in SVR) were in agreement with those observed in ponies (Chapter 4.1), but most of these effects were less pronounced and not significant in the overall analysis of the first 30 minutes after treatment. Several factors may have contributed to this finding. First, the cardiovascular status of individual colic horses can vary widely, leading to high standard deviations of the different variables, which may decrease the sensitivity of statistical tests. Secondly, dobutamine and fluid therapy were used in both groups, which may have further reduced cardiovascular differences between treatments. Although it has been shown that enoximone and dobutamine had additive or perhaps even synergistic effects on

cardiovascular function in ponies (Chapter 4.2), administration of enoximone did not reduce dobutamine requirement in the present study. Administration of colloids and placement of a second jugular catheter were also needed in comparable numbers of horses in both groups. Finally, cardiovascular function is often compromised in colic horses (Parry et al. 1983, Puotunen-Reinert 1986, French et al. 2002) and may be expected to be less responsive to inotropes, especially in case of hypovolaemia (due to decreased venous return and thus a low preload) and/or endotoxaemia (Takeuchi et al. 1999, Tavernier et al. 2001). In experimental models, endotoxaemia rapidly impaired myocardial intracellular calcium handling and contractile protein sensitivity to calcium, a state which was resistant to beta-agonist inotropic stimulation (Takeuchi et al. 1999). Vesnarinone, a PDE inhibitor like enoximone, was able to normalize lipopolysaccharide-induced myocardial dysfunction and partially restore abnormal calcium cycling, but these effects were more likely a result of the drug's immunomodulatory effects than of myocardial PDE inhibition (Takeuchi et al. 2000). Nevertheless, even in patients with severe prolonged catecholamine and volume refractory endotoxin shock, enoximone could restore myocardial contractility in man (Ringe et al. 2003) and prevented mucosal hypoperfusion despite inducing hypotension during an early stage of sepsis (Schmidt et al. 2001). Therefore, enoximone might be valuable in endotoxaemic horses, but further studies are needed since only a limited number of horses in the present study were suspected to be endotoxaemic.

A potential limitation of this study is that the anaesthetist was not blinded to treatment. However, these horses were operated under emergency circumstances and cardiovascular function was often compromised. To optimize patient safety, it was preferred that the anaesthetist was aware of which drugs were being administered, such that appropriate action could be taken when needed. Additionally, enoximone is commercialised as a bright yellow solution, which makes it less practical to use in a blinded study performed under emergency circumstances, with limited staff available. By not performing this study blinded, the anaesthetist could have influenced cardiovascular function by changing the anaesthetic protocol or the depth of anaesthesia, by altering the fluid administration rate and the type of fluid used and by administering vasoactive/inotropic drugs. However, a similar anaesthetic protocol was used in all cases, the end tidal isoflurane concentration (correlated to depth of anaesthesia) was not significantly different between treatments, and was quite constant over the study period (maximal change within each group always less than 0,2%). Decisions about fluids and/or dobutamine administration rate were based on arterial blood pressure values (an

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objective criterion), with the aim to keep MAP above a fixed, predetermined value, which was the same in both treatment groups (70 mm Hg).

In conclusion, a bolus of enoximone induced increases in  $DO_2$ , CI and HR and a decrease in SVR in colic horses, but most of these differences were only transient and not significant over a 30 minute period after treatment. Further studies may be useful to investigate the effects of enoximone at different doses or as a CRI, in specific classes of colic or other disease.

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# GENERAL DISCUSSION

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The anaesthetic risk in horses is markedly higher than in most other commonly anaesthetized species. The results of different studies, including the confidential enquiry into perioperative equine fatalities (CEPEF) (Johnston et al. 2002), suggested that one of the important targets when attempting to reduce anaesthesia related mortality in horses, is the optimization of tissue oxygen supply.

In the introductory chapter to this PhD thesis, existing methods to diagnose and prevent or treat inadequate tissue oxygen supply in horses and other species were reviewed. Several conclusions were drawn from this literature review. One general finding was that no easily applicable, safe, noninvasive, continuous and accurate method for measuring  $\dot{Q}_t$  is available although optimizing cardiac output ( $\dot{Q}_t$ ) during anaesthesia is important to augment oxygen delivery ( $\text{DO}_2$ ) in horses. However, pulse contour analysis appeared to be an attractive alternative. Other conclusions drawn from our literature review were that, in order to optimize  $\dot{Q}_t$ , inotropes are needed more often in horses compared to other species, and that extensive research therefore has been performed regarding  $\beta$ -sympathomimetic drugs. Of these, dobutamine appears to be the most effective and safe drug to maintain cardiac output in anaesthetized horses. Some other classes of inotropic drugs had received little to no attention in equine anaesthesia, although in humans, phosphodiesterase (PDE) III inhibitors had shown characteristics that, if similar in horses, could be of interest.

Based on the first conclusion from the literature review, i.e. the lack of an ideal  $\dot{Q}_t$  measurement technique in horses, the reliability of a novel method of estimating  $\dot{Q}_t$ , namely analysis of the arterial pressure waveform, or Pulse Contour analysis (PulseCO<sup>®</sup>), was investigated in equids. The experimental part of this PhD research, which investigated the cardiovascular effects of different inotropic and/or vasoactive drugs in ponies, enabled us to simultaneously evaluate the accuracy and precision of the PulseCO<sup>®</sup> software by comparing this technique with the validated lithium dilution method (LiDCO<sup>®</sup>). In the past, agreement between two measurement techniques has often been evaluated inappropriately by the use of correlation coefficients. In 1986, Bland & Altman proposed a different statistical approach,

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the so-called Bland-Altman plot, which has been used extensively to display and describe data from studies comparing two different techniques for measuring the same variable. This statistical method is based on the bias and limits of agreement. Bias refers to the average difference between the new and reference techniques and therefore allows an estimation of the accuracy of the new technique as compared to the reference technique, which is considered to be the gold standard (Cecconi et al. 2009). The limits of agreement, i.e. the limits within which 95% of the observations fall (corresponding to  $\pm 1.96$  times the standard deviation around the bias), give an estimation of the precision or random error around the bias (Cecconi et al. 2009). Ideally, a measurement device is both accurate and precise. If a technique has a high bias and narrow limits of agreement, this indicates low accuracy but high precision, so repeated measurements will be close together although their mean will not be close to the actual value. This often results from a systematic error, which in many cases can be corrected for by calibrating the measurement device, or taking the systematic error into account if it is known. On the other hand, a technique with wide limits of agreement has low precision, which is much more difficult to correct for. One solution is to perform each measurement more than once and calculate the mean of these values as a better estimate of the true value, a strategy that is often performed with the intermittent thermodilution technique (Colgan & Stewart 1977).

In chapter 3, Bland-Altman plots were obtained and bias and limits of agreement were calculated to evaluate the accuracy and precision of the PulseCO<sup>®</sup> technique in ponies under experimental conditions. In most treatment groups, bias appeared to be acceptable, but limits of agreement were very wide. Critchley and Critchley (1999) advised that the limits of agreement of a new technique compared to the thermodilution technique should not be wider than -30 and +30%. These maximal values were calculated by assuming that the reference technique (thermodilution) had a precision of around 20%, while a similar precision was desired for the new technique. Cecconi et al. (2009) recently accentuated that the precision of the reference technique should be known before limits of agreement can be evaluated, because this precision influences the maximally acceptable values for the limits of agreement. To the authors' knowledge, no data are available regarding the precision of LiDCO<sup>®</sup> measurements in ponies or horses. Nevertheless, because LiDCO<sup>®</sup> and thermodilution measurements showed good agreement in anaesthetized horses (Linton et al. 2000), maximally acceptable limits of agreement of -30 and +30%, as suggested by Critchley and Critchley (1999), seem reasonable. In fact, in the study of Linton et al. (2000), it was even



shown that single LiDCO<sup>®</sup> measurements agreed well with the mean of triplicate thermodilution measurements, so the error of LiDCO<sup>®</sup> measurements may actually be lower than 20%. Assuming this is true, the acceptable limits of agreement between LiDCO<sup>®</sup> and PulseCO<sup>®</sup> would be even lower than  $\pm 30\%$ . In the saline treated ponies of the present PhD study, where cardiovascular performance was stable, limits of agreement were -19.7 and +29.5%. When the ponies were treated with enoximone, alone or combined with other drugs, the limits of agreement were even higher, i.e. clearly above the  $\pm 30\%$  limits. This demonstrates an unacceptably low precision for PulseCO<sup>®</sup> measurements under changing haemodynamic conditions.

It must be noted that the Bland-Altman method was developed to compare two independent measurement techniques and is in fact not suitable for repeated measures data, although many authors have (mis)used the technique for such analyses (Myles & Cui 2007). In our experimental study, the two techniques for cardiac output measurement were not independent, since the PulseCO<sup>®</sup> algorithm was calibrated using the reference technique (LiDCO<sup>®</sup>). This equalized both measurements at the start of the study, so the initial bias was actually set at zero. It is therefore not surprising that mean bias was quite acceptable in most groups. However, limits of agreement in the placebo group were wide despite zero bias in each individual pony at the start of the study and the short study duration, and became even larger when inotropic and vasoactive drugs were administered. This indicates that the reliability of the PulseCO<sup>®</sup> values in the individual patient will be low, and both over- and underestimation of the actual value can occur. Furthermore, the precision of an intermittent, absolute technique for  $\dot{Q}t$  measurement can be augmented by averaging repeated measurements, but this is not an option in the individual patient when using a continuous, relative method such as pulse contour analysis, which does not measure  $\dot{Q}t$  but attempts to estimate the change in  $\dot{Q}t$  from the change in the arterial waveform compared to the time of initial calibration. Because of the rather low bias, it might be hypothesized that, if a sufficient number of animals are used in an experimental study of similar duration, the average value for  $\dot{Q}t$  would be quite acceptable. Yet, because of the low precision, standard deviations would most likely be ‘artificially’ high, i.e. not caused by differences in the response to treatment between animals, but due to measurement errors.

Another limitation of the Bland-Altman method is that it does not analyze whether the differences found between the two techniques are significant. Therefore, the data were also

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evaluated using a paired t-test and a mixed model approach. The paired t-test compared overall values for  $\dot{Q}t$  and systemic vascular resistance (SVR) during the placebo treatment with saline. As mentioned for the Bland-Altman analysis, PulseCO<sup>®</sup> and LiDCO<sup>®</sup> were equal at the start of the study. Because the difference between both techniques would therefore be expected to be low during the initial phase of the experiment, an overall comparison carried the risk of masking significant differences occurring mainly at the end of the study period. Nevertheless, a significant difference between both measurement techniques was found during the placebo treatment. This difference significantly increased over time and was even larger during treatment with enoximone, alone or combined with dobutamine.

Based on the results from both statistical approaches, it was concluded that the reliability of the PulseCO<sup>®</sup> software was insufficient in ponies under stable haemodynamic conditions and became worse during induced haemodynamic changes, especially when arterial pressure changed. Unfortunately, a  $\dot{Q}t$  monitor would of course mainly be useful when changes in  $\dot{Q}t$  or SVR occur. Although the study was performed in ponies, in the authors' opinion it seems unlikely that better results would be obtained in horses. For this reason, the PulseCO<sup>®</sup> software was not used for  $\dot{Q}t$  measurements during the clinical study in colic horses.

The second conclusion that could be drawn from our literature review was that, in order to maintain oxygen supply to the tissues (especially the muscles), inotropic drugs are probably needed/used more often in anaesthetized horses than in humans or small animals without cardiac disease, for several reasons. It has been documented that horses are prone to develop inadequate respiratory function and cardiovascular depression during anaesthesia, while intracompartmental pressures in the limbs are high because of their high body weight. In anaesthetized, recumbent horses, the occurring ventilation-perfusion mismatching often results in arterial hypoxaemia (Hall et al. 1968, Nyman & Hedenstierna 1989, Nyman et al. 1990). Although the sigmoid shape of the oxyhaemoglobin dissociation curve serves as a safety factor (Bohr et al. 1904), pronounced hypoxaemia with a reduction in arterial oxygen content ( $CaO_2$ ) may still decrease delivery of oxygen ( $DO_2$ ) to the tissues. Many strategies to prevent or treat arterial hypoxaemia were reported to be rather ineffective (Young et al. 1999, Kalchofner et al. 2009), caused further deterioration of  $PaO_2$  (Dodam et al. 1993) or decreased  $\dot{Q}t$  (Hall & Trim 1975, Wilson & Soma 1990, Mizuno et al. 1994, Edner et al. 2005), which can negate any beneficial effect of increases in  $CaO_2$  on  $DO_2$ . An alternative possibility to restore  $DO_2$  when  $CaO_2$  is low, is to increase  $\dot{Q}t$ . One might even hypothesize that, under

some circumstances, higher than normal  $\dot{Q}_t$  values may be beneficial. Not only could this normalize  $\text{DO}_2$  despite a limited degree of arterial hypoxaemia, but it may also prove to be useful to optimize muscle oxygen delivery in a species where intracompartamental pressure in the muscles reaches high values during recumbency. In this respect, to increase vascular transmural pressure in dependent muscles of horses, blood pressure needs to be increased to levels higher than those usually needed in other species to maintain perfusion of vital tissues such as the brain and kidneys. Although this increase in blood pressure may be achieved by increasing SVR using vasopressors, perfusion of certain tissues, such as the splanchnic organs, muscles and/or skin may be reduced. Vasopressors are therefore best reserved for situations where hypotension is mainly attributable to vasodilation. More desirable would be an increase in  $\dot{Q}_t$  and although this can be achieved using chronotropic drugs (such as antimuscarinics), this strategy is not advisable, for many reasons which were mentioned in Chapter 1. It would be a better option to reduce anaesthetic depth using balanced anaesthetic techniques, with the aim to minimize cardiovascular depression, but this is less straightforward in horses than in many other species. Opioids, which are often used for perioperative analgesia in humans and small animals, appear to have less clear analgesic effects in horses and produced little to no decrease or in some cases even an increase in the minimal alveolar concentration (MAC) of inhalant anaesthetics (Pascoe et al. 1993, Steffey et al. 2003, Bennett et al. 2004, Thomasy et al. 2006, Knych et al. 2009). Furthermore, locoregional anaesthetic techniques are not always without risk in horses, e.g. epidural anaesthesia using local anaesthetic drugs causes paralysis or muscle weakness and ataxia (LeBlanc et al. 1988, Olbrich & Mosing 2003), while regional anaesthesia of the limbs at the level of or proximal to the fetlock may interfere with normal proprioception (Dreverno et al. 1999). Both techniques may therefore increase the risk of injury during recovery in horses.

Fluid therapy is also important to maintain or improve  $\dot{Q}_t$ . However, because of the high body weight of horses, administration of large volumes of intravenous fluids on a 'per kg' basis is difficult to achieve under clinical conditions. In dogs with symptoms of shock due to absolute hypovolaemia, the use of 'shock doses' of crystalloids with rates up to 90 mL/kg in 10 to 15 minutes has been advised (Day 2000). In a typical 500 kg horse, this infusion would be equivalent to a rate of 180-270 L/hour, which is hard to achieve even when using more than one catheter and/or pressurized infusion systems. Hypertonic saline offers an attractive alternative but only a limited amount can be administered, mainly because cellular

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dehydration has to be avoided. Colloids are another possibility, but these solutions are quite expensive and not completely free of side effects.

Since balanced anaesthetic techniques and fluid administration are not always effective, inotropes can be regarded as indispensable to optimize  $\dot{Q}_t$  during anaesthesia in horses. These drugs often need to be administered even before adequate fluid resuscitation is achieved. This situation differs from the one in other species including humans, where inotropes are mostly reserved for patients with compromised cardiac contractility, e.g. due to cardiac disease or sepsis. Probably, this is partly related to the fact that  $\dot{Q}_t$  during anaesthesia can usually be maintained at an acceptable level using balanced anaesthetic techniques and fluid therapy. On the other hand, there is less need for a 'supra-normal'  $\dot{Q}_t$  compared to the situation in horses, because arterial hypoxaemia occurs less frequently in humans without respiratory disease and lower levels of blood pressure are acceptable to maintain tissue perfusion. Additionally, inotropic drugs usually increase myocardial work and oxygen consumption (Notterman 1991), which is preferably avoided in the human population, with a high incidence of cardiovascular disease, including arteriosclerosis, chronic hypertension and coronary artery disease (Franklin 2006).

Because of the clear need for inotropic drugs in horses, the relevant literature was reviewed in order to summarize which agents were presently used, what their positive and negative effects were, and which drugs may be promising for use in horses. Some inotropic drugs, including calcium salts, calcium sensitizers and digitalis glycosides, appeared to be less suitable for use during anaesthesia for different reasons, as mentioned in Chapter 1. Extensive research has been performed on the effects of  $\beta$ -sympathomimetic drugs in anaesthetized horses. These drugs can indeed be quite effective at increasing  $\dot{Q}_t$ , while most of them are suitable for use as a constant rate infusion (CRI). Their rapid onset and short duration of action enable quick alterations of the obtained effects. Still, negative side effects, which are dose-dependent and differ between the individual drugs, may occur and include tachycardia, excessive vasoconstriction or vasodilation, increased myocardial oxygen consumption and arrhythmias (Notterman 1991). Dobutamine appeared to be the most effective and a relatively safe  $\beta$ -sympathomimetic for use in horses. In humans, dobutamine mainly produces positive inotropic effects, together with some vasodilation (Morrill 2000). Phosphodiesterase (PDE) III inhibitors have similar effects in humans and are associated with few side effects during short-term perioperative use (Barnard & Linter 1993). It was therefore hypothesized that these

drugs may be useful in anaesthetized horses. Furthermore, their combined use with a  $\beta$ -sympathomimetic appeared attractive, because this may theoretically result in additive or even synergistic effects. Finally, because PDE III inhibitors cause inotropic effects through increased intracellular calcium concentrations in the myocardium, it was hypothesized that calcium salts may accentuate their inotropic effects. Up to now, milrinone and enoximone are probably the most often used PDE III inhibitors in human medicine. The effects of milrinone have already been described in horses (Muir 1995), but no reports were available on the use of enoximone. Because the drug has a rather long half-life (Morita et al. 1995), it was preferred to evaluate the effects of a single bolus in anaesthetized ponies, alone or followed by infusions of dobutamine or calcium chloride.

As illustrated in Chapter 4.1, an intravenous bolus of 0.5 mg/kg enoximone administered over 1-2 minutes, induced significant increases in  $\dot{Q}_t$  and stroke volume (SV) during 100 minutes and an increase in heart rate (HR) during 40 minutes, while right atrial pressure (RAP) decreased during at least 2 hours. These findings were similar to the ones reported in human medicine, except that SVR was somewhat lower, but not significantly different from saline treatment in our ponies. This situation appears similar to the one described for dobutamine, which mainly has inotropic, but also some vasodilating activity in humans (Morrill 2000), while most authors reported clear inotropic, but limited or no effects on SVR in anaesthetized ponies (Gasthuys et al. 1991) and horses (Swanson et al. 1985, Rasis et al. 2000). It is unclear why this difference between species actually occurs. In most anaesthetic protocols for horses,  $\alpha_2$  agonists, including romifidine, are administered for sedation before the induction of general anaesthesia. By inducing vasoconstriction, these agents may counteract the vasodilatory effects of other drugs. Nonetheless, it seems unlikely that romifidine had a clear effect on the response to enoximone in our experimental study, since a period of 105 minutes elapsed between the administration of romifidine (for sedation) and enoximone (during anaesthesia). Another difference between humans and horses is the dose of dobutamine that is usually administered. The vasodilatory effects of dobutamine in humans are mostly observed when higher doses are infused (Morrill 2000), while the doses routinely used during clinical anaesthesia in horses are quite low. It is possible that the effects of enoximone are also dose-dependent. Furthermore, slow injection of PDE III inhibitors largely prevents hypotension compared to rapid bolus administration in humans (Barnard & Linter 1993). In our study, enoximone was administered over 1-2 minutes, which may have attenuated the drug's vasodilatory effects. As mentioned in the literature review, not only low

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$\dot{Q}_t$ , but also hypotension with decreased transmural pressures in the vessels of the muscles may be detrimental in horses. In this respect, it is beneficial that enoximone did not induce excessive vasodilation. It must also be noted that SVR is a general reflection of changes in (mainly) arteriolar tone throughout the body, but changes may differ between individual tissues. In humans, enoximone preferentially reduced limb vascular resistance and augmented blood flow to the peripheral musculoskeletal system (Leier et al. 1987). It would therefore be interesting to evaluate the effects of enoximone on local tissue perfusion, especially of the muscles, in horses.

Unlike SVR, RAP significantly decreased during at least 2 hours after administration of enoximone in the experimental part of this PhD. This may have been related to venous vasodilation (Grossman et al. 1998), causing a reduction in mean systemic filling pressure (Pmsf) and therefore venous pooling of blood. This could reduce venous return and  $\dot{Q}_t$ , especially in hypovolaemic horses where Pmsf is already low. However, since enoximone did not seem to affect SVR, which mainly reflects arteriolar tone, pronounced venous vasodilation seems rather unlikely. On the other hand, positive inotropic drugs shift the  $\dot{Q}_t$  curve upwards and to the left, such that the equilibrium point (the intersection of the cardiac output and venous return curves) is equally shifted upwards and to the left. The upward shift of the equilibrium point indicates increased venous return and  $\dot{Q}_t$ , while the left shift indicates a reduction in RAP (Power & Kam 2001). Therefore, the decrease in RAP was probably mainly attributable to the inotropic effects of enoximone.

Enoximone significantly increased HR, which is not always desirable with respect to myocardial oxygen balance and/or efficiency of the heart (work done per unit of energy used), especially when pre-existing HR is already high, e.g. due to hypotension induced by hypovolaemia, endotoxaemia, etc. When cardiac oxygen supply becomes inadequate, myocardial contractility will be lower (Jose & Stitt 1969, Nayler et al. 1971) and arrhythmias may occur (Senges et al. 1979, Hjalmarson 1980). However, the maximal increase in HR occurred 5 minutes after enoximone administration, with a mean difference to saline of  $7 \pm 1$  beats/min, which gradually decreased and became nonsignificant 40 minutes after administration, while the effects on SV and  $\dot{Q}_t$  lasted for 100 minutes. Consequently, the increase in HR appears to be primarily associated with bolus administration and might be less pronounced during a CRI of enoximone. Furthermore, no excessive tachycardia was noted during the study, and arrhythmias were not observed.

When enoximone was combined with low-dose dobutamine, additional increases in SV, HR and  $\dot{Q}t$  were observed in isoflurane anaesthetized ponies. When comparing to the reports on dobutamine administration in horses, it became clear that dobutamine's effects on SV and  $\dot{Q}t$  were more pronounced than would be expected at the dose given. This observation suggests that enoximone and dobutamine may have synergistic effects on SV and  $\dot{Q}t$  in ponies. Fortunately, such synergism was not observed for the effects on HR. During the first 40 minutes after enoximone administration, when HR was significantly higher than after saline administration, dobutamine did not significantly induce further increases in HR. It was only after this time, when HR started to decrease again in the enoximone group but remained constant in the group receiving enoximone and dobutamine, that the difference in HR between both groups became significant. This suggests that an infusion of dobutamine after a bolus of enoximone maintains the increase in HR seen after administration of enoximone alone, but does not significantly affect its magnitude. At the same time, no arrhythmias were observed.

Other beneficial effects of the combination of enoximone and dobutamine, compared to enoximone alone, were increases in blood pressure, RAP, packed cell volume (PCV) and  $DO_2$ . As outlined earlier, not only  $\dot{Q}t$ , but also blood pressure is important in maintaining peripheral tissue perfusion, especially in horses with a high bodyweight. The increase in blood pressure was caused by an increase in  $\dot{Q}t$ , since SVR was even slightly lower compared to enoximone treatment. Again, it would be interesting to see the effects of a combination of enoximone and dobutamine on muscle blood flow in anaesthetized horses. Right atrial pressure and PCV were higher during dobutamine administration, which may both be related to splenic contraction (Fuchs et al. 1980). Additionally, increased RAP may also have been the result of venoconstriction in response to dobutamine administration, due to the  $\alpha_1$  effects of dobutamine (Fuchs et al. 1980). The increase in PCV caused a significant increase in  $CaO_2$ . This, together with the increase in  $\dot{Q}t$ , explains the improvement in  $DO_2$ , which is of course highly desirable during cardiovascular support in horses.

The results of combining enoximone with calcium chloride were somewhat disappointing, but not unexpected given the data mentioned in literature. As explained in Chapter 1, inconsistent results have been reported regarding the cardiovascular effects of calcium salts in different species, which may be explained by differences in cardiovascular status, pre-existing serum calcium levels, etc. Furthermore, calcium salts did not produce any effects when combined with other inotropes, such as amrinone (Butterworth et al. 1992) and adrenaline

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(Royster et al. 1992), and even reduced the effects of dobutamine (Butterworth et al. 1992) and milrinone (Goyal & McNeill 1986).

Based on the experimental part of this PhD thesis, it was concluded that a single bolus of enoximone induced beneficial effects on cardiovascular performance in isoflurane anaesthetized healthy ponies, with rather long lasting increases in SV and  $\dot{Q}_t$ , without reducing blood pressure, overly increasing HR or producing other undesirable effects. These effects were not altered by additional administration of calcium chloride, but could be accentuated by infusing low doses of dobutamine after administration of enoximone, with at least additive but possibly even synergistic effects on SV and  $\dot{Q}_t$ , while increasing blood pressure,  $\text{CaO}_2$  and  $\text{DO}_2$ . Because of these encouraging results in experimental ponies, it was decided to investigate the cardiovascular effects of enoximone in a clinical study. Horses undergoing colic surgery were selected as study population, because many of these patients require pharmacological cardiovascular support.

The results of the clinical study in colic horses indicated that enoximone initially produced similar effects to those in experimental ponies, with increases in  $\dot{Q}_t$ , SV, HR and  $\text{DO}_2$  and a decrease in SVR 10 minutes after enoximone administration. However, most of these changes were less pronounced and of shorter duration compared to the ones observed under experimental (standardized) conditions in anaesthetized ponies. This may be related to several factors, including variability of the cardiovascular status of individual patients and other factors concurrently affecting cardiovascular performance, including surgical manipulations and administration of dobutamine and fluids, which possibly masked some of enoximone's effects. On the other hand, the effects of enoximone may have been limited by the presence of hypovolaemia, endotoxaemia or other factors which reduce the response to inotropes in colic horses. In humans, PDE III inhibitors are in fact avoided in patients with inadequate filling pressures, pre-existing severe vasodilation (Barnard & Linter 1993) or hypotension (Hall 1993). Simultaneous administration of vasopressors may even be needed to avoid hypotension (Barnard & Linter 1993).

Hypovolaemia in colic horses results from reduced intake and intestinal absorption of fluids, combined with (sometimes excessive) sweating and increased losses to the interstitium, intestinal lumen or intraperitoneal space (transudate or exudate). In hypovolaemic patients, inotropes are expected to be less effective because Pmsf, and therefore preload, is low. Consequently, in humans and small animals, fluid resuscitation is usually performed before



inotropes are administered. In anaesthetized horses, as indicated earlier, inotropes are often already administered during fluid resuscitation. Clinical experience suggests that dobutamine remains quite effective at improving cardiovascular function in these cases, despite incomplete restoration of the circulating volume. Possibly, enoximone is less effective in hypovolaemic animals.

Endotoxaemia also occurs frequently in colic horses, usually because the normal gut barrier function is lost in strangulated intestines. In those cases, circulating endotoxins induce hypotension by causing vasodilation, depressing myocardial contractility and reducing the response to  $\beta$ -agonistic inotropic drugs (Takeuchi et al. 1999). It might therefore be hypothesized that the effects of enoximone in the clinical study were reduced because endotoxaemia occurred in several horses. However, strangulation of some part of the intestines was only found in 19 of 48 horses in our clinical study, and certainly not all of these horses were endotoxaemic at the time of surgery. Furthermore, enoximone was able to restore myocardial contractility in human patients with severe and prolonged endotoxaemic shock, unresponsive to catecholamine and fluid administration (Ringe et al. 2003). The drug also prevented mucosal hypoperfusion despite the induction of hypotension during an early stage of sepsis (Schmidt et al. 2001). Based on these results, enoximone might even prove to be valuable in endotoxaemic horses with a low response to sympathomimetic drugs, although further studies are needed to confirm this hypothesis.

Based on the results of this PhD thesis, it can be concluded that enoximone is an effective inotrope in healthy equids, with few undesirable effects. These results are encouraging for future research. Since HR increased only initially after bolus administration of enoximone, it may be interesting to investigate whether this increase in HR can be avoided by administering the drug as a CRI. To establish suitable loading doses and infusion rates for such a CRI, pharmacokinetic and pharmacodynamic studies in anaesthetized horses are required. Also, enoximone's effects on tissue perfusion in horses remain unknown. Studies looking at the effects of enoximone on intramuscular blood flow, splanchnic perfusion, etc. in horses are therefore needed. When administered after enoximone, several of dobutamine's cardiovascular effects appeared to be more pronounced compared to previous reports, but a specifically designed study would be needed before synergism between both drugs can be confirmed with certainty. In view of the positive effects of enoximone in humans with endotoxaemia and/or sepsis, further studies under similar clinical conditions are also justified in horses. Other possible uses of enoximone would be to counteract the negative inotropic

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effects of other drugs administered in the perioperative period, mainly anaesthetics, and in the treatment of cardiac failure in horses or ponies.

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## SUMMARY

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In anaesthetized horses, the combined effects of recumbency, a high body weight, respiratory disturbances and cardiovascular depression often cause decreases in arterial oxygen content, blood pressure and cardiac output ( $\dot{Q}_t$ ). As a result, tissue oxygenation often becomes inadequate, which is one of the major factors contributing to the high death rate associated with anaesthesia in horses. Pulmonary ventilation-perfusion mismatching, which results in arterial hypoxaemia, is difficult to treat and most strategies using artificial ventilation have the propensity to compromise cardiovascular function. However, oxygen delivery to the tissues ( $DO_2$ ) can also be improved by optimizing tissue perfusion. Routine monitoring of the cardiovascular system during equine anaesthesia includes subjective clinical assessment, electrocardiography and measurement of heart rate (HR) and blood pressure. Although these techniques provide the anaesthetist with valuable information, measuring  $\dot{Q}_t$  would allow an even better estimation of  $DO_2$ . Most previously described techniques for  $\dot{Q}_t$  measurements in horses only provide intermittent values, are difficult to use routinely and/or were found to have low accuracy. However, pulse contour analysis (PulseCO<sup>®</sup>) appeared promising for use in horses, since it is a continuous, noninvasive and easily applicable method that was found to be quite accurate over prolonged periods of time in humans. The first aim of this PhD thesis was therefore to evaluate the reliability of the pulse contour analysis algorithm implemented in the LiDCO-Plus<sup>®</sup> monitor.

Once cardiovascular depression has been diagnosed, an appropriate treatment should be initiated. Reduction of anaesthetic depth and fluid therapy are often insufficient in anaesthetized horses and the use of cardiovascular stimulant drugs, such as antimuscarinics, inotropic drugs and vasopressors, is often needed. Antimuscarinic drugs increase HR and, for many reasons, are not suitable to augment  $\dot{Q}_t$  unless under specific circumstances. Vasopressors, such as vasopressin analogues, calcium salts and  $\alpha$ -sympathomimetics, are only useful when hypotension is caused by vasodilation, e.g. induced by drugs or endotoxins, while myocardial contractility and  $\dot{Q}_t$  are normal or even increased and vascular transmural pressure needs to be restored to maintain normal tissue perfusion. Inotropic drugs include digitalis glycosides,  $\beta$ -sympathomimetics, calcium salts, calcium sensitizers and phosphodiesterase

## Summary

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(PDE) III inhibitors. Most of these drugs increase the availability of calcium to the contractile apparatus of the cardiac muscle. Extensive research has been performed on the effects of  $\beta$ -sympathomimetics in horses. Many of these agents are suitable to be used as a constant rate infusion (CRI) during anaesthesia and effectively increase cardiac contractility, but some negative side effects can occur, including tachycardia, arrhythmias and in some cases undesirable vasoconstriction or vasodilation. Digitalis glycosides seem to be less useful for routine perioperative cardiovascular support in anaesthetized horses, because of unfavourable pharmacokinetic properties, toxicity and possibly lower efficacy in equine patients without cardiac disease. The effectiveness of calcium salts for cardiovascular support in horses varied between different studies and probably depends on different factors such as pre-existing serum calcium levels and degree of cardiovascular depression. Calcium sensitizers are quite expensive and long acting and are probably better used only in patients with cardiac disease. While PDE III inhibitors, i.e. inodilators, are potent inotropes with few important side effects during short-term use in humans, very little information is available on the use of these drugs in horses. In human medicine, milrinone and enoximone are nowadays the most widely used inodilatory PDE III inhibitors. Because the effects of milrinone, but not those of enoximone, had previously been described in horses, the second major aim of this PhD thesis was to evaluate the cardiovascular effects and possible side effects of enoximone in ponies under experimental conditions, alone or combined with dobutamine or calcium chloride. If beneficial, the drug's effectiveness during colic surgery in horses would be additionally evaluated.

In an experimental randomized cross-over study, 6 ponies were anaesthetized 4 times with a minimal interval of 3 weeks between treatments. Their age ranged between 4 and 6.5 years and body weight between 212 and 368 kg (mean bodyweight  $286 \pm 53$  kg). The ponies were sedated with romifidine [80  $\mu$ g/kg intravenously (IV)] and anaesthesia was induced with midazolam (0.06 mg/kg IV) and ketamine (2.2 mg/kg IV) and maintained with isoflurane in oxygen (FE Iso 1.7%). Normocapnia (PaCO<sub>2</sub> 4.66-6.00 kPa) was maintained using artificial ventilation. Ninety minutes after induction (=T0), the ponies received 1 of 4 treatments: slow IV administration of enoximone 0.5 mg/kg (E), an equivalent volume of saline (S), enoximone 0.5 mg/kg IV followed by a dobutamine CRI at 0.5  $\mu$ g/kg/min during the remaining period of anaesthesia (ED) or an infusion of calcium chloride 0.5 mg/kg/min from T5 until T15 (EC). On all occasions, cardiopulmonary function was monitored during 120 minutes after the end of enoximone administration. Heart rate, blood pressure and right atrial



pressure (RAP) were measured before treatment, every 5 minutes between T0 (treatment) and T30 and then every 10 minutes until T120. Before T0, the pulse contour analysis monitor was calibrated three times using the lithium dilution technique. Thereafter, no further recalibrations were performed. Cardiac output measurements (lithium dilution ( $\dot{Q}_{t_{LiDCO}}$ ) and pulse contour analysis ( $\dot{Q}_{t_{PulseCO}}$ ) techniques) and blood gas analysis (arterial and central venous samples) were performed before treatment and at T5, T10, T20, T40, T60, T80, T100 and T120. Stroke volume (SV), systemic vascular resistance ( $SVR_{LiDCO}$  and  $SVR_{PulseCO}$ ), venous admixture ( $\dot{Q}_s/\dot{Q}_t$ ) and  $DO_2$  were calculated. Additionally, for each pair of  $\dot{Q}_t$  measurements after T0, the absolute and relative differences between both techniques were calculated.

For all statistical analyses, a 5 % significance level was used. The differences between  $\dot{Q}_{t_{LiDCO}}$  and  $\dot{Q}_{t_{PulseCO}}$  in the saline group were analyzed using a paired t-test. Mixed models were used to evaluate whether these differences changed over time and whether they were influenced by the different treatments or by changes in HR, blood pressure, RAP, packed cell volume (PCV) and  $SVR_{LiDCO}$ . Additionally, bias and precision were documented using Bland-Altman plots and mean bias and limits of agreement between both techniques were calculated for each treatment group. The cardiopulmonary effects of enoximone were compared to those of the other treatments using a mixed model with treatment, time and their interaction as fixed categorical effects and pony as random effect, comparing the treatments both globally and at specific timepoints after treatment.

During treatment S, the limits of agreement between both  $\dot{Q}_t$  measurement techniques were wide and  $\dot{Q}_{t_{PulseCO}}$  was  $4.9 \pm 12.3$  % lower than  $\dot{Q}_{t_{LiDCO}}$  ( $P < 0.001$ ), while  $SVR_{PulseCO}$  was  $6.9 \pm 14.4$  % higher than  $SVR_{LiDCO}$  ( $P < 0.01$ ). These differences increased over time and were significantly larger during treatments E and ED. At the same time, the limits of agreement were wider during treatments E, ED and EC compared to treatment S. Furthermore, the differences between both techniques were significantly affected by changes in blood pressure. It was concluded from these results that the reliability of the pulse contour analysis algorithm was low in anaesthetized ponies, despite recent calibration and even under stable haemodynamic conditions, and became worse when haemodynamics changed.

Compared to saline treatment, enoximone induced significant increases in  $\dot{Q}_t$  and SV during 100 minutes and an increase in HR during 40 minutes. Right atrial pressure decreased during

## Summary

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at least 2 hours. Despite increases in  $\dot{Q}_s/\dot{Q}_t$ ,  $DO_2$  to the tissues was improved. Additional administration of dobutamine as a constant rate infusion caused further increases in  $\dot{Q}_t$  and SV, which were larger than previously reported with dobutamine infusions in horses and ponies, suggesting that enoximone might augment the inotropic potency of dobutamine. At the same time, the increase in HR seen after enoximone administration was maintained during the entire dobutamine infusion period, although the magnitude of this increase was not altered. Other effects of dobutamine administration were an increase in blood pressure, RAP, PCV and  $DO_2$ . In contrast to the findings with a dobutamine infusion, administration of calcium chloride did not have any detectable influence on the cardiovascular effects of enoximone in anaesthetized ponies. No clinically important adverse effects were noted during any of the treatments in this experimental study. Based on these results, it was concluded that a single bolus of enoximone is able to improve cardiac performance during almost 2 hours in isoflurane anaesthetized ponies, appears to be quite safe and can be combined with low doses of dobutamine when blood pressure needs to be increased or when more pronounced increases in  $\dot{Q}_t$  are desired.

Based on these beneficial results under experimental conditions, a prospective, randomized clinical trial was set up to investigate the cardiovascular effects of enoximone in anaesthetized colic horses undergoing emergency laparotomy. After sedation (xylazine 0.7 mg/kg) and induction (midazolam 0.06 mg/kg, ketamine 2.2 mg/kg), anaesthesia was maintained with isoflurane in oxygen and a lidocaine constant rate infusion (1.5 mg/kg, 2 mg/kg/h). All 48 horses were ventilated to maintain  $PaCO_2$  below 8.00 kPa. Dobutamine and/or colloids were administered when hypotension occurred. Ten minutes after skin incision, an intravenous bolus of enoximone (0.5 mg/kg) or an equivalent volume of saline was administered (= T0). Respiratory and arterial blood gases, HR, blood pressure and cardiac index (CI) were monitored. Systemic vascular resistance (SVR), stroke index (SI) and oxygen delivery index ( $DO_2I$ ) were calculated. For each variable, changes between baseline and T10 within each treatment group and/or colic type (small intestines, large intestines or mixed) were analyzed and compared between treatments in a fixed effects model. Differences between treatments and colic types until T30 were investigated using a mixed model. For all analyses, the significance level was set at 5 %.

Ten minutes after enoximone administration, CI ( $P=0.0010$ ), HR ( $P=0.0033$ ) and  $DO_2I$  ( $P=0.0007$ ) were higher and SVR lower ( $P=0.0043$ ) than at baseline. However, during the

first 30 minutes after enoximone treatment, only  $DO_2I$  ( $P=0.0224$ ) and HR ( $P=0.0003$ ) were higher than after saline administration. Furthermore, all differences were less pronounced and of shorter duration than in the experimental study in ponies. This may have been caused by variability of the cardiovascular status of individual colic horses, other factors affecting cardiovascular function (thus masking the effects of enoximone) or the presence of factors which possibly reduced the efficacy of enoximone, such as hypovolaemia or endotoxaemia.

One of the general conclusions that can be drawn from these studies is that the pulse contour analysis algorithm is of limited usefulness to estimate cardiac output in anaesthetized ponies. Secondly, enoximone is able to improve cardiac performance and appeared to be quite safe in anaesthetized ponies and colic horses. The drug can also be safely combined with low doses of a dobutamine infusion. This combination causes a more pronounced increase in cardiac function and results in a higher arterial pressure compared to enoximone administration alone. However, the cardiovascular effects of enoximone were less pronounced and of shorter duration in colic horses. Further studies evaluating the cardiovascular effects and influence on muscle perfusion of different doses of enoximone, administered as a bolus or as a constant rate infusion, the drug's pharmacokinetics and its efficacy under different clinical conditions, are warranted.



# SAMENVATTING

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Tijdens de anesthesie van paarden veroorzaken de gecombineerde effecten van decubitus, een hoog lichaamsgewicht, ademhalingsproblemen en cardiovasculaire depressie vaak een duidelijke daling in het arterieel zuurstofgehalte, de bloeddruk en het hartdebiet ( $\dot{Q}t$ ). Dit kan leiden tot onvoldoende zuurstofvoorziening van de weefsels, wat één van de belangrijkste factoren is die bijdragen tot de hoge sterftepercentages tijdens of kort na de anesthesie van paarden. Een slecht evenwicht tussen ventilatie en perfusie van de longen is moeilijk te corrigeren en de meeste beademingstechnieken die men hiervoor gebruikt onderdrukken in meer of mindere mate de functie van het cardiovasculair systeem. De zuurstofvoorziening van de weefsels kan echter ook verbeterd worden door de weefseldoorbloeding te optimaliseren. Voor routine monitoring van het cardiovasculair systeem tijdens de anesthesie wordt bij paarden doorgaans gebruik gemaakt van subjectieve klinische beoordeling, electrocardiografie en het meten van de hartfrequentie (HR) en de bloeddruk. Alhoewel deze technieken waardevolle informatie opleveren, zou het meten van het hartdebiet een nog betere inschatting van de zuurstofvoorziening van de weefsels mogelijk maken. De meeste technieken die beschreven zijn om  $\dot{Q}t$  te bepalen bij paarden laten alleen intermitterende metingen toe, zijn moeilijk routinematig te gebruiken en/of zijn weinig betrouwbaar. Het nieuwe algoritme voor het analyseren van de arteriële bloeddrukgolven van de LiDCO-Plus<sup>®</sup> monitor leek echter veelbelovend voor gebruik bij paarden, aangezien het een continue, non-invasieve en eenvoudig te gebruiken methode is, die vrij accuraat bleek te zijn over lange periodes in de humane geneeskunde. De eerste doelstelling van deze doctoraatsthesis was dan ook de betrouwbaarheid na te gaan van het algoritme waarmee de LiDCO-Plus<sup>®</sup> monitor veranderingen in  $\dot{Q}t$  schat op basis van de arteriële bloeddruk golf.

Eens cardiovasculaire depressie vastgesteld is, moet een gepaste behandeling ingesteld worden. Het verminderen van de diepte van de anesthesie en toedienen van vloeistoffen volstaan vaak niet bij paarden, zodat farmaca met een stimulerend effect op het cardiovasculair systeem, zoals antimuscarinica, inotropica en vasopressoren vaak nodig zijn. Antimuscarinica verhogen de hartfrequentie en zijn om vele redenen niet geschikt om het

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hartdebiet te verhogen, tenzij onder zeer specifieke omstandigheden. Vasopressoren, zoals vasopressine analogen, calciumzouten en  $\alpha$ -sympathicomimetica, zijn enkel nuttig wanneer hypotensie veroorzaakt wordt door vasodilatatie, bv. uitgelokt door farmaca of endotoxines, terwijl de myocardiale contractiliteit en  $\dot{Q}_t$  normaal of zelfs verhoogd zijn en de transmurale druk in de bloedvaten verhoogd moet worden om de perfusie van de weefsels in stand te houden. Bij de inotropica horen de digitalis glycosides,  $\beta$ -sympathomimetica, calciumzouten, calcium 'sensitizers' en phosphodiesterase (PDE) III inhibitors. De meeste van deze producten veroorzaken een inotropie effect door de beschikbaarheid van calcium voor het contractiele apparaat van de hartspier te verhogen. Uitgebreid onderzoek werd reeds uitgevoerd aangaande de effecten van  $\beta$ -sympathomimetica bij paarden. Vele leden van deze groep zijn geschikt voor gebruik als continu infuus tijdens de anesthesie en zijn vrij effectief om de contractiliteit van het hart te verhogen, maar kunnen ook neveneffecten veroorzaken, zoals tachycardie, aritmieën en in sommige gevallen overmatige vasoconstrictie of vasodilatatie. Digitalis glycosides lijken minder nuttig voor routine cardiovasculaire ondersteuning van paarden tijdens de anesthesie, omwille van ongunstige farmacokinetische eigenschappen, toxiciteit en een mogelijks lagere efficaciteit bij paarden zonder hartproblemen. Het effect van calciumzouten voor cardiovasculaire ondersteuning bij paarden varieerde tussen verschillende studies en hangt wellicht af van verschillende factoren zoals de calciumconcentratie in het serum en de graad van cardiovasculaire depressie. Calcium sensitizers zijn vrij duur, werken lang en worden waarschijnlijk beter gereserveerd voor patiënten met hartfalen. Phosphodiesterase III inhibitors of zogenoemde inodilatoren zijn potente inotropica met relatief weinig belangrijke neveneffecten wanneer ze gebruikt worden voor korte periodes bij mensen. Toch is er zeer weinig informatie voorhanden over het gebruik van deze farmaca bij het paard. In de humane geneeskunde zijn milrinone en enoximone momenteel de meest gebruikte inodilatorische PDE III inhibitors. Omdat de effecten van milrinone, maar niet deze van enoximone, reeds beschreven waren bij paarden, was de tweede algemene doelstelling van dit doctoraatswerk de cardiovasculaire effecten en eventuele neveneffecten van enoximone te onderzoeken bij pony's, onder experimentele omstandigheden, alleen of gecombineerd met dobutamine of calcium chloride. Indien de resultaten gunstig waren zou de efficaciteit van enoximone voor het verhogen van het hartdebiet tijdens koliekchirurgie bij paarden bestudeerd worden.

In een experimentele, gerandomiseerde cross-over studie, werden 6 pony's 4 keer onder anesthesie gebracht, met een interval van minimum 3 weken tussen elke behandeling. De

dieren waren tussen 4 en 6,5 jaar oud en hun lichaamsgewicht varieerde tussen 212 en 368 kg (gemiddeld  $286 \pm 53$  kg). Na sedatie met romifidine [ $80 \mu\text{g}/\text{kg}$  intraveneus (IV)] en inductie met midazolam ( $0.06 \text{ mg}/\text{kg}$  IV) en ketamine ( $2.2 \text{ mg}/\text{kg}$  IV), werd de anesthesie onderhouden met isofluraan in zuurstof (FE<sub>Iso</sub> 1.7%). Aan de hand van kunstmatige beademing werd er gezorgd voor normocapnie ( $\text{PaCO}_2$  4.66-6.00 kPa). Negentig minuten na de inductie (= T0) werd 1 van de 4 behandelingen toegediend: trage IV toediening van enoximone  $0.5 \text{ mg}/\text{kg}$  (E), een equivalent volume fysiologische zoutoplossing (S), enoximone  $0.5 \text{ mg}/\text{kg}$  IV gevolgd door een dobutamine infuus aan  $0.5 \mu\text{g}/\text{kg}/\text{min}$  gedurende het verder verloop van de anesthesie (ED) of een infuus met calcium chloride aan  $0.5 \text{ mg}/\text{kg}/\text{min}$  van T5 tot T15 (EC). De cardiopulmonaire functie werd telkens opgevolgd gedurende 120 minuten na het einde van de toediening van enoximone. De HR, bloeddruk en rechter atriale druk (RAP) werden gemeten voor de behandeling, om de 5 minuten tussen T0 (behandeling) en T30 en daarna om de 10 minuten tot T120. Vóór T0 werd de ‘Pulse contour analysis’ (PulseCO) software drie maal gecalibreerd met behulp van de lithium-dilutietechniek (LiDCO). Daarna werden geen verdere calibraties meer uitgevoerd over het verloop van de studie. De metingen van het hartdebiet (lithium dilutie ( $\dot{Q}_{\text{tLiDCO}}$ ) en pulse contour analysis ( $\dot{Q}_{\text{tPulseCO}}$ ) technieken) en bloedgas-analyses (arteriële en centraal veneuze stalen) werden uitgevoerd vóór de behandeling en op T5, T10, T20, T40, T60, T80, T100 and T120. Het slagvolume (SV), de systemisch vasculaire weerstand ( $\text{SVR}_{\text{LiDCO}}$  en  $\text{SVR}_{\text{PulseCO}}$ ), het percentage veneuze bijmenging ( $\dot{Q}_s/\dot{Q}_t$ ) en de zuurstofvoorziening ( $\text{DO}_2$ ) werden berekend. Bijkomend werden voor elk paar  $\dot{Q}_t$  metingen na T0 de absolute en relatieve verschillen tussen beide technieken bepaald.

Voor alle statistische analyses werd een significantieniveau van 5 % aangehouden. De verschillen tussen  $\dot{Q}_{\text{tLiDCO}}$  en  $\dot{Q}_{\text{tPulseCO}}$  tijdens de placebo behandeling werden geanalyseerd met een gepaarde t-test. Mixed model variantie-analyse werd gebruikt om te evalueren of deze verschillen veranderden over de tijd en of ze beïnvloed werden door de verschillende behandelingen of door de HR, bloeddruk, RAP, hematocriet (PCV) of  $\text{SVR}_{\text{LiDCO}}$ . Bijkomend werden de accuraatheid en precisie gedocumenteerd op basis van Bland-Altman plots en berekeningen van de gemiddelde bias en zogenaamde ‘grenzen van overeenkomst’ (limits of agreement) tussen de beide technieken tijdens de verschillende behandelingen. De cardiopulmonaire effecten van enoximone werden vergeleken met deze van de andere behandelingsprotocols op basis van een mixed model met behandeling, tijd en hun interactie

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als vaste categorische effecten en pony als random effect, waarbij de verschillen zowel globaal als op specifieke tijdstippen geanalyseerd werden.

Tijdens behandeling S werden wijde limits of agreement gevonden tussen de  $\dot{Q}_{\text{LiDCO}}$  en  $\dot{Q}_{\text{PulseCO}}$  waarden. Bovendien was  $\dot{Q}_{\text{PulseCO}}$   $4.9 \pm 12.3$  % lager dan  $\dot{Q}_{\text{LiDCO}}$  ( $P < 0.001$ ), terwijl  $\text{SVR}_{\text{PulseCO}}$   $6.9 \pm 14.4$  % hoger was dan  $\text{SVR}_{\text{LiDCO}}$  ( $P < 0.01$ ). Deze verschillen werden geleidelijk groter tijdens het verloop van de studie en waren significant hoger tijdens behandelingen E en ED. Daarnaast waren de limits of agreement wijder tijdens behandelingen E, ED en EC dan tijdens behandeling S. Er werd eveneens vastgesteld dat veranderingen in de bloeddruk de verschillen tussen de twee meettechnieken beïnvloedden. Uit deze resultaten werd afgeleid dat het PulseCO algoritme bij pony's weinig betrouwbaar is, ondanks recente calibratie en zelfs onder haemodynamisch stabiele omstandigheden. Wanneer er medicatie toegediend werd met een invloed op het cardiovasculair systeem verminderde de betrouwbaarheid verder.

Vergeleken met de placebo behandeling veroorzaakte enoximone een significante stijging van  $\dot{Q}_t$  en SV gedurende 100 minuten en een stijging van HR gedurende 40 minuten. De RAP daalde gedurende minstens 2 uur. Ondanks een stijging van de  $\dot{Q}_s/\dot{Q}_t$  was de  $\text{DO}_2$  hoger. Bijkomende toediening van dobutamine als continu infuus zorgde voor een verdere stijging van  $\dot{Q}_t$  en SV, waarbij deze stijging meer uitgesproken was dan voorheen gerapporteerd met het gebruik van dobutamine aan vergelijkbare of zelfs hogere dosissen bij pony's en paarden. Het is daarom mogelijk dat enoximone de inotrope eigenschappen van dobutamine versterkt. Terzelfdertijd bleef de HR gedurende de volledige periode waarin dobutamine toegediend hoger dan tijdens behandeling S, alhoewel deze stijging kwantitatief niet groter was dan tijdens behandeling E. Andere effecten van het toedienen van dobutamine waren een stijging van de bloeddruk, RAP, PCV en  $\text{DO}_2$ . Daarentegen had toediening van calcium chloride geen enkele invloed op de effecten van enoximone bij pony's. Er werden trouwens geen klinisch belangrijke neveneffecten vastgesteld na toediening van enoximone in de experimentele studie. Uit deze resultaten werd afgeleid dat een enkele bolus enoximone in staat is het slagvolume en hartdebiet gedurende bijna 2 uur te verhogen bij pony's tijdens algemene anesthesie met isofluraan, vrij veilig lijkt te zijn en ook gecombineerd kan worden met een lage dosis dobutamine wanneer de arteriële bloeddruk moet verhoogd worden of wanneer een meer uitgesproken stijging van het hartdebiet nodig is.



Op basis van de gunstige resultaten onder experimentele omstandigheden werd een prospectieve, gerandomiseerde klinische studie uitgevoerd om de cardiovasculaire effecten van enoximone te bestuderen tijdens koliekchirurgie bij paarden. Na sedatie (xylazine 0.7 mg/kg) en inductie (midazolam 0.06 mg/kg, ketamine 2.2 mg/kg) werd de anesthesie onderhouden met isofluraan in zuurstof en een continu lidocaïne-infuus (1.5 mg/kg, 2 mg/kg/h). Alle 48 paarden werden kunstmatig beademd om de PaCO<sub>2</sub> lager dan 8.00 kPa te houden. Dobutamine en/of colloïden werden toegediend in geval van hypotensie. Tien minuten na incisie van de huid werd een intraveneuze bolus enoximone (0.5 mg/kg) of eenzelfde volume fysiologische zoutoplossing toegediend (= T0). Respiratoire en arteriële bloed-gassen, HR, bloeddruk en het hartdebiet per kg lichaamsgewicht (cardiac index, CI) werden opgevolgd. Verder werden ook de systemisch vasculaire weerstand (SVR), slagvolume index (SI) en zuurstofvoorzieningsindex (DO<sub>2</sub>I) berekend. Voor elke variabele werd het verschil bekeken tussen de waarden op T10 en deze net voor de toediening van enoximone, om vervolgens deze verschillen te vergelijken tussen de 2 behandelingen en tussen de verschillende koliektypes (dunne darm, dikke darm of gemengd), aan de hand van variantie-analyse ('vast effect' model). De waardes tot T30 van de beide behandelingen en de drie koliektypes werden eveneens met elkaar vergeleken aan de hand van variantie-analyse (gemengd model). Voor alle analyses werd een significantieniveau van 5 % aangehouden.

Tien minuten na de toediening van enoximone waren de CI (P=0.0010), HR (P=0.0033) en DO<sub>2</sub>I (P=0.0007) hoger en SVR lager (P=0.0043) dan op T0. Daarentegen waren alleen DO<sub>2</sub>I (P=0.0224) en HR (P=0.0003) tijdens de eerste 30 minuten na behandeling met enoximone hoger dan na de placebobehandeling. Bovendien waren alle verschillen minder uitgesproken en van kortere duur dan in de experimentele studie bij pony's. Dit kan te wijten zijn aan de variabiliteit van de cardiovasculaire status van individuele koliekpaarden, andere factoren die een effect hadden op het cardiovasculair systeem (en zo de effecten van enoximone maskeerden) of factoren die mogelijks de efficaciteit van enoximone verminderden, zoals hypovolemie of endotoxemie.

Eén van de algemene conclusies van deze studies is dat het PulseCO algoritme van de LiDCO-Plus<sup>®</sup> monitor weinig betrouwbaar is om veranderingen in het hartdebiet te schatten bij pony's tijdens de anesthesie. Daarnaast werd vastgesteld dat enoximone de hartfunctie stimuleert en vrij veilig lijkt te zijn bij pony's en koliekpaarden, ook wanneer gecombineerd met lage doses van een dobutamine-infuus. Deze combinatie leidt tot een sterkere stijging van

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het slagvolume en het hartdebiet en een hogere arteriële bloeddruk vergeleken met toediening van enoximone alleen. Anderzijds waren de cardiovasculaire effecten van enoximone minder uitgesproken en van kortere duur bij koliekpaarden. Verdere studies die de cardiovasculaire effecten en de invloed op de spierperfusie van verschillende doses enoximone nagaan, toegediend als een bolus of als continu infuus, evenals studies die de farmacokinetiek van enoximone bij paarden en de efficaciteit van deze molecule onder verschillende omstandigheden onderzoeken, zijn aangewezen.

# CURRICULUM VITAE

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Stijn Schauvliege werd geboren op 13 september 1978 te Brugge. Na het beëindigen van het secundair onderwijs aan het Onze-Lieve-Vrouwecollege in Assebroek, richting Latijn-Wiskunde, is hij in 1996 gestart met de studies Diergeneeskunde aan de Universiteit van Gent en behaalde in 2002, met grote onderscheiding, het diploma van dierenarts.

Na een jaar internship aan de Faculteit Diergeneeskunde te Merelbeke trad hij in oktober 2003 in dienst bij de Vakgroep Heelkunde en Anesthesie van de Huisdieren als voltijds assistent, waar zijn taak voornamelijk bestond uit het verzorgen van de anesthesie van paarden en herkauwers en het geven van klinisch onderricht aan de studenten diergeneeskunde onder leiding van Prof. Dr. F. Gasthuys. Hij verrichtte eveneens geregeld chirurgische ingrepen bij herkauwers en nam deel aan de nacht- en weekenddiensten van de vakgroep. Daarnaast verleende hij medewerking aan wetenschappelijk onderzoek door verschillende andere vakgroepen, faculteiten en externe firma's en voerde vanaf 2004 zelf wetenschappelijk onderzoek uit naar de diagnose, behandeling en preventie van cardiovasculaire depressie tijdens de anesthesie bij paarden, wat leidde tot deze doctoraatsstudie. Omwille van zijn interesse voor anesthesie werd hij lid van de Association of Veterinary Anaesthetists (AVA), nam deel aan de meeste activiteiten van deze organisatie en startte, parallel met zijn doctoraatsonderzoek, in april 2004 met een residencyprogramma bij de European College of Veterinary Anaesthesia and Analgesia (ECVAA). Na deze opleiding nam hij in 2009 met succes deel aan het ECVAA examen en verkreeg dan ook de titel Diplomate ECVAA.

Stijn Schauvliege is auteur of mede-auteur van verschillende wetenschappelijke publicaties, was spreker op 6 internationale congressen en won de prijs voor de beste orale presentatie door een resident op de AVA congressen in Parijs (2007) en Helsinki (2009, 2<sup>e</sup> plaats) en de Langley prijs voor de beste publicatie in Veterinary Anaesthesia and Analgesia in 2009.



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