INTRODUCTION

Alpha-2 adrenoceptor agonists are frequently used for anaesthetic premedication, analgesia and as part of balanced anaesthesia in horses (Gozalo-Marcilla et al., 2015). Besides the desirable central sedative and analgesic effects, there are characteristic peripheral cardiovascular effects including reflex bradycardia, reduced cardiac output, increased vascular resistance as well as cardiac conduction disturbances in this drug class (Yamashita et al., 2000). In addition, gastrointestinal motility is negatively affected by alpha-2 adrenoceptor agonistic action (Tapio, Raekallio, Mykkänen, Männikkö, et al., 2019; Vainionpää et al., 2013; Vries et al., 2016).

Dexmedetomidine, a highly selective alpha-2 adrenoceptor agonist (α2: α1 = 1620: 1) (Virtanen et al., 1988), is characterized by...
The aim of the study was to determine the effect of a CRI of both dexmedetomidine and vatinoxan on global and peripheral perfusion and oxygenation parameters. Furthermore, a potential influence of vatinoxan on dexmedetomidine plasma concentration was investigated.

**Hypothesis**

**Main:** The co-administration of vatinoxan (bolus followed by CRI) to dexmedetomidine partial intravenous anaesthesia alleviates pharmacodynamic changes induced by dexmedetomidine, especially oxygenation variables and microperfusion.

**Second:** The addition of vatinoxan decreases plasma concentrations of dexmedetomidine.

## 2 | MATERIALS AND METHODS

### 2.1 | Animals

Horses in this study were part of a surgical terminal study. Study protocol of the concomitant study necessitated a median laparotomy and included an ischaemic small intestine model to assess a pharmacological preconditioning effect of dexmedetomidine in combination with vatinoxan. After conclusion of the study, the cadavers were used for anatomical teaching purposes. All horses had a history of chronic orthopaedic issues or idiopathic headshaking but were considered healthy regarding cardiovascular and intestinal function based on clinical, haematological and faecal examination. The experiment was reviewed and approved by the Ethical Committee of Lower Saxony, Germany (approval number 33.19-42502-04-16/2212).

### 2.2 | Study design

Prospective, randomized and final experimental study with the observers being aware of the treatment administered. Twelve horses were allocated to two groups by drawing lots:

- group DEX \((n = 6)\)
  - dexmedetomidine 3.5 µg kg\(^{-1}\) intravenously (IV) followed by a CRI of 7 µg kg\(^{-1}\) h\(^{-1}\)
- group VAT \((n = 6)\)
  - dexmedetomidine 3.5 µg kg\(^{-1}\) IV followed by a CRI of 7 µg kg\(^{-1}\) h\(^{-1}\)
  - vatinoxan 130 µg kg\(^{-1}\) IV followed by a CRI of 40 µg kg\(^{-1}\) h\(^{-1}\)

### 2.3 | Instrumentation

Horses were kept in stalls with daily access to a paddock and were fed with hay. They were denied food for 6 h, but water was provided ad libitum before each experiment. A complete blood count was run prior to each procedure. The deworming status was verified by faecal analysis.
In the morning of each experiment and after subcutaneous infiltration of lidocaine (Lidocainhydrochlorid 2%, Bela-Pharm GmbH & Co. KG, Germany), a 12G catheter (Intraflon 2, 12G-80 mm, VYGON GmbH & CO.KG, France) was aseptically placed in the left jugular vein. Additionally, a port system (Exacta, 8.5 Fr; Argon Medical Devices Inc., IL, USA) for a pulmonary catheter (Balloon wedge pressure catheter, 7 Fr, 160 cm; Arrow International Inc., NC, USA) was placed aseptically in the right jugular vein. The pulmonary catheter was then inserted into a pulmonary artery under ultrasound guidance and control of location-specific pressure curves.

During anaesthesia, an arterial catheter (Venocan™ PLUS IV Catheter 20G.33 mm, Kruuse A/S, Denmark) was placed in the facial artery to measure the arterial blood pressure and the blood gases. The cardiac output measurements were performed by the lithium dilution technique as described (Linton et al., 2000). The arterial and pulmonary catheters were connected to a fluid-filled, low compliance extension line of a pressure transducer (Argon Safedraw Transducer; Argon Medical Devices Inc., IL, USA), which was placed at the level of the scapulohumeral joint and zeroed to atmospheric pressure.

2.4 Anaesthesia

The vatinoxan powder was weighed individually for each horse and was then dissolved in sterile saline to reach a concentration of 10 mg ml$^{-1}$. Group VAT received an intravenous bolus of dexmedetomidine (Dexdomitor®, 0.5 mg ml$^{-1}$; Orion Pharma, Finland) and vatinoxan (Vetcare, Finland). Simultaneously, a CRI of dexmedetomidine and of vatinoxan was started by using a syringe driver (Braun Perfusor® Compact pump, BBraun, Germany). In group DEX, a bolus of dexmedetomidine was administered by concurrent start of a CRI of dexmedetomidine, which was also administered by using a syringe driver. In all horses, anaesthesia was induced with 2.2 mg kg$^{-1}$ ketamine IV (Narketan 100 mg ml$^{-1}$; Vetoquinol GmbH, Germany) and 50 µg kg$^{-1}$ diazepam IV (Ziapam® 5 mg ml$^{-1}$; Ecuphar, Germany). During the induction and throughout the procedure none of the CRIs used in group DEX or VAT was disconnected. After the induction, the horses were endotracheally (Cuffed endotracheal tube ET 26–30, Surgivet®, Smiths Medical PM, Inc., USA) intubated and placed in a dorsal recumbency on a padded surgical table. A large animal ventilator (Vet.-Tec. Model JAVC 2000; J.D. Medical Distribution Company, AZ, USA) was connected and intermittent positive pressure ventilation was initiated with a positive inspiratory pressure of 20–25 cm H$_2$O. The respiratory rate was adjusted to keep the horses normocapnic with an end-tidal carbon dioxide partial pressure (EtCO$_2$) of 35–45 mmHg. The anaesthesia was maintained with isoflurane (Isofluran CP; CP-Pharma GmbH, Germany) in 100% oxygen, the end-expiratory isoflurane concentration was adjusted to approximately 1.1 vol.-%. and the clinical signs of adequate depth of anaesthesia were assessed. Lactated Ringer’s (Ringer-Laktat 5 l, B. Braun Melsungen AB, Germany) solution was administered at 5 ml kg$^{-1}$ h$^{-1}$. In case of the decrease of mean arterial blood pressure below 60 mmHg, the infusion rate was increased to 10 ml$^{-1}$ kg$^{-1}$ h$^{-1}$ and a CRI of dobutamine (Dobutamin-ratiopharm® 250 mg Trockensubstanz, Ratiopharm, Germany) starting at 0.33 µg kg$^{-1}$ min$^{-1}$ was initiated. However, in case of a dobutamine requirement, CRI was withheld 5 min before each measurement.

2.5 Measurements

2.5.1 Cardiovascular and respiratory variables parameters

Heart rate and pulmonary artery pressure variables (systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), and mean pulmonary artery pressure (mPAP)) were obtained before and after sedation. During the anaesthesia, the following cardiovascular and respiratory variables were measured by a multiparameter anaesthesia monitor (GE Datex-Ohmeda S/5 Compact Anästhesie Monitor, Duisburg, Germany): Heart rate (HR), respiratory rate (fR), end-tidal carbon dioxide tension (Et$_{\text{CO}_2}$), inspired (Fi$_{\text{O}_2}$) and end-tidal (Et$_{\text{ISO}}$) isoflurane concentrations, systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP, respectively), sPAP, dPAP and mPAP. Before each experiment a 2-point calibration of the monitor was performed according to the expected concentrations (CO$_2$ 5%, O$_2$ 55%, N$_2$O 33%, Desflurane 2%; Quick CalTM Calibrationgas, GE Healthcare Finland OY, Finland). Mixed-venous blood gas samples (2 ml) were taken before as well as five minutes after sedation and simultaneously with arterial blood gas samples (2 ml) and cardiac output measurements during anaesthesia. Blood gas samples were withdrawn in heparinised syringes and were analysed by AVL (AVL995, AVL Medizintechnik, Germany) for oxygen partial pressure (PaO$_2$ and PvO$_2$, respectively), carbon dioxide partial pressure (PaCO$_2$ and PvCO$_2$, respectively), pH (pHa and pHv, respectively), haemoglobin and electrolytes.

2.5.2 Tissue perfusion and oxygenation

Micro-light guide spectrophotometry (O2C, LEA Medizintechnik, Germany) was used to assess the oral and rectal microperfusion in arbitrary units (AU) by laser-Doppler flowmetry and the oxygenation in percentage (%) by white light spectrophotometry as described before (Krug, 2006). On the buccal mucosa and rectal mucosa a flat surface probe (LF-2 probe) was placed with a light penetration depth of 2.5 mm.

2.5.3 Blood sampling and drug analysis

Venous blood samples (10 ml) were withdrawn from the port system placed in the right jugular vein and transmitted into EDTA tubes. Sampling was performed at predefined time intervals as followed: Baseline (untreated horse), 1, 3, 5, 10, 20, 30, 60, 90, 120, 150, 180,
210, 240 min after premedication according to the treatment group. The plasma was frozen by −80°C until further analysis of the plasma concentrations.

The concentration of dexmedetomidine (reference standard: racemic medetomidine, TRC, Toronto, Ontario, Canada) was determined with a high-performance liquid chromatography/mass spectrometry after a solid-phase extraction (Sep-Pak®C18 96-well extraction plates, Waters Co., Milford, MA, USA). After separation with a Gemini® C18 column (2 × 150 mm, 5 µm, Phenomenex, Torrance, CA, USA) with a gradient flow system (0.1% formic acid in water and methanol), a quantitative detection was performed in multi-reaction monitoring mode with a triple quadrupole mass spectrometer (AB Sciex 4000 QTrap) connected to a high-performance liquid chromatography system (Agilent 1200). For dexmedetomidine and the internal standard, the respective precursor ions (m/z) were 201.2 and 204.2. The fragment ions (m/z) monitored and used for quantitation were from 0.02 to 5 ng/ml. The inter-assay accuracy of the quality control samples (at five different concentration levels, 0.06, 0.15, 1.0, 4.0 and 40 ng/ml) ranged from 92.9% to 106.9%.

The concentration of vatinax (reference standard: MK-467, PCAS Finland Oy, Turku, Finland) in horse plasma was determined with a high-performance liquid chromatography/mass spectrometry after solid-phase extraction with Sep-Pak®C18 96-well extraction plates with RS-79948 (Tocris Bioscience, Bristol, U.K.) as internal standard. A reversed-phase separation (SunFire C18 column, 2.1 × 150 mm, 3.5 µm, Waters Corp.) and a gradient solvent system (0.1% formic acid in water and acetonitrile) were used. A quantitative detection was performed in a multi-reaction monitoring mode with the same HPLC-MS/MS system as dexmedetomidine. For vatinax and RS-79948, the respective precursor ions (m/z) scanned were 419.3 and 365.3. The fragment ions monitored and used for quantitation were 200.1 for MK-467 and 190.2 for RS-79948. The chromatograms were analysed and processed using AB Sciex Analyst® 1.6.1 software. The linear concentration range was from 25 to 460 ng/ml. The inter-assay accuracy of the quality control samples (at three concentration levels, 70, 250 and 380 ng/ml) ranged from 92.2% to 102.1%.

2.5.4 Study protocol

The study was conducted every Wednesday for 12 consecutive weeks with one horse per week. The days leading up to the experiments, horses were familiarized with the stock by being fed in them without manipulation. Every Wednesday morning (7 am), horses were brought into a stock, where they were instrumented with the pulmonary artery catheter. Baseline values (B), as well as sedation values (S), were obtained for tissue perfusion (blood flow), oxygenation (S\(\text{O}_2\)) variables, and cardiovascular variables. To indicates the application of dexmedetomidine and the start of CRI of dexmedetomidine in group DEX and the application of dexmedetomidine and vatinax and the start of a CRI of dexmedetomidine and vatinax in group VAT. Thereafter, additional measurements were performed during the anaesthesia. According to the protocol of the concomitant study, further measurements were performed after 60 min of induction (A60), 80 min (A80), 200 min (A200) and 230 min (A230). One set of measurements consisted of recordings of cardiovascular variables starting with the determination of cardiac output by simultaneous blood gas sampling and was then followed by the tissue perfusion and oxygenation measurements. The latter was always performed by the same person and in the same order, beginning with rectal, then buccal measurements.

The concurrent study consisted of three main episodes including (1) an equilibration and instrumentation time for 90 min, (2) small intestinal ischaemia for 120 min and (3) reperfusion of the small intestine for 30 min.

Horses were euthanized with 60 mg kg\(^{-1}\) pentobarbital (Release®, 500 mg ml\(^{-1}\), WDT, Germany) at the end of the study.

2.5.5 Calculated variables

To calculate the systemic vascular resistance (SVR) a simplified formula was used (Skimming et al., 1997). Stroke volume, alveolar dead space (Severinghaus & Stupfel, 1957) and alveolar-arterial oxygen difference (\(P_{(A-a)}\text{O}_2\)), arterial and venous oxygen content (\(\text{CaO}_2\), \(\text{CvO}_2\)), oxygen consumption (\(\text{VO}_2\)) and delivery (\(\text{DO}_2\)), oxygen extraction ratio (ERO\(_2\)) and venous admixture were determined by standard equations (see Supplement).

2.6 Statistical analysis

Data analysis and graph creation were performed using GraphPad software (GraphPad Prism 8, GraphPad Software, USA). The concurrent study determined the number of subjects used in this study. However, based on data on oxygen delivery from Pakkanen et al., (2015) 5 horses per group would be needed to obtain a power of 80% an alpha error of 5%. Tissue perfusion in arbitrary units and oxygenation (%) variables were recorded at a frequency of 2 Hz, resulting in 20–25 data points for each parameter and time point. Consequently, the average of each point in time and location was calculated, resulting in one value for each respective variable. Cardiovascular parameters were obtained every 10 min. However, only values recorded simultaneously to the tissue perfusion assessment were analysed (A60; A80; A200; A230). The reason for that was to reduce the influence of inotropic support on cardiovascular and perfusion parameters which was suspended for the measurement period. Visual assessment of qq-plots and the Shapiro–Wilk test were performed to confirm the normal distribution of model residuals on dependent variables. All parametric data are presented as means ± SD and non-parametric as median with min and max. The statistical analysis of global and tissue parameters was undertaken in terms of a two-factorial variance analysis for repeated measurements. In case of
TABLE 1  Cardiorespiratory data, presented as mean and standard deviation, from twelve horses sedated with either dexmedetomidine 3.5 µg kg⁻¹ followed by a CRI of 7 µg kg⁻¹ h⁻¹ (group DEX) or dexmedetomidine 3.5 µg kg⁻¹ intravenously (IV) followed by a CRI of 7 µg kg⁻¹ h⁻¹ and vatinoxan 130 µg kg⁻¹ IV followed by 40 µg kg⁻¹ h⁻¹ (group VAT) under general anaesthesia with isoflurane.

| Variables | Group | Points in time | p-value (group difference) |
|-----------|-------|----------------|-----------------------------|
|          |       | Baseline | Sedation | A60 | A80 | A200 | A230 |
| HR (beats min⁻¹) | DEX | 43 ± 8 | 32 ± 6* | 35 ± 2* | 33 ± 5 | 31 ± 2* | 30 ± 3* | 0.93 |
|          | VAT | 40 ± 5 | 32 ± 6* | 32 ± 8 | 33 ± 6 | 33 ± 12 | 35 ± 11 |
| MAP (mmHg) | DEX | 61 ± 9 | 62 ± 11 | 61 ± 3 | 55 ± 8 | 55 ± 8 | 55 ± 8 | 0.49 |
|          | VAT | 56 ± 6 | 59 ± 7 | 57 ± 6 | 60 ± 5 | 60 ± 5 | 60 ± 5 | 0.49 |
| CI (ml min⁻¹ kg⁻¹) | DEX | 47 ± 14 | 39 ± 5 | 54 ± 17 | 45 ± 17 | 0.09 |
|          | VAT | 58 ± 8 | 44 ± 9 | 60 ± 8 | 55 ± 13 | 0.09 |
| SVI (ml beat⁻¹ kg⁻¹) | DEX | 1.4 ± 0.4 | 1.3 ± 0.1 | 1.7 ± 0.5 | 1.5 ± 0.6 | 0.13 |
|          | VAT | 1.9 ± 0.3 | 1.5 ± 0.3 | 2 ± 0.7 | 1.7 ± 0.4 | 0.13 |
| SVR (dyne s⁻¹ cm⁻⁵) | DEX | 233 ± 116 | 309 ± 54 | 195 ± 69 | 207 ± 41 | 0.02* |
|          | VAT | 153 ± 31 | 190 ± 42 | 154 ± 28 | 177 ± 42 | 0.02* |
| RR (breath min⁻¹) | DEX | 6 ± 2 | 8 ± 2 | 8 ± 1 | 8 ± 1 | 0.82 |
|          | VAT | 7 ± 1 | 7 ± 2 | 8 ± 2 | 8 ± 1 | 0.82 |
| EtIso (Vol.- %) | DEX | 1.15 ± 0.06 | 1.13 ± 0.05 | 1.06 ± 0.07 | 1.05 ± 0.08 | 1.05 ± 0.08 | 0.01* |
|          | VAT | 0.99 ± 0.07 | 1.02 ± 0.09 | 1.03 ± 0.08 | 1.03 ± 0.08 | 1.03 ± 0.08 | 0.01* |
| EtCO₂ (mmHg) | DEX | 36 ± 7 | 33 ± 5 | 36 ± 6 | 38 ± 7 | 0.05* |
|          | VAT | 39 ± 2 | 41 ± 3 | 42 ± 1 | 40 ± 2 | 0.05* |
| PaCO₂ (mmHg) | DEX | 48 ± 11 | 46 ± 7 | 48 ± 4 | 48 ± 3 | 0.46 |
|          | VAT | 46 ± 3 | 49 ± 3 | 54 ± 3 | 50 ± 2 | 0.46 |
| PvvCO₂ (mmHg) | DEX | 54 ± 9 | 54 ± 6 | 56 ± 4 | 54 ± 12* | 0.8 |
|          | VAT | 54 ± 2* | 57 ± 1* | 59 ± 3* | 55 ± 5* | 0.8 |
| SaO₂ (%) | DEX | 96 ± 1 | 95 ± 1 | 96 ± 1 | 96 ± 1 | 0.16 |
|          | VAT | 97 ± 0.1 | 97 ± 0.1 | 97 ± 0.1 | 97 ± 0.1 | 0.16 |
| PvvO₂ (mmHg) | DEX | 31 ± 8 | 29 ± 3 | 36 ± 2 | 33 ± 7 | 34 ± 10 | 0.04* |
|          | VAT | 34 ± 3 | 34 ± 2 | 40 ± 6 | 45 ± 14 | 0.04* |
| PaO₂ (mmHg) | DEX | 214 ± 174 | 200 ± 184 | 204 ± 186 | 186 ± 180 | 186 ± 180 | 0.66 |
|          | VAT | 279 ± 111 | 234 ± 98 | 216 ± 128 | 229 ± 145 | 0.66 |
| CaO₂ (ml dl⁻³) | DEX | 14 ± 1.1 | 14 ± 1.4 | 13 ± 9 | 13 ± 1.5 | 13 ± 1.5 | 0.41 |
|          | VAT | 14 ± 2.2 | 14 ± 1.8 | 15 ± 1.9 | 16 ± 2.9 | 16 ± 2.9 | 0.41 |
| ERO₂ (%) | DEX | 31 ± 1 | 35 ± 1 | 35 ± 1 | 34 ± 2 | 0.02* |
|          | VAT | 25 ± 1 | 24 ± 0 | 23 ± 1 | 21 ± 1 | 0.02* |
| VO₂I (ml min⁻¹ kg⁻¹) | DEX | 2 ± 0.4 | 1.8 ± 0.3 | 2.4 ± 0.7 | 1.9 ± 1.1 | 0.58 |
|          | VAT | 2 ± 0.4 | 1.7 ± 0.2 | 2 ± 0.7 | 1.6 ± 0.9 | 0.58 |
| DO₂I (ml min⁻¹ kg⁻¹) | DEX | 6.6 ± 1.8 | 5.1 ± 0.3 | 7.2 ± 2.4 | 5.7 ± 2.2 | 0.03* |
|          | VAT | 8.1 ± 1.6 | 6.3 ± 0.5 | 8.8 ± 1.3 | 8.4 ± 1.8 | 0.03* |
| Venous admixture (%) | DEX | 15.6 ± 0.2 | 16.7 ± 0.2 | 17.0 ± 0.3 | 17.5 ± 0.5 | 0.02* |
|          | VAT | 14 ± 0.1 | 13.8 ± 0.1 | 13.7 ± 2 | 13.3 ± 0.2 | 0.02* |
| PA-aO₂ (mmHg) | DEX | 417 ± 181 | 433 ± 197 | 429 ± 207 | 447 ± 196 | 0.69 |
|          | VAT | 353 ± 116 | 400 ± 107 | 416 ± 135 | 405 ± 151 | 0.69 |
| Alveolar dead space (%) | DEX | 27 ± 1 | 23 ± 1 | 29 ± 1 | 23 ± 1 | 0.01* |
|          | VAT | 23 ± 1 | 15 ± 1 | 18 ± 0 | 15 ± 1 | 0.01* |

Note: Stars indicate a significant difference (p ≤ 0.05) between groups. Hashes indicate a significant difference (p ≤ 0.05) to baseline values in group VAT. Plus indicates a significant difference (p ≤ 0.05) to baseline values in group DEX.

Abbreviations: HR: heart rate; MAP: mean arterial blood pressure; CI: cardiac index; SVI: stroke volume index; SVR: systemic vascular resistance; RR: respiratory rate; EtIso: end-tidal isoflurane concentration; EtCO₂: end-tidal carbon dioxide concentration; PaCO₂: arterial partial pressure of carbon dioxide; PvvCO₂: mixed venous partial pressure of carbon dioxide; SaO₂: arterial oxygen saturation; PvvO₂: mixed venous partial pressure of oxygen; PaO₂: arterial partial pressure of oxygen; CaO₂: arterial content of oxygen; ERO₂: oxygen extraction ratio; VO₂I: oxygen consumption index; DO₂I: oxygen delivery index; PA-aO₂: alveolar-arterial oxygen gradient.
missing values, the mixed effect model with Geisser-Greenhouse correction was used. Dunnett’s and Sidak’s post hoc test for multiple paired comparisons was used for tissue perfusion parameters within one group and between groups, respectively. The Wilcoxon’s signed-rank test was applied for non-parametric data. The values for plasma concentration were compared using the unpaired-t-test. The level of significance was set at 5%.

3 | RESULTS

3.1 | Animals

The study included 12 horses of different breeds (group DEX: 5 warmblood horses, 1 standardbred; group VAT: 4 warmblood, 1 standardbred, 1 islandic horse) and different sexes (group DEX: 3 geldings and 3 mares; group VAT: 1 gelding and 5 mares). The mean age was 9 ± 7 years in DEX and 14 ± 8 years (p = 0.26) in VAT and mean body weight was 518 ± 96 kg and 507 ± 84 kg in DEX and VAT, respectively.

3.2 | Cardiovascular and respiratory variables

Due to technical problems, six out of 48 cardiac output (CO) measurements failed. Data for the cardiovascular and respiratory variables and pMAP are depicted in Table 1 and Figure 4, respectively.

3.3 | Tissue perfusion and oxygenation

One horse in group DEX did not tolerate the baseline tissue perfusion and the oxygenation measurements, which precluded their further analysis due to the relative nature of the values. However, the cardiovascular and the sedation parameters were obtained. The tissue oxygenation was equally maintained in both groups (Figure 1). Tissue perfusion significantly differed between baseline and points in time within the groups and is depicted in Figure 2.

3.4 | Plasma concentrations

Due to implausible high plasma concentrations in one horse in group DEX, only five horses of this group were included for analysis. One other horse in this group also had implausible high plasma concentrations after 1 and 3 min. Therefore, these measurements were excluded for further analysis. There was no significant difference in the AUC plasma concentration of dexmedetomidine between both groups (Table 2). The dexmedetomidine/vatinoxan plasma concentration ratio is depicted in Figure 3.

3.5 | Anaesthesia

The period of anaesthesia was similar for all horses. The end-expiratory isoflurane concentration is depicted in Table 1. All horses in group VAT and two horses in group DEX needed inotropic support. The average dobutamine dose was 0.51 ± 0.24 µg kg⁻¹ min⁻¹ (n = 2) over a period of 120 ± 42 min in group DEX and 0.44 ± 0.26 µg kg⁻¹ min⁻¹ (n = 6) over a period of 140 ± 27 min in group VAT (p = 0.14). The cessation of dobutamine infusion before the measurement of cardiovascular and peripheral perfusion parameters led to a decrease in blood pressure resulting in a slight hypotension in both groups (Table 1).

4 | DISCUSSION

This is the first study investigating the effect of the co-administration of vatinoxan CRI and dexmedetomidine CRI on global and peripheral

**FIGURE 1**  Tissue oxygen saturation (tSO₂%) measured with white light spectrophotometry at different time points (B = baseline; S = sedation; A60; A80; A200; A230 = A refers to anaesthesia and the numbers to 60 min; 80 min; 200 min; 230 min after induction of anaesthesia) at the buccal (A) and rectal (B) mucosa in horses sedated with either dexmedetomidine 3.5 µg kg⁻¹ intravenously (IV) followed by a CRI of 7 µg kg⁻¹ h⁻¹ (group DEX) or dexmedetomidine 3.5 µg kg⁻¹ IV followed by a CRI of 7 µg kg⁻¹ h⁻¹ and vatinoxan 130 µg kg⁻¹ IV followed by 40 µg kg⁻¹ h⁻¹ (group VAT) and under general anaesthesia with isoflurane. Stars and hashes indicate a significant difference (p < 0.05) to baseline values in group DEX and VAT respectively.
co-administration of vatinoxan to medetomidine significantly increased the cardiac output in a dose-dependent fashion (Dancker Raekallio, Mykkänen, Männikkö, et al., 2019). The MAP in our study increased CI and decreased SVR ten minutes after application (Tapio, Mykkänen, Al-Ramahi, et al., 2019). Nevertheless, in sedated horses CRI was not discontinued before measurements of CI, it is nearly pronounced hypotension in vatinoxan treated horses. As dobutamine compared to group DEX. In the literature, higher CI is reported when CI without reaching significancy and significantly lower SVR values (Grosenbaugh & Muir, 1998). Group VAT showed minimally higher blocking effect and the additional vasodilatory effect of isoflurane during isoflurane anaesthesia is related to the alpha-2 adrenoceptor-concentrations of dexmedetomidine in horses in the current study but hypothesis. The addition of vatinoxan did not alter the plasma concentrations of dexmedetomidine in horses in the current study but increased the requirements for inotropic support to sustain MAP.

The marked hypotension induced by the addition of vatinoxan during isoflurane anaesthesia is related to the alpha-2 adrenoceptor-blocking effect and the additional vasodilatory effect of isoflurane (Grosenbaugh & Muir, 1998). Group VAT showed minimally higher CI without reaching significance and significantly lower SVR values compared to group DEX. In the literature, higher CI is reported when vatinoxan was added to an alpha-2 adrenoceptor agonist, however, an increased dose of dobutamine CRI was used due to more pronounced hypotension in vatinoxan treated horses. As dobutamine CRI was not discontinued before measurements of CI, it is nearly impossible to distinguish between the effects of vatinoxan and dobutamine, respectively (Pakkanen et al., 2015; Tapio, Raekallio, Mykkänen, Al-Ramahi, et al., 2019). Nevertheless, in sedated horses co-administration of vatinoxan to medetomidine significantly increased CI and decreased SVR ten minutes after application (Tapio, Raekallio, Mykkänen, Männikkö, et al., 2019). The MAP in our study was similarly sustained in both groups due to the fact that MAP in group VAT was maintained in physiological limits by starting a dobutamine CRI. As dobutamine increases the gastrointestinal perfusion, as well as the cardiac output in a dose-dependent fashion (Dancker et al., 2018), dobutamine was ceased five minutes before measuring the cardiac output and the peripheral perfusion to prevent marked influence. Inotropic support was initiated in case of hypotension due to protocol requirements of the concomitant surgical study. Other potential reasons for the exacerbating hypotension might be seen in the nature of dorsal recumbency (Tapio, Raekallio, Mykkänen, Al-Ramahi, et al., 2019) and IPPV (Araos et al., 2020), since both could have led to a reduced venous return and cardiac output, which again can induce hypotension. Another possible explanation for the hypotension in this study is an endotoxaemia induced by imitating a small intestinal strangulation according to the concurrent study protocol as endotoxins can lead to vasodilation and vasoplegia (Burrows, 1970) as well as reduced cardiac contractility (Brady et al., 1992). The potential endotoxaemia might have influenced the blood pressure especially at the end of the study where reperfusion was allowed. However, this does not explain why a hypotension was present straight from the beginning and during equilibration time.

The slight increase in CI and decrease in SVR also influenced perfusion and oxygenation variables as well as plasma concentrations. Results indicate superior oxygenation variables and tissue perfusion in horses treated with vatinoxan, thereby confirming our main hypothesis. The addition of vatinoxan did not alter the plasma concentrations of dexmedetomidine in horses in the current study but increased the requirements for inotropic support to sustain MAP.

The marked hypotension induced by the addition of vatinoxan during isoflurane anaesthesia is related to the alpha-2 adrenoceptor-blocking effect and the additional vasodilatory effect of isoflurane (Grosenbaugh & Muir, 1998). Group VAT showed minimally higher CI without reaching significance and significantly lower SVR values compared to group DEX. In the literature, higher CI is reported when vatinoxan was added to an alpha-2 adrenoceptor agonist, however, an increased dose of dobutamine CRI was used due to more pronounced hypotension in vatinoxan treated horses. As dobutamine CRI was not discontinued before measurements of CI, it is nearly impossible to distinguish between the effects of vatinoxan and dobutamine, respectively (Pakkanen et al., 2015; Tapio, Raekallio, Mykkänen, Al-Ramahi, et al., 2019). Nevertheless, in sedated horses co-administration of vatinoxan to medetomidine significantly increased CI and decreased SVR ten minutes after application (Tapio, Raekallio, Mykkänen, Männikkö, et al., 2019). The MAP in our study was similarly sustained in both groups due to the fact that MAP in group VAT was maintained in physiological limits by starting a dobutamine CRI. As dobutamine increases the gastrointestinal perfusion, as well as the cardiac output in a dose-dependent fashion (Dancker et al., 2018), dobutamine was ceased five minutes before measuring the cardiac output and the peripheral perfusion to prevent marked influence. Inotropic support was initiated in case of hypotension due to protocol requirements of the concomitant surgical study. Other potential reasons for the exacerbating hypotension might be seen in the nature of dorsal recumbency (Tapio, Raekallio, Mykkänen, Al-Ramahi, et al., 2019) and IPPV (Araos et al., 2020), since both could have led to a reduced venous return and cardiac output, which again can induce hypotension. Another possible explanation for the hypotension in this study is an endotoxaemia induced by imitating a small intestinal strangulation according to the concurrent study protocol as endotoxins can lead to vasodilation and vasoplegia (Burrows, 1970) as well as reduced cardiac contractility (Brady et al., 1992). The potential endotoxaemia might have influenced the blood pressure especially at the end of the study where reperfusion was allowed. However, this does not explain why a hypotension was present straight from the beginning and during equilibration time.

The slight increase in CI and decrease in SVR also influenced oxygenation variables, illustrated by a moderately higher arterial oxygen tension, significantly lower alveolar dead space and venous admixture in group VAT. The oxygen delivery index was significantly lower and the ERO2 was significantly higher in group DEX leading to similar VO2I compared to values obtained from group VAT. The increase in the ERO2 in group DEX is most likely responsible for the sustained tissue oxygenation at the buccal and rectal mucosa. This protective mechanism was well-maintained, even though blood flow

**FIGURE 2** Tissue perfusion (AU) measured with doppler flowmetry at different time points (B = baseline; S = sedation; A60; A80; A200; A230 = A refers to anaesthesia and the numbers to 60 min; 80 min; 200 min; 230 min after induction of anaesthesia) at the buccal (A) and rectal (B) mucosa in horses sedated with either dexmedetomidine 3.5 µg kg⁻¹ intravenously (IV) followed by a CRI of 7 µg kg⁻¹ h⁻¹ (group DEX) or dexmedetomidine 3.5 µg kg⁻¹ IV followed by a CRI of 7 µg kg⁻¹ h⁻¹ and vatinoxan 130 µg kg⁻¹ IV followed by 40 µg kg⁻¹ h⁻¹ (group VAT) and under general anaesthesia with isoflurane. Stars and hashes indicate a significant difference (p < 0.05) to baseline values in group DEX and VAT respectively.

**TABLE 2** Area under the curve (AUC) for plasma concentrations are presented as means and standard deviation from eleven horses sedated with either dexmedetomidine 3.5 µg kg⁻¹ intravenously (IV) followed by a CRI of 7 µg kg⁻¹ h⁻¹ (group DEX) or dexmedetomidine 3.5 µg kg⁻¹ IV followed by a CRI of 7 µg kg⁻¹ h⁻¹ and vatinoxan 130 µg kg⁻¹ IV followed by 40 µg kg⁻¹ h⁻¹ (group VAT) under general anaesthesia with isoflurane.

| Drug          | Group     | AUC₀⁻₂⁰ₘᵋₙₖ (min ng⁻¹ ml⁻¹) | AUC₀⁻₂⁴₀ₘᵋₙₖ (min ng⁻¹ ml⁻¹) |
|--------------|-----------|-----------------------------|-------------------------------|
| Dexmedetomidine | DEX (n = 5) | 23.5 ± 13.9                 | 770 ± 185                     |
| Dexmedetomidine | VAT (n = 6) | 17.8 ± 8.6                  | 794 ± 126                     |
| Vatinoxan     | VAT (n = 6) | 2155 ± 281                  | 19119 ± 1205                  |

The slight increase in CI and decrease in SVR also influenced oxygenation variables, illustrated by a moderately higher arterial oxygen tension, significantly lower alveolar dead space and venous admixture in group VAT. The oxygen delivery index was significantly lower and the ERO2 was significantly higher in group DEX leading to similar VO2I compared to values obtained from group VAT. The increase in the ERO2 in group DEX is most likely responsible for the sustained tissue oxygenation at the buccal and rectal mucosa. This protective mechanism was well-maintained, even though blood flow
was significantly reduced at the buccal mucosa. The tissue perfusion is directly related to CO and MAP, which can explain the minimal decrease in the buccal tissue perfusion in group DEX and the modest increase in tissue perfusion after the co-administration of vatinoxan. This observation is in accordance with studies concluding that the bolus administration of alpha-2 adrenoceptor agonists reduce the tissue blood flow by increasing SVR and decreasing CO resulting in a decreased DO₂ (Edner et al., 2002; Neudeck et al., 2018). By alleviating these effects with the addition of vatinoxan, the tissue blood flow can be promoted. In dogs, the concomitant administration of vatinoxan and dexmedetomidine prevented the dexmedetomidine induced reduction in intestinal blood flow measured by contrast-enhanced ultrasonography (Restitutti et al., 2013). This result is in contrast with a study in horses where vatinoxan decreased the gastrointestinal tissue blood flow 5 min after the bolus administration during anaesthesia, although these horses were markedly hypotensive (MAP 32–43 mmHg). In this study, the MAP was most likely beneath a critical perfusion pressure (MAP <50 mmHg and CI <40 ml kg⁻¹ min⁻¹) which is associated with a deteriorated intestinal tissue perfusion (Hopster et al., 2017). In medetomidine sedated sheep the atipamezole administration failed to restore distributional changes in organ blood flow enhanced by medetomidine (Talke et al., 2000). In this study, the perfusion pressure was well maintained even though slight hypotension occurred. The effect of
FIGURE 4 Mean pulmonary artery pressure obtained from eleven horses (DEX n = 5; VAT n = 6) sedated with either dexmedetomidine 3.5 µg kg\(^{-1}\) intravenously (IV) followed by a CRI of 7 µg kg\(^{-1}\) h\(^{-1}\) (group DEX) or dexmedetomidine 3.5 µg kg\(^{-1}\) IV followed by a CRI of 7 µg kg\(^{-1}\) h\(^{-1}\) and vatinoxan 130 µg kg\(^{-1}\) IV followed by 40 µg kg\(^{-1}\) h\(^{-1}\) (group VAT) and under general anaesthesia with isoflurane. Hashes indicate a significant difference (p < 0.05) to baseline values in group VAT. (B = baseline; S = sedation; A60; A80; A200; A230 = A refers to anaesthesia and the numbers to 60 min; 80 min; 200 min; 230 min after induction of anaesthesia)

a potential endotoxaemia cannot be excluded, as tissue blood flow decreased over time in this study almost equally in both groups. The infusion of endotoxin in horses decreases caecal blood flow (CLARK & Moore, 1989), yet this had an effect on the macrocirculation, thus predictions on microvascular effect cannot be prepared. Although it is known that endotoxins can induce changes in microcirculation by loss of vasomotor tone, leading to arteriolar dilation and venular constriction (McCuskey et al., 1996).

The mean pulmonary artery pressure was equally increased after sedation and decreased during anaesthesia between both groups (Figure 4). Dexmedetomidine, like other alpha-2 adrenoceptor agonists led to a minimal increase in mPAP as reported in ponies (Bettschart-Wolfensberger et al., 2005). Although the baseline values and three points in time differed significantly during anaesthesia in group VAT, there was no distinction amongst the groups. The decrease in mPAP in group VAT during anaesthesia is most likely attributed to an isoflurane effect (Marshall et al., 1984), also the addition of vatinoxan slightly enhanced this effect, probably due to the adrenolytic effect on pulmonary vessels.

In both groups, the plasma concentrations of dexmedetomidine equally declined for 20 min after administering the initial bolus. Thereafter concentrations rose, reaching a steady-state after 60 min (Figure 3). Two potential scenarios might explain this observation. On the one hand, the induction of anaesthesia 20 min after bolus administration markedly influenced the dexmedetomidine plasma concentrations by increasing volume of distribution, leading to decreased dexmedetomidine plasma concentrations. Dexmedetomidine potential influence on its own metabolism by decreasing hepatic blood flow might have led to the raised steady-state concentrations during the maintenance of anaesthesia (Dutta et al., 2000). On the other hand, the early distribution phase might have been ended leading to a decrease followed by an increase in dexmedetomidine plasma concentrations. Thus, plasma concentrations of dexmedetomidine were similar between groups. Similar observations have been prepared by Tapio, Raekallio, Mykkänen, Al-Ramahi, et al., (2019) where plasma concentrations of dexmedetomidine were similar in isoflurane anaesthetized horses treated with either medetomidine or medetomidine/vatinoxan. However, this is not in accordance with other reports where the addition of vatinoxan decreased plasma concentrations of various alpha-2 adrenoceptor agonists by alleviating their hemodynamic effects (Bennett et al., 2016; Honkavaara et al., 2012; Pypendop et al., 2016; Vainionpää et al., 2013). A possible reason for this observation might be the influence of the isoflurane concentration masking any difference. Interestingly, the vatinoxan plasma concentration was not affected by the anaesthesia induction and maintenance, which might lead to the assumption that hepatic metabolism and changes in volume distribution do not play a major role.

The ‘ideal’ dose ratio of medetomidine and vatinoxan was investigated in dogs but not in horses. In dogs under isoflurane anaesthesia a medetomidine/vatinoxan dosing ratio of 1:12.5 and lower <1:18 alleviated hemodynamic effects induced by medetomidine.

Tapio, Raekallio, Mykkänen, Al-Ramahi, et al., (2019) used vatinoxan (140 µg kg\(^{-1}\) IV) as a bolus and a similar alpha-2 adrenoceptor agonist drug dose compared to our study, assuming that 7 µg kg\(^{-1}\) IV medetomidine equals 3.5 µg kg\(^{-1}\) IV dexmedetomidine, observing a marked hypotension after anaesthesia induction in vatinoxan treated horses. The same dose combination was investigated in standing horses, where medetomidine induced cardiovascular changes (bradycardia, increased systemic vascular resistance) could be alleviated by vatinoxan, indicating that inhalational anaesthetics will exacerbate vasodilatation leading to hypotension (Tapio, Raekallio, Mykkänen, Männikkö, et al., 2019). However, the comparability to this study is limited as vatinoxan was not given as CRI. In the present study, we used a slightly lower dose of vatinoxan bolus than previously reported leading to a dose ratio of 1:37 for the bolus. For the CRI of both drugs, we used a higher drug dose ratio with 1:6 based on pharmacokinetic studies in standing horses (Figure 3). In these studies, prevention of bradycardia, hypertension and gastrointestinal hypomotility by vatinoxan were seen when the plasma concentrations were around 100 ng ml\(^{-1}\) (Vainionpää et al., 2013; Vries et al., 2016). Based on this assumption we calculated our vatinoxan CRI (µg kg\(^{-1}\) h\(^{-1}\)) with the clearance values obtained by Vries et al., (2016). In the present study, the vatinoxan plasma concentration actually plateaued at approximately 100 ng ml\(^{-1}\) with a plasma concentration ratio between vatinoxan and dexmedetomidine of 1:20 from 60 to 240 min. Nevertheless, inotropic support was still needed to maintain MAP within acceptable limits. Therefore, one may assume that lower vatinoxan plasma concentrations might be preferable during anaesthesia. However, potential beneficial effects of vatinoxan on cardiovascular variables other than the arterial blood pressure might be reduced by decreasing vatinoxan dosages.

The restrictions imposed by the primary surgical study and the small number of horses are a limitation of the study, which might have contributed to some mitigation of differences in cardiovascular
variables induced by vatinoxan. However, the surgical intervention in these horses represents a clinical anaesthesia. Sex distribution was not equal in this study which might lead to higher risk of bias. However, stratified randomization was not possible due to the unpredictable availability of the horses and, therefore, their sex. The unaccountably high dexmedetomidine plasma concentrations in one horse and in another horse for two measurements most likely resulted from inadvertent use of the wrong catheter, thereby, further limiting the explanatory power of the remaining values. Another limitation is that the CO was measured by the lithium dilution technique (Linton et al., 2000), as it is a feasible and easy method for CO measurements with good accuracy. However, the influence on sensor voltage by various drugs might lead to erroneous results (Ambrisko et al., 2012, 2013). Dexmedetomidine had only a minor influence on sensor voltage in vitro (Ambrisko et al., 2013) and changes in sensor voltage could not be seen in vivo (Neudeck et al., 2018). The influence of vatinoxan on the lithium dilution technique has not been investigated, however, in the present study the sensor voltage was monitored, and no obvious changes could be seen in group VAT, which indicates an unlikely influence on the accuracy of CO measurements.

5 | CONCLUSION

Our pilot study demonstrated peripheral and global perfusion parameters were better sustained in vatinoxan treated horses, indicated by a lower SVR, higher oxygen variables and superior tissue blood flow. Vatinoxan treatment increased the need for inotropic support. Taking these results into account vatinoxan implementation in the anaesthetic protocol can be beneficial for oxygenation and perfusion parameters. Furthermore, the concurrent administration of vatinoxan with dexmedetomidine as bolus followed by CRI in horses did not alter the plasma concentrations of dexmedetomidine. However, more clinical studies are needed to optimize the dose ratio of dexmedetomidine and vatinoxan to avoid hypotension.

ACKNOWLEDGEMENT

We are grateful for the contribution from Lauri Vuorilehto, Bioanalytical Laboratory, Institute of Biomedicine, University of Turku, Finland, for drug analysis and to Vetcare Ltd., Mäntsälä, Finland, for donating vatinoxan. Additionally, we want to thank Marja Raekallio and Outi Vainio (Department of Equine and Small Animal Medicine, Faculty of Veterinary Medicine, University of Helsinki, Helsinki, Finland) for their helpful contribution to this article. We also want to thank Manfred Kietzmann (Department of Pharmacology, Toxicology and Pharmacy, University of Veterinary Medicine Hannover, Foundation, Hannover, Germany) for advice on the data processing of plasma concentrations.

CONFLICT OF INTEREST

The authors have declared that there is no competing interests exist.

ANIMAL WELFARE AND ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal’s author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The authors confirm that they have adhered to European standards for the protection of animals used for scientific purposes Germany (approval number 33.19–42502–04/16–2212; LAVES The Office for Consumer Protection and Food Safety of Lower Saxony).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

Adam, M., Raekallio, M. R., Keskitalo, T., Honkavaara, J. M., Scheinin, M., Kajula, M., Mõlsä, S., & Vainio, O. M. (2018). The impact of MK-467 on plasma drug concentrations, sedation and cardiopulmonary changes in sheep treated with intramuscular medetomidine and atipamezole for reversal. Journal of Veterinary Pharmacology and Therapeutics, 41(3), 447–456. https://doi.org/10.1111/jvp.12486.

Ambrisko, T. D., Coppons, P., Kabes, R., & Moens, Y. (2012). Lithium dilution, pulse power analysis, and continuous thermodilution cardiac output measurements compared with bolus thermodilution in anaesthetized ponies. British Journal of Anaesthesia, 109(6), 864–869. https://doi.org/10.1093/bja/aes269.

Ambrisko, T. D., Kabes, R., & Moens, Y. (2013). Influence of drugs on the response characteristics of the LiDCO sensor: an in vitro study. British Journal of Anaesthesia, 110(2), 305–310. https://doi.org/10.1093/bja/aes380.

Araos, J., Kenny, J.-E.-S., Rousseau-Blass, F., & Pang, D. S. J. (2020). Dynamic prediction of fluid responsiveness during positive pressure ventilation: a review of the physiology underlying heart–lung interactions and a critical interpretation. Veterinary Anaesthesia and Analgesia, 47(1), 3–14. https://doi.org/10.1016/j.vaan.2019.08.004.

Bennett, R. C., Salla, K. M., Raekallio, M. R., Hänninen, L., Rinne, V. M., Scheinin, M., & Vainio, O. M. (2016). Effects of MK-467 on the antinoceptive and sedative actions and pharmacokinetics of medetomidine in dogs. Journal of Veterinary Pharmacology and Therapeutics, 39(4), 336–343. https://doi.org/10.1111/j.vpt.2016.35.Bennett-2016.Effects-of-MK-467-on-the-antinociceptive.pdf. https://doi.org/10.1111/jvp.12292.

Betttschart-Wolfensberger, R., Freeman, S. L., Bowen, I. M., Aliabadi, F. S., Weller, R., Huhtinen, M., & Clarke, K. W. (2005). Cardiopulmonary effects and pharmacokinetics of iv dexmedetomidine in ponies. Equine Veterinary Journal, 37(1), 60–64. https://doi.org/10.1111/j.1744-0596.2004.00078.x.

Brady, A. J., Poole-Wilson, P. A., Harding, S. E., & Warren, J. B. (1992). Nitric oxide production within cardiac myocytes reduces their contractility in endotoxemia. American Journal of Physiology-Heart and Circulatory Physiology, 263(6), H1963–H1966. https://doi.org/10.1152/ajpheart.1992.263.6.H1963.

Burrows, G. E. (1970). Hemodynamic alterations in the anesthetized pony produced by slow intravenous administration of Escherichia coli endotoxin. American Journal of Veterinary Research, 31, 1975–1982.

Clark, E. S., & Moore, J. N. (1989). The effects of slow infusion of a low dosage of endotoxin in healthy horses. Equine Veterinary Journal, 21(57), 33–37. https://doi.org/10.1111/j.2042-3306.1989.tb05652.x.

Clineschmidt, B. V., Pettibone, D. J., Lott, V. J., Hucker, H. B., Sweeney, B. M., Reiss, D. R., Lis, E. V., Huff, J. R., & Vacca, J. (1988). A peripherally acting alpha-2 adrenoceptor antagonist: L-659,066. Journal of Pharmacology and Experimental Therapeutics, 245(1), 32–40. http://jpet.aspetjournals.org/content/245/1/32.long.
Dancker, C., Hopster, K., Rohn, K., & Kästner, S. B. (2018). Effects of dobutamine, dopamine, phenylephrine and noradrenaline on systemic haemodynamics and intestinal perfusion in isoflurane anaesthetised horses. *Equine Veterinary Journal, 50*(1), 104–110. https://doi.org/10.1111/evj.12721.

Dutta, S., Lal, R., Karol, M. D., Cohen, T., & Ebert, T. (2000). Influence of cardiac output on dexmedetomidine pharmacokinetics. *Journal of Pharmaceutical Sciences, 89*(4), 519–527. internal-pdf://184.4.130.62/Dutta-2000-Influence_of_cardiac_output_on_dexm.pdf. https://doi.org/10.1002/(SICI)1520-6017(200004)89:4<519:AID-JPS9>3.0.CO;2-U.

Edner, A., Nyman, G., & Essén-Gustavsson, B. (2002). The relationship of muscle perfusion and metabolism with cardiovascular variables before and after detomidine injection during propofol-ketamine anaesthesia in horses. *Veterinary Anaesthesia and Analgesia, 29*(4), 182–199. https://doi.org/10.1046/j.1467-2995.2002.00101.x.

Gozo, A., Gartner, L., & Schauvliege, S. (2015). Partial intravenous anaesthesia in the horse: a review of intravenous agents used to supplement equine inhalation anaesthesia. Part 2: opioids and alpha-2 adrenoceptor agonists. *Veterinary Anaesthesia and Analgesia, 42*(1), 1–16.

Grosenbaugh, D. A., & Muir, W. W. (1998). Cardiorespiratory effects of sevoflurane, isoflurane, and halothane anesthesia in horses. *American Journal of Veterinary Research, 59*(1), 101–106.

Honkavaara, J., Raekallio, M. R., & Vainio, O. M. (2010). Influence of MK-467, a peripheral α2-adrenoceptor antagonist, on the cardiopulmonary effects of intravenous desflurane in conscious dogs. *Journal of Veterinary Pharmacology and Therapeutics, 34*(4), 332–337. internal-pdf://88.11.215.143/Honkavaara-2011-The_effects_of_increasing_dose.pdf. https://doi.org/10.1111/j.1365-2885.2010.01242.x.

Honkavaara, J., Restitutti, F., Raekallio, M., Sallu, E., Kusela, E. K., & Vainio, O. M. (2011). The effects of increasing doses of MK-467, a peripheral alpha2-adrenergic receptor antagonist, on the cardiopulmonary effects of intravenous dexmedetomidine in conscious dogs. *Journal of Veterinary Pharmacology and Therapeutics, 34*(4), 332–337. internal-pdf://88.11.215.143/Honkavaara-2011-The_effects_of_increasing_dose.pdf. https://doi.org/10.1111/j.1365-2885.2010.01242.x.

Hopster, K., Wittenberg-Voges, L., Geburek, F., Hopster-Iversen, C., & Kästner, S. B. (2017). Effects of controlled hypoxemia or hypoxia on the alpha2-adrenoceptor antagonist on the disposition of intravenous dexmedetomidine in dogs. *Drug Metabolism and Disposition, 45*(9), 445–449. internal-pdf://10.1122/791032975/Honkavaara-2012-Influence_of_MK-467_a_periphe.pdf.

Hautajärvi, H. J., Männikkö, S., & Vainio, O. (2019). Effects of vaptanox on cardiorespiratory function, fecal output and plasma drug concentrations in horses anesthetized with isoflurane and the combination of detomidine and MK-467, a peripheral alpha2-adrenoceptor antagonist, as premedication in horses anaesthetized with isoflurane. *Veterinary Anaesthesia and Analgesia, 42*(5), 527–536. https://doi.org/10.1111/vaa.12238.

Pakkanen, S. E. A., Raekallio, M. R., Mykkänen, A. K., Sallu, K. M., Vries, A., Vuorihehto, L., Scheinlin, M., & Vainio, O. M. (2015). Detomidine and the combination of detomidine and MK-467, a peripheral alpha-2 adrenoceptor antagonist, as premedication in horses anaesthetised with isoflurane. *Veterinary Anaesthesia and Analgesia, 42*(5), 527–536. https://doi.org/10.1111/vaa.12238.

Pypendop, B. H., Honkavaara, J., & Ilkiw, J. E. (2016). Pharmacokinetics of dexmedetomidine, MK-467, and their combination following intravenous administration in male cats. *Journal of Veterinary Pharmacology and Therapeutics, 39*(5), 460–468. internal-pdf://0959997301/jvp.12302.pdf. https://doi.org/10.1111/jvp.12302.

Pypendop, B. H., Honkavaara, J., & Ilkiw, J. E. (2017). Pharmacokinetics of dexmedetomidine, MK-467 and their combination following intramuscular administration in male cats. *Veterinary Anaesthesia and Analgesia, 44*(4), 823–831. https://doi.org/10.11101/j.vaa.2017.02.008.

Raekallio, M. R., Honkavaara, J. M., & Vainio, O. M. (2010). The effects of L-659,066, a peripheral α2-adrenoceptor antagonist, and verapamil on the cardiovascular influences of dexmedetomidine in conscious sheep. *Journal of Veterinary Pharmacology and Therapeutics, 33*(5), 434–438. https://doi.org/10.1111/j.1365-2885.2009.01156.x.

Rahe, R., Risberg, A. I., Spadavecchia, C., Landsem, R., & Haga, H. A. (2015). The pharmacokinetics of dexmedetomidine administered as a constant rate infusion in horses. *Journal of Veterinary Pharmacology and Therapeutics, 38*(1), 93–96. https://doi.org/10.1111/jvp.12157.

Restitutti, F., Kaartinen, M. J., Raekallio, M. R., Weijberg, O., Mikkola, E., Del Castillo, J. R. E., Scheinlin, M., & Vainio, O. M. (2017). Plasma concentration and cardiovascular effects of intramuscular medetomidine combined with three doses of the peripheral α2-antagonist MK-467 in dogs. *Veterinary Anaesthesia and Analgesia, 44*(3), 417–426. https://doi.org/10.1116/j.vaa.2016.04.006.

Ristomin, M., Laitinen, M. R., Raekallio, M. R., Vainio, O. M., Brien, R. T., Kuusela, E., & Vainio, O. M. (2013). Effect of MK-467 on organ blood flow parameters detected by contrast-enhanced ultrasound in dogs treated with dexmedetomidine. *Veterinary Anaesthesia and Analgesia, 40*(6), e48–e56. https://doi.org/10.1111/vaa.12058.

Saveringhaus, J. W., & Stupfel, M. (1957). Alveolar dead space as an index of distribution of blood flow in pulmonary capillaries. *Journal of Applied Physiology, 10*(3), 335–348.

Skimming, J. W., Cassin, S., & Nichols, W. W. (1997). Calculating vascular resistances. *Clinical Cardiology, 20*(9), 805. http://search.ebscohost.com/login.aspx?direct=true&db=edb&AN=910722880&lang=de&site=eds-live. https://doi.org/10.1002/cic.4960200918.

Talke, P. O., Traber, D. L., Richardson, C. A., Harper, D. S., & Trabber, L. D. (2000). The effect of α2 agonist-induced sedation and its reversal with an α2 antagonist on organ blood flow in sheep. *Anesthesia & Analgesia, 90*(5), 1060–1066. internal-pdf://144.15.143.202/The_Effect_of_2_Agonist_Induced_Sedation_and.pdf. https://doi.org/10.1095/900000539-200005000-00011.

Tapio, H., Raekallio, M. R., Mykkänen, A. K., Al-Ramahi, D., Scheinlin, M., Hautajärvi, H. J., Männikkö, S., & Vainio, O. (2019). Effects of vatinox on cardiorespiratory function, fecal output and plasma drug concentrations in horses anesthetized with isoflurane and infusion of medetomidine. *The Veterinary Journal, 251*, 105345. https://doi.org/10.1016/j.tvjl.2019.105345.

Tapio, H., Raekallio, M. R., Mykkänen, A., Männikkö, S., Scheinlin, M., Bennett, R. C., & Vainio, O. (2019). Effects of vatinox on cardiorespiratory function and gastrointestinal motility during constant-rate medetomidine infusion in standing horses. *Equine Veterinary Journal, 51*(5), 646–652. https://doi.org/10.1111/ejv.13085.
Vainionpää, M. H., Raekallio, M. R., Pakkanen, S. A. E., Ranta-Panula, V., Rinne, V. M., Scheinin, M., & Vainio, O. M. (2013). Plasma drug concentrations and clinical effects of a peripheral alpha-2-adrenoceptor antagonist, MK-467, in horses sedated with detomidine. *Veterinary Anaesthesia and Analgesia, 40*(3), 257–264. https://doi.org/10.1111/vaa.12012.

Virtanen, R., Savola, J.-M., Saano, V., & Nyman, L. (1988). Characterization of the selectivity, specificity and potency of medetomidine as an α2-adrenoceptor agonist. *European Journal of Pharmacology, 150*(1–2), 9–14. https://doi.org/10.1016/0014-2999(88)90744-3.

Vries, A., Pakkanen, S. A. E., Raekallio, M. R., Ekiri, A., Scheinin, M., Taylor, P. M., & Vainio, O. M. (2016). Clinical effects and pharmacokinetic variables of romifidine and the peripheral α2-adrenoceptor antagonist MK-467 in horses. *Veterinary Anaesthesia and Analgesia, 43*(6), 599–610. internal-pdf://139.247.43.20/Vries_et_al-2016-Veterinary_Anaesthesia_and_An.pdf

Wittenberg-Voges, L., Kästner, S. B. R., Raekallio, M., Vainio, O. M., Rohn, K., & Hopster, K. (2017). Effect of dexmedetomidine and xylazine followed by MK-467 on gastrointestinal microperfusion in anaesthetized horses. *Veterinary Anaesthesia and Analgesia, 45*(2), 165–174.

Yamashita, K., Tsubakishita, S., Futaok, S., Ueda, I., Hamaguchi, H., Seno, T., Katoh, S., Izumisawa, Y., Kotani, T., & Muir, W. W. (2000). Cardiovascular effects of medetomidine, detomidine and xylazine in horses. *Journal of Veterinary Medical Science, 62*(10), 1025–1032. http://www.ncbi.nlm.nih.gov/pubmed/11073071 https://www.jstage.jst.go.jp/article/jvms/62/10/62_10_1025/_pdf. https://doi.org/10.1292/jvms.62.1025.

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**How to cite this article:** Neudeck, S., Twele, L., Kopp, V., & Kästner, S. (2021). Pharmacodynamics and plasma concentrations of dexmedetomidine with or without vatinoxan as a constant-rate infusion in horses anaesthetized with isoflurane—A pilot study. *Journal of Veterinary Pharmacology and Therapeutics, 00*, 1–12. https://doi.org/10.1111/jvp.12992