

Cardiovascular Effects of Dobutamine and Phenylephrine Infusion in Sevoflurane-anesthetized Thoroughbred Horses

Minoru OHTA^{1)*,**}, Shinjiro KURIMOTO^{1)**}, Yuhiro ISHIKAWA¹⁾, Hirotaka TOKUSHIGE¹⁾, Naomi MAE¹⁾, Shun-ichi NAGATA²⁾ and Masayuki MAMADA¹⁾

¹⁾Racehorse Clinic, Ritto Training Center, Japan Racing Association (JRA), 1028 Misono, Ritto-shi, Shiga 520-3085, Japan

²⁾Analytical Chemistry Section, Laboratory of Racing Chemistry, 1731-2 Tokami-cyo, Utsunomiya-shi, Tochigi 320-0851, Japan

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ABSTRACT. To determine dose-dependent cardiovascular effects of dobutamine and phenylephrine during anesthesia in horses, increasing doses of dobutamine and phenylephrine were infused to 6 healthy Thoroughbred horses. Anesthesia was induced with xylazine, guaifenesin and thiopental and maintained with sevoflurane at 2.8% of end-tidal concentration in all horses. The horses were positioned in right lateral recumbency and infused 3 increasing doses of dobutamine (0.5, 1.0 and 2.0 $\mu\text{g}/\text{kg}/\text{min}$) for 15 min each dose. Following to 30 min of reversal period, 3 increasing doses of phenylephrine (0.25, 0.5 and 1.0 $\mu\text{g}/\text{kg}/\text{min}$) were infused. Cardiovascular parameters were measured before and at the end of each 15-min infusion period for each drug. Blood samples were collected every 5 min during phenylephrine infusion period. There were no significant changes in heart rate throughout the infusion period. Both dobutamine and phenylephrine reversed sevoflurane-induced hypotension. Dobutamine increased both mean arterial blood pressure (MAP) and cardiac output (CO) as the result of the increase in stroke volume, whereas phenylephrine increased MAP but decreased CO as the result of the increase in systemic vascular resistance. Plasma phenylephrine concentration increased dose-dependently, and these values at 15, 30 and 45 min were 6.2 ± 1.2 , 17.0 ± 4.8 and 37.9 ± 7.3 ng/ml , respectively.

KEY WORDS: cardiovascular effect, dobutamine, equine, phenylephrine, sevoflurane.

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Sevoflurane is commonly used inhalation anesthetic in various surgical procedures in Thoroughbred horses, because of its rapid induction and recovery from anesthesia and easiness in controlling of the depth of anesthesia [3, 4, 18]. On the other hand, sevoflurane is known to induce dose-dependent hypotension resulting from decrease in cardiac output (CO), systemic vascular resistance (SVR) or both in horses [2, 10]. Anesthetic-induced hypotension reduces blood flow to peripheral tissues, and the incidence of post-anesthetic complications, such as myopathy or lameness, is increased by duration of hypotension [9, 21, 26].

Of the cardiovascular stimulating agents that have been advocated for the treatment of anesthetic-induced hypotension, dobutamine is the initial drug of choice in equine practice. Dobutamine is a synthetic catecholamine, which directly increases myocardial contractility by stimulating β_1 -adrenergic receptors and reverses anesthetic-induced hypotension in small animals [19, 24] and horses [5–7, 17, 22]. On the other hand, dobutamine is known to increase myocardial oxygen consumption and sometimes induce tachycardia and ventricular arrhythmias [15].

In cases that dobutamine use is limited due to its adverse effects, phenylephrine has been recommended as alternative

drug for the treatment of anesthetic-induced hypotension. Phenylephrine acts selectively at α_1 -adrenergic receptors, increasing blood pressure by increasing vascular resistance [5]. It is reported that phenylephrine has been in use for serious hypotensive situations in equine clinical cases [11, 13]. However, its usage during anesthesia usually depends on anesthetists' clinical experiences, because there is minimal published information about cardiovascular effects of phenylephrine in anesthetized horses.

The purpose of this study is to examine the dose-dependent cardiovascular effects of dobutamine and phenylephrine infusion in sevoflurane-anesthetized Thoroughbred horses. Correlations between plasma phenylephrine concentrations and changes in cardiovascular variables are also investigated.

MATERIALS AND METHODS

Animals: Six Thoroughbred horses (3 females and 3 males) were used in this study. Mean age was 4.2 ± 1.6 years (range, 2 to 6 years), and mean body weight was 447 ± 40 kg (range, 410 to 514 kg). All horses were considered healthy on the basis of preanesthetic physical examination, CBC and ECG. Food, but not water, was withheld for 12 hr prior to anesthesia. This study was carried out according to the Guidelines for Animal Experiments at Equine Research Institute, Japan Racing Association.

Anesthesia and instrumentation: A 14-G catheter was placed in the left external jugular vein for drug and fluid administration. Another 14-G catheter was placed in the right external jugular vein for venous blood sample collection. Horses were premedicated with xylazine 1.0 mg/kg

*CORRESPONDENCE TO: OHTA, M., Racehorse Clinic, Ritto Training Center, Japan Racing Association (JRA), 1028 Misono, Ritto-shi, Shiga 520-3085, Japan.

e-mail: Minoru_Ota@jra.go.jp

**These authors contributed equally to this study

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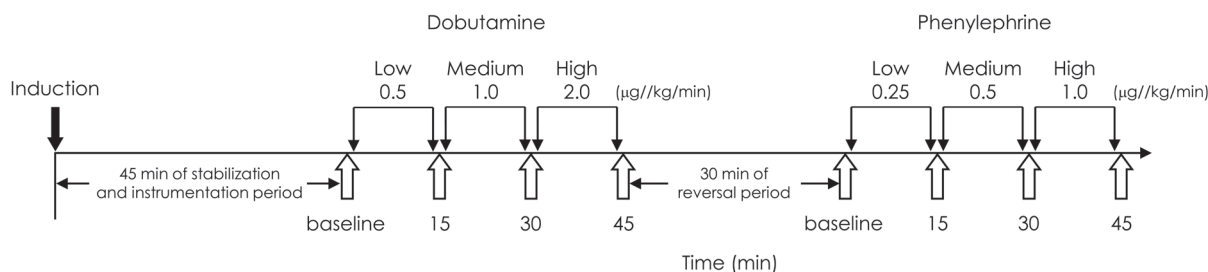


Fig. 1. The schematic diagram of the experiment protocol for six sevoflurane-anesthetized horses. Measurement points of cardiovascular values are expressed as white arrows.

(Celactar; Bayer, Osaka, Japan) and induced anesthesia by a rapid injection of approximately 2.0 ml/kg of 5% guaifenesin (Shinyo Pure Chemicals Co., Ltd., Osaka, Japan) (800 ml in 2 horses and 1,000 ml in 4 horses) with approximately 2.0 mg/ml of thiopental sodium (Ravonal; Mitsubishi Tanabe Pharma Co., Osaka, Japan) (1.6 g in 3 horses, 1.8 g in 2 horses and 2.0 g in 1 horse). After induction of anesthesia, the horses were intubated endotracheally and positioned in right lateral recumbency on a padded surgical table. Anesthesia was maintained with sevoflurane (Sevofrane; Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) and oxygen (approximately 5 l/min) delivered via a large-animal rebreathing circle system (MOK 94; Silver Medical Co., Tokyo, Japan). Horses were mechanically ventilated at a rate of 8 to 12 breaths/min with peak airway pressure of 25 cmH₂O to maintain arterial carbon dioxide tension (PaCO₂) between 45 and 55 mmHg.

A base-apex lead electrocardiogram was used to monitor heart rate (HR) and rhythm. A 20-G catheter was placed in the facial artery for measurement of systemic arterial blood pressure and for arterial blood sample collection. A Swan-Ganz catheter (93A-191-8F; Baxter, Co., Tokyo, Japan) was introduced into right atrium via the left jugular vein for measurement of mean right atrial pressure (MRAP). These catheters were connected to the pressure transducers. Respiratory gas was collected continuously from the circuit end of the endotracheal tube. End-tidal sevoflurane concentration (ET_{SEVO}), HR, systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), mean arterial blood pressure (MAP) and MRAP were monitored by an anesthesia monitoring system (BP608; Omron Colin Co., Ltd., Tokyo, Japan).

Left ventricular internal diameter in diastole (LVIDd) and left ventricular internal diameter in systole (LVIDs) were measured according to the M-mode echocardiographic imaging method as previously described [16]. Images were obtained using an ultrasound machine (Apron EUB-7000HV; Hitachi Medical Co., Tokyo, Japan) with a 2.0 MHz transducer with 30 cm maximum depth of penetration. All measurements were conducted by the same operator to reduce variability between investigators. Left ventricular end-diastole volume (LVEDV) and left ventricular end-systole volume (LVESV) were calculated by Pombo's method [20]. Stroke volume (SV), CO and SVR were calculated as fol-

lows; $SV (ml) = LVEDV (ml) - LVESV (ml)$, $CO (l/min) = SV (ml) \times HR (beats/min) / 1,000$ and $SVR (dynes \cdot sec/cm^5) = 60 \times [MAP (mmHg) - MRAP (mmHg)] \times 1,332 / [CO (l/min) \times 1,000]$. Fractional shortening of the left ventricle (FS) (%) was calculated as the percentage change in LVID between diastole and systole as follows; $FS (\%) = (LVIDd - LVIDs) / LVIDd \times 100$.

Experimental protocol: The schematic diagram of the experiment protocol is shown in Fig. 1. ET_{SEVO} was adjusted to reach 2.8% (approximately 1.2 times of minimum alveolar concentration [MAC] of sevoflurane for horses [1]) within 15 min after induction of anesthesia and then maintained constantly at the same level throughout the experiment. Lactated Ringer's solution (Hartmann's solution; Nipro Pharma Co., Osaka, Japan) was administered at a rate of approximately 10 ml/kg/hr throughout anesthesia to compensate for insensible fluid losses by respiration and sweating [8]. Each horse was allowed 45 min of stabilization and instrumentation period prior to dobutamine (Dobutrex; Shionogi & Co., Ltd., Osaka, Japan) infusion. Dobutamine was continuously infused at three increasing doses of 0.5 (low), 1.0 (medium) and 2.0 (high) µg/kg/min for 15 min each dose. From the end of dobutamine infusion, each horse was allowed 30 min of reversal period. Following this, phenylephrine (Neo-Synesis Kowa Inj.; Kowa Pharmaceutical Co., Ltd., Nagoya, Japan) was continuously infused at three increasing doses of 0.25 (low), 0.5 (medium) and 1.0 (high) µg/kg/min for 15 min each dose. Each drug was diluted in 500 ml of 0.9% saline solution (Otsuka normal saline; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) and infused by using a computer-driven infusion pump (IVAC 599; Cardinal Health 303, Inc., San Diego, CA, U.S.A.).

HR, SAP, DAP, MAP, MRAP and echocardiographic variables were recorded immediately before infusion (as baseline values) and at the end of each 15-min infusion period for each drug. Arterial blood samples were also collected at the same time points. PaCO₂, arterial oxygen tension (PaO₂) and pH were immediately analyzed by a blood-gas analyzer (ABL800 FLEX; Radiometer Co., Ltd., Tokyo, Japan).

Plasma phenylephrine analysis: Blood samples were collected every 5 min during phenylephrine infusion period. All blood samples were immediately placed on ice, and then, the plasma was separated from blood and stored at -20°C for later analysis. Extraction of phenylephrine from the

Table 1. Changes in heart rate (HR), systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), mean arterial blood pressure (MAP), mean right atrial pressure (MRAP), stroke volume (SV), cardiac output (CO), systemic vascular resistance (SVR) and fractional shortening of the left ventricle (FS) during dobutamine infusion in sevoflurane-anesthetized horses

Dobutamine infusion rate	Time (min)			
	Baseline	15	30	45
	←0.5 μg/kg/min→ (Low)	←1.0 μg/kg/min→ (Medium)	←2.0 μg/kg/min→ (High)	
HR (beats/min)	31 ± 5	28 ± 6	27 ± 6	29 ± 7
SAP (mmHg)	75 ± 13 ^A	94 ± 12 ^A	111 ± 17 ^B	139 ± 24 ^C
DAP (mmHg)	40 ± 8 ^A	53 ± 9 ^A	61 ± 15 ^{AB}	69 ± 17 ^B
MAP (mmHg)	51 ± 10 ^A	67 ± 11 ^{AB}	77 ± 16 ^B	90 ± 18 ^C
MRAP (mmHg)	7 ± 4 ^A	8 ± 3 ^A	10 ± 4 ^{AB}	12 ± 4 ^B
SV (ml)	724 ± 219 ^A	792 ± 223 ^A	930 ± 269 ^{AB}	1101 ± 339 ^B
CO (l/min)	22 ± 3 ^A	21 ± 4 ^A	24 ± 2 ^A	31 ± 6 ^B
SVR (dyne·s/cm ⁵)	163 ± 48	226 ± 52	228 ± 77	204 ± 51
FS (%)	27 ± 6 ^A	32 ± 5 ^A	38 ± 7 ^A	46 ± 6 ^B

Data are presented as mean ± SD. Data with no superscript or with the same superscript are not significantly different from each other in the same row.

Table 2. Changes in heart rate (HR), systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), mean arterial blood pressure (MAP), mean right atrial pressure (MRAP), stroke volume (SV), cardiac output (CO), systemic vascular resistance (SVR) and fractional shortening of the left ventricle (FS) during phenylephrine infusion in sevoflurane-anesthetized horses

Phenylephrine infusion rate	Time (min)			
	Baseline	15	30	45
	←0.25 μg/kg/min→ (Low)	←0.5 μg/kg/min→ (Medium)	←1.0 μg/kg/min→ (High)	
HR (beats/min)	32 ± 3	30 ± 4	29 ± 4	28 ± 4
SAP (mmHg)	75 ± 14 ^A	90 ± 11 ^A	98 ± 16 ^A	122 ± 32 ^B
DAP (mmHg)	41 ± 10 ^A	53 ± 7 ^A	59 ± 10 ^A	80 ± 15 ^B
MAP (mmHg)	54 ± 12 ^A	65 ± 9 ^A	71 ± 11 ^A	96 ± 17 ^B
MRAP (mmHg)	8 ± 4 ^A	8 ± 4 ^A	12 ± 3 ^A	17 ± 3 ^B
SV (ml)	878 ± 214	744 ± 199	644 ± 188	594 ± 228
CO (l/min)	28 ± 6 ^A	22 ± 5 ^A	17 ± 4 ^{AB}	16 ± 5 ^B
SVR (dyne·s/cm ⁵)	132 ± 21 ^A	216 ± 41 ^{AB}	258 ± 49 ^B	412 ± 129 ^C
FS (%)	34 ± 5 ^A	28 ± 5 ^A	23 ± 5 ^{AB}	20 ± 6 ^B

Data are presented as mean ± SD. Data with no superscript or with the same superscript are not significantly different from each other in the same row.

plasma samples was performed with Oasis HLB extraction cartridges (Waters Co., Milford, MA, U.S.A.). Etilefrin hydrochloride was used as the internal standard. The extracted phenylephrine was analyzed by a high-performance liquid chromatography-mass spectrometry system (Shimadzu Co., Tokyo, Japan). The assay was duplicated for each sample. The recovery rate, the intra-day precision and the inter-day precision of phenylephrine were 82.8%, 1.71% and 9.04%, respectively (n=5).

Statistical analysis: Data are presented as mean ± SD. Data were analyzed with one-way repeated-measures analysis of variance (ANOVA), and pairwise comparisons were made with Tukey's post-test. Correlations between plasma phenylephrine concentrations and cardiovascular variables (HR, MAP, CO and SVR) were evaluated using Pearson's correlation coefficient test. Statistical analyses were per-

formed with using JMP v6.0.3 (SAS Institute Inc., Cary, NC, U.S.A.), and significance was set at $P < 0.05$.

RESULTS

Changes in cardiovascular variables during dobutamine infusion are shown in Table 1. Infusion of dobutamine resulted in significant increases in SAP, DAP, MAP, MRAP, SV, CO and FS (%). There were significant increases from baseline values at medium (1.0 μg/kg/min) to high (2.0 μg/kg/min) dose in SAP and MAP and at high dose in DAP, MRAP, SV, CO and FS (%). There were no significant changes in HR and SVR throughout the infusion period.

Changes in cardiovascular variables during phenylephrine infusion are shown in Table 2. Infusion of phenylephrine resulted in significant increases in SAP, DAP, MAP, MRAP

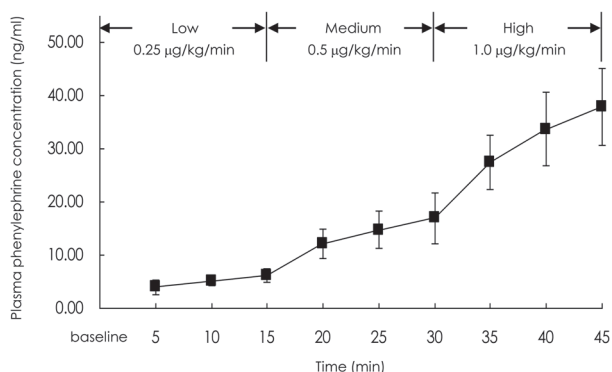


Fig. 2. Mean plasma phenylephrine concentrations during phenylephrine infusion period in six sevoflurane-anesthetized horses.

and SVR. In contrast, infusion of phenylephrine resulted in significant decreases in CO and FS (%). SVR changed markedly, and there were significant increases from baseline values at medium (0.5 µg/kg/min) to high (1.0 µg/kg/min) dose. Significant increases in SAP, DAP, MAP and MRAP and significant decreases in CO and FS (%) were observed only at high dose. There were no significant changes in HR and SV throughout the infusion period.

Mean plasma phenylephrine concentrations during infusion period are shown in Fig. 2. Plasma phenylephrine concentration increased with each increase in infusion dose, and these values at 15 (the end of 15-min low dose infusion), 30 (the end of 15-min medium dose infusion) and 45 (the end of 15-min high dose infusion) min were 6.2 ± 1.2 , 17.0 ± 4.8 and 37.9 ± 7.3 ng/ml, respectively.

Correlations between plasma phenylephrine concentrations and changes in HR, MAP, CO and SVR are shown in Fig. 3. There were no significant correlations between plasma phenylephrine concentrations and HR values ($r=0.27$). MAP and SVR values were significantly correlated with plasma phenylephrine concentrations (MAP: $r=0.61$, $P<0.05$; SVR: $r=0.71$, $P<0.01$). MAP and SVR increased with increase in plasma phenylephrine concentration and reached to 182 ± 31 and $310 \pm 71\%$ of the baseline values at the highest plasma concentration, respectively. In contrast, CO values were significantly negatively correlated with plasma phenylephrine concentrations ($r=-0.47$, $P<0.05$). CO decreased to $58 \pm 10\%$ of the baseline value at the highest plasma concentration.

There were no significant changes in PaCO₂, PaO₂ and pH throughout the experiment. PaCO₂ values were maintained within the target values at all the measurement points.

All drug infusions were completed without serious side effects. Recovery from anesthesia was calm and smooth with minimal ataxia in all horses. No apparent complications were observed after recovery in all cases.

DISCUSSION

Dosages of dobutamine in this study were determined on the basis of those commonly recommended in the previous literatures [6, 7, 17, 22], and these dosages have been rou-

tinely used in our clinical practice. On the other hand, dosages of phenylephrine in this study were determined on the basis of the results in the preliminary experimental trials in our clinic. In both drug infusions, low dose resulted in slight but non-significant changes in cardiovascular variables, whereas high dose resulted in significant changes without serious side effects, such as arrhythmia or excessive increase in HR or arterial blood pressures. Therefore, three steps of dosages applied in this study were considered to be appropriate for the study design.

It is known that dobutamine exerts a slight positive chronotropic effect as well as its major potent inotropic effect [14]. We often experience gradual increase in HR during surgery when using dobutamine (0.5–2.0 µg/kg/min) to maintain MAP at adequate level [18]. Others reported that the positive chronotropic effect of dobutamine was manifested at 2.5 µg/kg/min, and 10 µg/kg/min caused tachycardia and arrhythmias in 2 of 6 halothane-anesthetized ponies [15]. However, HR remained unchanged during dobutamine infusion in this study. It may be because the infusion period was shorter, and the infusion dose was lower in this study compared to those in previous studies.

It was considered that the increases in SV and FS (%) were associated with the direct β₁-stimulating effects of dobutamine on myocardial contractility. It is known that dobutamine exerts not only β₁-stimulating effects but also mild β₂- and α₁-stimulating effects at higher infusion rates [5, 15]. However, SVR remained unchanged, indicating that α₁-stimulating effects did not develop at the dosages applied in this study. From these results, it is suggested that the increase in MAP was mainly attributable to the increase in SV. This is also supported by the result that MAP increased almost parallel with SV increase. These results were similar to those of the previous reports in halothane [22]- and isoflurane [7, 17]-anesthetized horses.

Phenylephrine is a sympathomimetic amine that acts predominantly on α₁-adrenergic receptors [5, 11]. Unlike dobutamine, phenylephrine has little or no agonism on β-receptors of the heart [5]. Therefore, it is suggested that the increase in MAP was mainly attributable to the increase in SVR, which was associated with the direct vasoconstrictive effect of phenylephrine. However, the marked increase in SVR induced the significant decrease in CO at high dose.

Both dobutamine and phenylephrine increased MAP to the same level and reversed sevoflurane-induced hypotension in this study. However, these 2 drugs increased MAP in different ways as described above. In fact, dobutamine increased both MAP and CO as the result of the increase in SV. In contrast, phenylephrine increased MAP but decreased CO as the result of the increase in SVR. These results indicate that dobutamine is more effective for the treatment of sevoflurane-induced hypotension compared with phenylephrine.

To maintain peripheral blood flow at sufficient level under anesthesia, not only adequate MAP but also adequate CO are necessary [15]. In other words, peripheral blood flow under anesthesia does not depend only on MAP. Therefore, it is suggested that high dose of phenylephrine succeeded

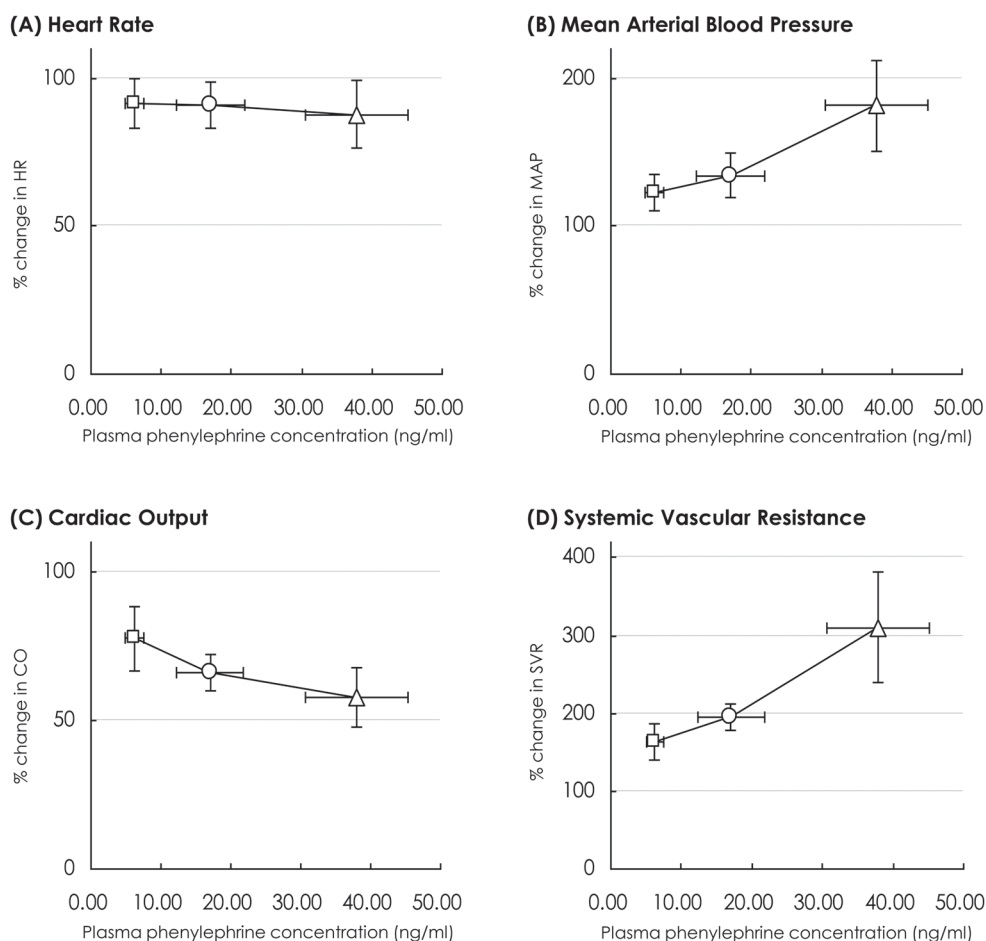


Fig. 3. Percent changes in heart rate (A), mean arterial blood pressure (B), cardiac output (C) and systemic vascular resistance (D) at three different plasma phenylephrine concentrations (low□, medium○ and highΔ) in six sevoflurane-anesthetized horses.

to reverse sevoflurane-induced hypotension, but failed to improve peripheral blood flow.

Plasma phenylephrine concentration increased over time in each dose. The increasing rate also increased, as the infusion dose increased. To avoid excessive vasoconstriction due to the rapid increase in plasma concentration, low ($0.25 \mu\text{g}/\text{kg}/\text{min}$) to medium ($0.5 \mu\text{g}/\text{kg}/\text{min}$) dose is recommended in clinical use. Although the half-life of phenylephrine in horses has not been investigated as far as we know, it is reported that the half-life of phenylephrine in man is 2 to 3 hr, and its cardiovascular effect lasts for longer period [12]. Considering the long-lasting effect of phenylephrine, infusion should be stopped immediately when MAP reaches the target value in clinical use.

In this study design, 45 min of stabilization and instrumentation period was set prior to the drug infusion to minimize the influence of premedication and induction drugs on measurements. Moreover, 30 min of reversal period was set between the end of dobutamine infusion and the onset of phenylephrine infusion. It is reported that the half-life of

dobutamine in man is 2 min and the duration of action is 10 min [23], and therefore, it is considered that the effects of dobutamine have almost disappeared at the onset of phenylephrine infusion in this study. According to the previous reports on time-related cardiovascular changes during 3 hr of sevoflurane anesthesia, MAP and SVR slightly increased with time at the latter half of the experiments, and the maximum values in MAP and SVR were 116% and 124% of the baseline values, respectively [25]. Time-related changes in MAP and SVR in that experiment are quite smaller than the changes in MAP and SVR during phenylephrine infusion in this study. Therefore, it was considered that the marked increases in MAP and SVR during phenylephrine infusion in this study were mainly caused by phenylephrine itself.

The results of the cardiovascular responses of dobutamine and phenylephrine in this study showed the similar tendency to those previously reported by Lee *et al.* [15]. However, the equivalent degrees of changes in cardiovascular responses appeared at the lower doses in this study compared with the previous study. These differences may be associated with the

differences in cardiovascular functions of the horses used in each study. In addition, drug distribution, metabolism and excretion can be influenced by various factors, such as age, breed and physical condition. The horses used in this study were well-trained young Thoroughbreds weighing from 410 to 514 kg, whereas those used in the previous study were adult Welsh Ponies weighing from 201 to 427 kg.

In conclusion, both dobutamine and phenylephrine reversed sevoflurane-induced hypotension in Thoroughbred horses. Dobutamine increased both MAP and CO as the result of the increase in SV, whereas phenylephrine increased MAP but decreased CO as the result of the increase in SVR. The results of this study suggest that dobutamine has advantages for the treatment of sevoflurane-induced hypotension over phenylephrine. Therefore, phenylephrine should not be used routinely, and its use is recommended only when other treatments have failed to reverse hypotension.

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