Effects of dobutamine on cardiac index and arterial blood pressure in isoflurane-anaesthetized horses under clinical conditions

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Volatile agent-induced hypotension may contribute to anaesthetic-related morbidity and mortality in horses. Dobutamine is commonly used to support arterial blood pressure (ABP) but little is known about its cardiovascular effects under clinical conditions. The aim of this clinical study was to elucidate the relationship between cardiovascular function and dobutamine infusion in isoflurane-anaesthetized horses. Forty-four horses anaesthetized for a variety of surgical procedures were studied. Premedication with acepromazine, methadone and detomidine was followed by induction of anaesthesia with ketamine and midazolam. Anaesthesia was maintained with isoflurane vaporized in oxygen. Routine anaesthetic monitoring was applied and cardiac output was measured by lithium dilution. Dobutamine was infused to maintain mean ABP above 70 mmHg. The relationship between dobutamine infusion rate, heart rate (HR), ABP and cardiac index was investigated immediately prior to (T_0) and 15 min (T_1) after dobutamine infusion started, followed at 30 min intervals (T_2, etc.). Arterial blood pressure increased significantly after dobutamine infusion started, HR and cardiac index increased significantly only with dobutamine infusion in combination with surgical stimulus. Although isoflurane decreases blood pressure mainly by vasodilation, dobutamine is an effective treatment for hypotension under clinical conditions in isoflurane-anaesthetized horses. The effect of dobutamine is not directly proportional to dose and surgical stimulus probably contributes to the cardiovascular improvement.

INTRODUCTION

Anaesthesia-related mortality in horses lies between 0.12% and 0.9% (Johnston *et al.*, 2002; Bidwell *et al.*, 2007). Major causes are cardiac arrest, post-operative cardiovascular collapse, post-operative fractures and myopathy. One of the proposed reasons for this high mortality rate is the cardiovascular depression caused by volatile anaesthetic agents (Johnston *et al.*, 2002). Of these agents, isoflurane is the most commonly used; in common with other volatile agents it decreases cardiac output but vasodilation also makes a substantial contribution to the hypotension (Steffey & Howland, 1980). There is a close association between hypotension during anaesthesia and the development and severity of postoperative myopathy in horses (Grandy *et al.*, 1987; Lindsay *et al.*, 1989; Richey *et al.*, 1990; Young & Taylor, 1993). Dobutamine, a synthetic positive inotrope, is widely used to treat the anaesthetic-induced hypotension in conjunction with intravenous fluid therapy and minimizing the delivered concentration of volatile agent. Although clinical treatment of hypotension during anaesthesia has not been shown to alter the recovery quality or incidence of post-anaesthetic myopathy, the severity of myopathy is markedly reduced (Young & Taylor, 1993). The cardiovascular responses to dobutamine in anaesthetized horses have been extensively examined under laboratory conditions (Swanson *et al.*, 1985; Dyson & Pascoe, 1990; Gasthuys *et al.*, 1991; Wertz *et al.*, 1992; Lee *et al.*, 1998; Young *et al.*, 1998; Raisis *et al.*, 2000a). However, there is still a paucity of information available on the cardiovascular effects of dobutamine under clinical conditions where it is titrated to effect to treat hypotension, rather than administered at fixed rates often in the absence of low blood pressure.

This study aimed to investigate the effect of dobutamine on the relationship between cardiac index and arterial blood pressure (ABP) in isoflurane-anaesthetized horses under clinical conditions. The study was conducted with local ethical committee approval.

MATERIALS AND METHODS

Forty-four healthy horses were anaesthetized for a variety of procedures, of which the majority was arthroscopy (Table 1). Feed was withheld overnight but water was available *ad libitum* until pre-anaesthetic medication which consisted of an intramuscular (i.m.) injection of 0.03 mg/kg acepromazine (ACP Injection; Novartis Animal Health, Litlington, UK). Thirty minutes later, 20 000 IU/kg Na-benzyl penicillin (Benzylpenicilline Natrium; Eurovet Animal Health BV, Bladel, the Netherlands) and 1.1 mg/kg flunixin meglumine (Finadyne®; Intervet/Schering-Plough Animal Health, Brussels, Belgium) were administered intravenously (i.v.) after sedation was achieved with an i.v. injection of 10 μg/kg detomidine (Domidine®; Eurovet Animal Health BV) and 0.1 mg/kg methadone (Methadone HCL; Eurovet Animal Health BV). A 14G, 13.75 cm catheter (Abbocath®-T; Hospira, Donegal Town, Ireland) was aseptically placed in a jugular vein and the horse clipped and prepared for surgery. If sedation had waned, additional detomidine (3 μg/kg, i.v.) was given 5 min before induction. A venous

Table 1. Details of the horses and procedures

Total number of horses	44
Median body mass (kg)	511
Range	156–640
Median age (years)	5
Range	1–22
Gender	
Mares	17
Entire males	13
Geldings	14
Breed	
Warmblood	30
Friesian	3
Arab	3
Pony	3
Irish Cob	2
Thoroughbred	1
Welsh Section K	1
Welsh Cob	1
Procedures	
Arthroscopy	23
Annular ligament release via tenoscopy	7
Distal metatarsal II or IV removal	4
Castration	3
Skin transplantation	2
Ultrasound adductor muscles	1
M2 extraction mandible	1
Septic bursitis treatment, tenoscopy	1
Tumour removal	2

blood sample was collected immediately before induction for determination of sodium concentration (Vetlyte® analyzer; IDEXX Laboratories, ME, USA) and haematocrit (high speed micro-capillary centrifuge; Tomy Kogyoto, Tokyo, Japan), as required for lithium dilution cardiac output measurement.

Anaesthesia was induced with i.v. 0.06 mg/kg of midazolam (Dormicum®; Roche Nederland BV, Woerden, the Netherlands) and 2.2 mg/kg of ketamine (Ketamine 100 Inj.; AST Pharma BV, Oudewater, the Netherlands). After endotracheal intubation, the horses were hoisted onto a padded operating table. Anaesthesia was maintained with isoflurane (Isoflo™; Abbott Animal Health Laboratories Ltd, Queenborough, UK) vaporized in oxygen, administered via a large animal circle breathing system (Medec Holland BV, Wormerveer, the Netherlands). Sixteen horses were placed in lateral and 28 in dorsal recumbency. Fresh gas flow was set at 20 mL·kg/min for the first 30 min, followed by 10 mL·kg/min for the remainder of the anaesthetic period. Vaporizer settings were adjusted to maintain an adequate depth of anaesthesia. If necessary, ketamine (0.1–0.2 mg/kg, i.v.) was given to deepen anaesthesia rapidly. Intravenous crystalloids (Ecobag® Ringer or NaCl 0.9%; B Braun, Melsungen, Germany) were infused at approximately 10 mL·kg/h. Lungs of all patients were ventilated (Smith Respirator; BDO Medipass, Veterinary Technics Int., Katwijk, the Netherlands) to maintain an end-tidal carbon dioxide tension (EtCO$_2$) between 40–50 mmHg (5.3–6.6 kPa). Heart rate (HR), electrocardiogram (Monitor 78342A; Hewlett Packard, Boeblinger, Germany), respiratory rate and EtCO$_2$ (Anästhesiegasmonitor Typ 1304; Brüel & Kjaer, Naerum, Denmark) were monitored continuously. Systolic, mean and diastolic arterial blood pressure (SAP, MAP and DAP, respectively) were measured via a catheter (Optiva®; Medex Medical Ltd., Rossendale, UK) placed in a superficial artery, connected via a strain gauge pressure transducer (Edwards Lifesciences GmbH, Unterschleissheim, Germany) to a monitor (Minimon 7132B; Kontron Instruments Ltd., UK). Zero point was taken at the level of the shoulder for dorsal recumbency and the sternum for lateral recumbency. When MAP was below 70 mmHg, an i.v. infusion of dobutamine hydrochloride (Dobutamine Concentrate; Hameln Pharmaceuticals Ltd, Gloucester, UK), diluted to 250 μg/mL in normal saline, was started at 0.5 μg·kg/min (Flo-Gard® 6201 Volumetric Infusion Pump; Baxter Health Care Ltd., Thetford, UK). Dobutamine infusion rate (DIR) was increased every 5 min until MAP was above 70 mmHg, thereafter dobutamine was infused to effect to maintain MAP at or above this value. Cardiac output (CO) was measured by lithium dilution (Linton *et al.*, 2000) (LiDCO; LiDCO Ltd, London, UK), using 1.5 M lithium chloride (Lithium Chloride Injection; The Ipswich Hospital, Pharmacy Manufacturing Unit, Ipswich, UK). An arterial blood sample for blood gas analysis was taken 1 h after induction (i-STAT Portable Clinical Analyzer; Heska Corporation, Waukesha, WI, USA; with i-STAT® CG8+ cartridges; Abbott, East Windsor, WI, USA). CO was measured immediately prior to (T_0) and 15 min (T_1) after dobutamine infusion started, then at 30 min intervals (T_2, etc.). Measurements were postponed for at least 10 min after any ketamine injection as this interferes with

the lithium electrode signal (P.M. Taylor, unpublished observations). Cardiac index was calculated as CO/kg bodyweight).

Power calculations based on unpublished data indicated that 40 horses were required to detect a 10% change in cardiac index with a power of 90%. The Kruskal–Wallis test was used to examine differences in cardiac index, ABP and HR at each time point. Differences were further examined by Dunn's test for multiple comparison. Correlation between ABP, cardiac index and DIR was examined by Pearson's correlation test; $P < 0.05$ was considered significant. Data are given as mean ± SD unless otherwise stated.

RESULTS

Time from acepromazine administration to detomidine/methadone sedation was 33 ± 28 min; a further 46 ± 21 min elapsed before induction. Additional detomidine (3.8 ± 1.2 μg/kg, i.v.) was administered to 23 patients. Six horses received ketamine supplements prior to hoisting onto the operating table (0.5–1.5 mg/kg, i.v.). Two horses received additional ketamine (0.15 mg/kg, i.v.) between T_0 and T_2. Of the 44 horses, 43 received dobutamine.

T_0 was 26 ± 12 min after induction. Dobutamine infusion was started 29 ± 13 min after induction; T_1 was 17 ± 4 min and T_2 50 ± 14 min after the infusion started. Anaesthesia lasted 99 ± 34 min; time from induction to the start of surgery was 44 ± 12 min. In 31 horses, surgery started after T_1; at T_2 surgery had begun in all horses. Arterial blood gas analysis revealed 10 horses with an arterial carbon dioxide tension (P_aCO_2) below 45 mmHg (34.9–44.7 mmHg) but none above 55 mmHg; arterial oxygen tension (P_aO_2) ranged from 229–560 mmHg. No cardiac arrhythmias were detected.

At T_3, only seven horses were still undergoing surgery, hence data collected beyond T_2 were not analyzed. In one horse (cardiac index 38.5 mL·kg/min, MAP 46 mmHg and HR 41 beats per minute (BPM) at T_0), both HR and MAP increased markedly (up to 67 BPM and 93 mmHg, respectively) within 10 min of the start of dobutamine infusion (0.5 μg·kg/min). Infusion was terminated before another CO reading was prepared; therefore this horse was excluded from the analysis after T_0.

Between T_0 and T_2, ABP increased significantly ($P < 0.05$); HR ($P = 0.0002$) and cardiac index ($P = 0.0001$) increased significantly between T_1 and T_2. There was no significant difference in DIR between T_1 and T_2 (Table 2).

There was negative correlation between HR and DIR at T_2 ($P = 0.039$; $r = -0.37$) and between MAP and DIR at T_1 ($P = 0.006$; $r = -0.5$) and T_2 ($P = 0.0068$; $r = -0.47$) (Figs 1 and 2).

Breakdown of the results into lateral and dorsal positioning revealed that at T_0, T_1 and T_2 MAP was significantly higher in laterally than in dorsally recumbent horses ($P < 0.0001$ for T_0 and T_1; $P = 0.0067$ for T_2) (Fig. 3). At T_0 only, cardiac index was significantly higher in laterally than in dorsally recumbent horses ($P = 0.028$). At both T_1 and T_2, DIR was significantly

Table 2. Cardiovascular parameters and dobutamine infusion rate (mean ± SD) in 43 horses anaesthetized with isoflurane for clinical procedures, receiving dobutamine to maintain mean arterial blood pressure >70 mmHg

	T_0	T_1	T_2
DAP (mmHg)	41 ± 14	54 ± 11*	68 ± 12*,†
MAP (mmHg)	53 ± 13	68 ± 11*	83 ± 12*,†
SAP (mmHg)	77 ± 18	100 ± 13*	113 ± 16*,‡
HR (BPM)	34 ± 5	33 ± 5	40 ± 9§
CARDIAC INDEX (mL·kg/min)	47 ± 10	54 ± 11	73 ± 21*,†
DIR (μg·kg/min)	–	1.1 ± 0.6	1.0 ± 0.9

T_0: 26 ± 12 min after induction, before start dobutamine infusion. T_1: 17 ± 4 min after start of dobutamine infusion. T_2: 50 ± 14 min after start of dobutamine infusion.
*Significantly different from T_0 ($P = 0.0001$); †Significantly different from T_1 ($P = 0.0001$); ‡Significantly different from T_1 ($P = 0.0004$); §Significantly different from T_0 and T_1 ($P = 0.0002$).
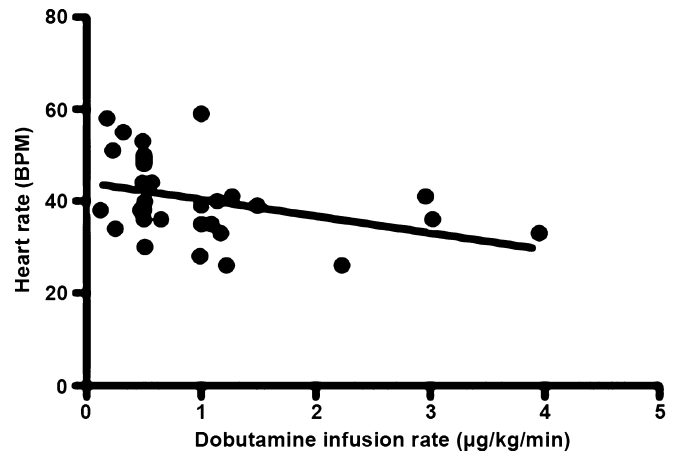

Fig. 1. Correlation between heart rate and DIR in 43 horses anaesthetized with isoflurane for clinical procedures, receiving dobutamine to maintain mean arterial blood pressure >70 mmHg, at T_2 (50 ± 14 min after start of dobutamine infusion); $P = 0.039$; $r = -0.37$.
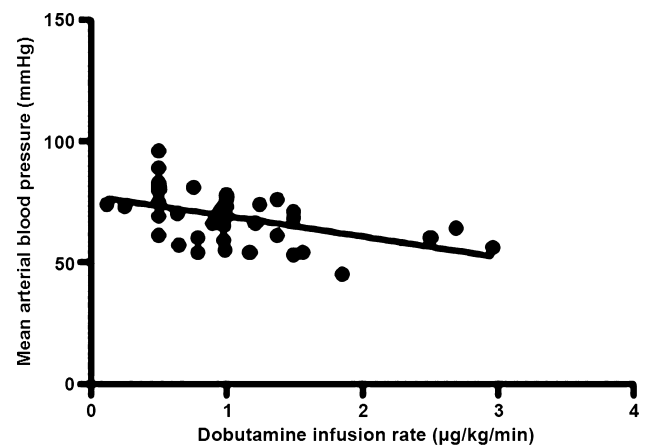

Fig. 2. Correlation between mean arterial blood pressure and DIR in 43 horses anaesthetized with isoflurane for clinical procedures, receiving dobutamine to maintain mean arterial blood pressure >70 mmHg, at T_1 (17 ± 4 min after start of dobutamine infusion); $P = 0.006$; $r = -0.5$.
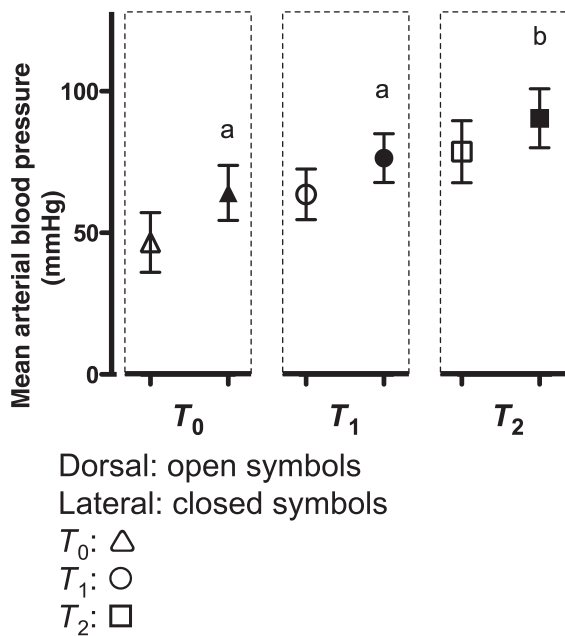
Fig. 3. Effect of recumbency on the mean arterial blood pressure in 43 horses anaesthetized with isoflurane for clinical procedures, receiving dobutamine to maintain mean arterial blood pressure >70 mmHg. T_0: 26 ± 12 min after induction, before start dobutamine infusion. T_1: 17 ± 4 min after start of dobutamine infusion. T_2: 50 ± 14 min after start of dobutamine infusion. (a) $P < 0.0001$; (b) $P = 0.0067$.

higher in dorsally than in laterally recumbent horses ($P = 0.003$ and $P = 0.039$, respectively).

Compared with the whole group, no significant differences were found in cardiovascular values between horses which received extra detomidine before induction or in those whose surgery had started before T_1. All horses recovered from anaesthesia without complications.

DISCUSSION

Postoperative myopathy results from ischaemic damage to muscles underperfused during recumbency. Hypotension, pressure within muscle compartments and restricted venous drainage may all be responsible (Taylor & Clarke, 2007). Richey et al. (1990) reported significant correlation between both magnitude and duration of hypotension and the incidence of post-anaesthetic lameness in horses undergoing clinical anaesthesia. Normotensive horses (MAP > 70 mmHg) had a significantly lower incidence of post-anaesthetic lameness than hypotensive horses (MAP < 70 mmHg). Blood pressure is commonly supported in clinical equine anaesthesia with dobutamine, an inotropic agent available as a racemic mixture. Its (−)-enantiomer is a relatively potent α-adrenergic and weaker β_1- and β_2-adrenergic agonist, whereas the (+)-enantiomer strong β_1- and β_2-adrenoceptor agonistic and only mild α-adrenergic activities exerts. The cardiovascular effects of dobutamine used clinically result from the combined effect of the individual

enantiomers on the various adrenergic receptors. The positive inotropic response is generally attributed to β_1-adrenoceptor stimulation, although α_1-adrenoceptors in the myocardium may also contribute (Ruffolo & Yaden, 1983).

There is a paucity of information on dobutamine's effect on cardiac index in horses anaesthetized under clinical conditions although effects on ABP and HR have been studied (Donaldson, 1988; Hellyer et al., 1998). Hallowell and Corley (2005) compared the LiDCO technique with pulse contour analysis in horses anaesthetized with either halothane or isoflurane under clinical conditions. In their study, MAP was maintained above 70 mmHg using dobutamine and/or norepinephrine given to effect. However, the relationship between dobutamine and CO was not reported. Taylor et al. (2000) undertook a preliminary clinical study in isoflurane- or halothane-anaesthetized horses to investigate the relationship between ABP and cardiac index in response to dobutamine infusion, administered to maintain MAP above 70 mmHg. Dobutamine increased ABP in both isoflurane and halothane groups, but without an associated significant increase in cardiac index. However, because of the small number of horses (total 23) the study lacked sufficient power to demonstrate true differences.

In conscious horses, cardiac index is around 70 mL·kg/min (Steffey et al., 1987a; Mizuno et al., 1994a). Inhalation anaesthesia may reduce this substantially, depending on mode of ventilation, depth of anaesthesia and volatile agent used (Wagner, 2000). Positive intrathoracic pressure during controlled ventilation may decrease CO by reducing venous return (Steffey & Howland, 1980; Mizuno et al., 1994b). Moderate hypercapnia (to 60–70 mmHg) may improve cardiovascular function (Wagner et al., 1990). In this study horses were ventilated with the intention to maintain P_aCO_2 between 45 mmHg and 55 mmHg, removing any potential effect of hypercapnia on cardiac index. Ventilation to values below 60 mmHg may have increased the need to support ABP, perhaps explaining why virtually all horses required dobutamine to maintain MAP above 70 mmHg.

Under laboratory conditions, cardiac index decreased to 50% of normal in isoflurane-anaesthetized, ventilated horses, especially with higher end-tidal isoflurane concentrations (Steffey & Howland, 1980; Mizuno et al., 1994a). In this study, cardiac index at T_0 was 47 ± 10 mL·kg/min: about two-thirds of normal. Two recent studies (Raisis et al., 2005; Blissitt et al., 2008) compared the cardiovascular effects of isoflurane and halothane in horses in lateral and dorsal recumbency anaesthetized for clinical procedures lasting >2 h. Horses requiring dobutamine were excluded from analysis to examine the effects of the anaesthetics only. Horses anaesthetized with isoflurane maintained a significantly higher cardiac index compared with those receiving halothane, presumably a result of higher preload and myocardial contractility as well as lower systemic vascular resistance (SVR) with isoflurane. Regardless of body position, cardiac index decreased progressively with both agents, which may be a contributing factor to the higher risk of peri-operative morbidity and mortality occurring with increased duration of anaesthesia (Johnston et al., 2002). The decrease in cardiac

index over time may result from the response to surgery, as an increase in sympathetic tone increases SVR and afterload. These data differ from previous, laboratory studies of isoflurane-anaesthesia where CO progressively increased in spontaneously breathing (Steffey *et al.*, 1987b) and ventilated (Dunlop *et al.*, 1987) horses. However, in those studies, anaesthesia was prolonged, no surgical stimulus was applied and end-tidal isoflurane concentration (1.2 minimal alveolar concentration, MAC) was maintained constant.

In this study, ABP increased significantly after dobutamine infusion commenced, without a concomitant (significant) increase in cardiac index. Although in 12 horses surgery had started at T_1, their cardiovascular function was not different from the rest and thus the overall increase in ABP may be attributable largely to the peripheral vasoconstrictive (α_1-adrenoceptor agonistic) effects of dobutamine. Between T_1 and T_2, MAP, HR and cardiac index all increased significantly, without a concomitant increase in DIR. The combination of dobutamine infusion and surgically induced sympathetic tone was probably responsible for this cardiovascular stimulation. The negative correlation between DIR and MAP at T_1 and T_2 was probably a result of the need for higher infusion rates to increase MAP in the most hypotensive horses.

Horses in lateral recumbency had higher MAP and cardiac index than those in dorsal recumbency. There may be greater cardiovascular depression in dorsal recumbency because of decreased venous return (Stegmann & Littlejohn, 1987; Blissitt *et al.*, 2008). Donaldson (1988) reported that horses in dorsal recumbency had the highest incidence of hypotensive problems with the poorest response to dobutamine. In this study, dorsally recumbent horses received more dobutamine at T_1, indicating indeed that the response to dobutamine was indeed less in dorsal than in lateral recumbent animals.

Wagner (2000) reported a need to treat hypotension in horses anaesthetized with various inhalational agents for elective clinical procedures to be as high as 91%. It is notable that in the studies by Raisis *et al.* (2005) and Blissitt *et al.* (2008) only a few horses required dobutamine in contrast with this study where only one in 44 did not. This may reflect a different population of horses, different premedication (use of acepromazine) and lower threshold at which dobutamine was started (58 vs. 70 mmHg). In this study, MAP of 70 mmHg was used as the threshold according to the logic described by Taylor and Clarke (2007). Use of acepromazine is associated with a reduced risk of death in equine anaesthesia (Johnston *et al.*, 2002); it blocks peripheral α_1-adrenergic receptors, leading to decreased SVR and ventricular afterload, presumably reducing the potential for low myocardial perfusion and resulting hypoxia. Donaldson (1988) reported that acepromazine premedication (0.02 mg/kg, i.m.) was associated with a sluggish response to dobutamine in halothane-anaesthetized horses, but also that fewer horses developed arrhythmias during the infusion. Tachycardia and arrhythmias have been described with dobutamine doses higher than 4 to 5 μg·kg/min (Swanson *et al.*, 1985; Young *et al.*, 1998). Acepromazine and the use of isoflurane instead of halothane, in addition to the low dobutamine dose may have prevented cardiac arrhythmias in this study, although one horse had a marked increase in HR and MAP.

The different mechanisms by which halothane and isoflurane cause hypotension (Steffey & Howland, 1980; Raisis *et al.*, 2000b) may favour isoflurane over halothane because vasodilation should result in better tissue perfusion (Brunson, 1990). Johnston *et al.* (2004) reported that use of isoflurane in horses aged 2–5 years reduced the risk of death compared with halothane, and in particular reduced cardiac-associated mortality by 60%. This was attributed to isoflurane causing less cardiovascular depression. It may be argued that dobutamine might not be the best choice for treatment of isoflurane-induced hypotension as it is mainly a positive inotropic agent. However, isoflurane does cause some myocardial depression (Steffey & Howland, 1980; Mizuno *et al.*, 1994a), though to a lesser extent than halothane. An α_1-agonist might in theory be more suitable to treat the isoflurane-induced hypotension; however, raised afterload would increase myocardial work with the risk of ventricular hypoxia, and clinical evidence to date does not support this approach (Johnston *et al.*, 2002, 2004). It may be difficult to administer an α_1-agonist to increase SVR to raise MAP sufficiently without an associated reduction in peripheral perfusion. Nevertheless, this study suggests that the effect of dobutamine may be partly attributable to peripheral α_1-mediated vasoconstriction.

In conclusion, this study confirms the efficacy of dobutamine, in combination with surgical stimulation, in treating clinical hypotension in isoflurane-anaesthetized horses, although the effect could not be linked with dose.

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