Cardiovascular effects of intravenous vatinoxan in wild boars (Sus scrofa) anaesthetised with intramuscular medetomidine-tiletamine-zolazepa

Einwaller, Joy

2022-01

Einwaller , J , Meyer , L C R , Auer , U , Raekallio , M , Nowack , J , Haw , A , Vetter , S , Painer , J & Stalder , G 2022 , ' Cardiovascular effects of intravenous vatinoxan in wild boars (Sus scrofa) anaesthetised with intramuscular medetomidine-tiletamine-zolazepam ' , Veterinary Record , vol. 190 , no. 2 , 835 . https://doi.org/10.1002/vetr.835

http://hdl.handle.net/10138/342620
https://doi.org/10.1002/vetr.835

Received: 25 November 2020 | Revised: 18 May 2021 | Accepted: 29 July 2021

DOI: 10.1002/vetr.835

Vet Record

ORIGINAL RESEARCH

Cardiovascular effects of intravenous vatinoxan in wild boars (*Sus scrofa*) anaesthetised with intramuscular medetomidine-tiletamine-zolazepam

Joy Einwaller[1] | **Leith C. R. Meyer**[2] | **Ulrike Auer**[3] | **Marja Raekallio**[4] | **Julia Nowack**[1,5] | **Anna Haw**[1] | **Sebastian Vetter**[1] | **Johanna Painer**[1,*] | **Gabrielle Stalder**[1,*]

[1] Research Institute of Wildlife Ecology, Department of Interdisciplinary Life Sciences, University of Veterinary Medicine Vienna, Vienna, Austria

[2] Department of Paraclinical Sciences and Centre for Veterinary Wildlife Studies, Faculty of Veterinary Science, University of Pretoria, Onderstepoort, South Africa

[3] Clinical Unit of Anaesthesiology and Perioperative Intensive-Care Medicine, University of Veterinary Medicine Vienna, Vienna, Austria

[4] Department of Equine and Small Animal Medicine, Faculty of Veterinary Medicine, University of Helsinki, Helsinki, Finland

[5] School of Biological and Environmental Sciences, Liverpool John Moores University, Liverpool, UK

Correspondence
Gabrielle Stalder, Research Institute of Wildlife Ecology, Department of Interdisciplinary Life Sciences, University of Veterinary Medicine Vienna, Savoyenstraße 1, Vienna, 1160 Austria.
Email: gabrielle.stalder@vetmeduni.ac.at

[*] Both the authors contributed equally to this work.

Abstract

Background: The potent sedative medetomidine is a commonly used adjunct for the immobilisation of non-domestic mammals. However, its use is associated with pronounced cardiovascular side effects, such as bradycardia, vasoconstriction and decreased cardiac output. We investigated the effects of the peripherally-acting alpha-2-adrenoceptor antagonist vatinoxan on cardiovascular properties in medetomidine-tiletamine-zolazepam anaesthetised wild boar (*Sus scrofa*).

Methods: Twelve wild boars, anaesthetised twice with medetomidine (0.1 mg/kg) and tiletamine/zolazepam (2.5 mg/kg) IM in a randomised, crossover study, were administered (0.1 mg/kg) vatinoxan or an equivalent volume of saline IV (control). Cardiovascular variables, including heart rate (HR), mean arterial blood pressure (MAP), pulmonary artery pressure (PAP), pulmonary artery occlusion pressure (PAOP) and cardiac output (CO), were assessed 5 min prior to vatinoxan/saline administration until the end of anaesthesia 30 min later.

Results: MAP ($p < 0.0001$), MPAP ($p < 0.001$) and MPAOP ($p < 0.0001$) significantly decreased from baseline after vatinoxan until the end of anaesthesia. HR increased significantly ($p < 0.0001$) from baseline after vatinoxan administration. However, the effect on HR subsided 3 min after vatinoxan. All variables remained constant after saline injection. There was no significant effect of vatinoxan or saline on CO.

Conclusion: Vatinoxan significantly reduced systemic and pulmonary artery hypertension, induced by medetomidine in wild boar.

KEYWORDS
alpha-2-adrenergic agonists, blood pressure, medetomidine, pulmonary artery pressure, vatinoxan, wild boar (*Sus scrofa*)

INTRODUCTION

Chemical immobilisation of the Eurasian wild boar (*Sus scrofa*) is essential for management and research purposes. Effective anaesthesia protocols in wild boars consist of combinations of dissociative anaesthetic agents (e.g., tiletamine), benzodiazepines (e.g., zolazepam) and alpha-2-adrenoceptor agonists (e.g., medetomidine).[1–3] Alpha-2-adrenoceptor agonists induce potent sedative, and analgesic effects mediated inter alia via alpha-2-adrenoceptors located in the central nervous system.[4]

However, alpha-2-adrenoceptors are also located in peripheral vasculature, the activation of which leads to vasoconstriction, followed by an increase in arterial blood pressure. Thus, clinically relevant hypertension, baroreceptor-induced sinus bradycardia and decreased cardiac output are commonly observed

with the use of alpha-2-adrenergic agonists.[4–6] In domestic swine (*Sus scrofa domestica*), medetomidine co-administered with midazolam led to increased arterial and pulmonary arterial pressure.[7]

A potential approach to alleviate these cardiovascular disturbances, while preserving sedation, is to selectively reverse the peripheral effects, while maintaining the central effects of alpha-2-agonists. Previous studies have shown the potential of the peripheral alpha-2-adrenergic antagonist vatinoxan to minimize cardiovascular side effects of alpha-2-adrenergic agonists without affecting sedation, for example, in dogs and sheep.[8–13] Vatinoxan improved cardiac output, decreased systemic vascular resistance and thereby improved tissue oxygen delivery in dogs, horses and cats.[9,10,14–16]

The effects of vatinoxan have been primarily investigated in domestic species. Only a few studies demonstrating the efficacy of vatinoxan in non-domestic species, namely markhors[17] and red deer[18], have been conducted.

The objective of this study was to investigate the cardiovascular effects of an intravenous bolus of vatinoxan in wild boars anaesthetised with medetomidine-tiletamine-zolazepam (MTZ). We hypothesized that vatinoxan would markedly alleviate the cardiovascular disturbances induced by medetomidine in wild boars anaesthetised with MTZ without affecting the level of anaesthesia. In particular, we expected that vatinoxan would lead to lower systemic arterial and pulmonary pressures, as well as higher heart rate, cardiac output, and arterial and tissue oxygen saturations.

MATERIAL AND METHODS

All procedures and experiments were approved by the institutional ethics and animal welfare committee and the animal experimental committee of the Austrian Federal Ministry of Science, Research and Economy in accordance to the Austrian Animal Experimentation Act (Tierversuchsgesetz 2012) (BMWFW-68.205/0191-WF/V/3b/2017).

Animals

The study was conducted in 12 healthy 3-month-old wild boars with a mean body weight of 15 kg (standard deviation: ± 1.7 kg; range: 12.3–18.3 kg). The animals originated from the wild boar population kept in outdoor enclosures at the Research Institute of Wildlife Ecology, University of Veterinary Medicine Vienna (48.22 N, 16.28 E) under close to natural conditions. Animals were kept in their social group structure, providing familiar conditions and social interactions with conspecifics (six sows with a total of 26 piglets). The piglets started to take up solid food in addition to suckling approximately 3 weeks after birth. They had access to water and natural forage in their enclosure *ad libitum* and were fed wild boar concentrate pellets, supplemented with corn, some apples and bananas.

All animals appeared healthy before the experimental trials and were clinically examined during each experimental trial.

Study design

The study had a randomised, controlled, experimental, crossover design.

Treatments and drug preparation

Wild boars were randomly assigned using a random sequence generator (random.org) into two treatments, namely:

1. vatinoxan (Vetcare Ltd, Finland) 0.1 mg kg^{-1} (VTX) and
2. equivalent volume of saline 0.9 % in ml (Isotonic sodium chloride solution 0.9 % ad us. vet., B. Braun GmbH, Austria) (CONTROL).

Each of the animals received both treatments, in a randomly assigned order, on two occasions with a 14–16 day wash-out period between treatments.

Anaesthesia was induced with 0.1 mg kg^{-1} medetomidine hydrochloride (HCl) (20 mg mL^{-1}, Medetomidine-hydrochloride 2 %, magistral formula, by Richter Pharma AG, Austria) combined with 2.5 mg kg^{-1} tiletamine-zolazepam (Zoletil, Virbac Österreich GmbH, Austria). MTZ were mixed in the same syringe and administered intramuscularly (IM) into the *Musculus (M.) biceps femoris*.

The powder form of vatinoxan HCl was mixed with sterile 0.9% saline solution to a final concentration of 2.5 mg mL^{-1}. VTX or CONTROL treatment were administered intravenously (IV) over a 30-s period via a catheter inserted into the *Vena* (*V.*) *jugularis* 5 min after baseline measurements, after which the 30 min assessment period was started.

Instrumentation

The anaesthesia protocols were identical for each of the trial rounds. However, during the second trial round, a Swan-Ganz thermodilution catheter was inserted into the *V. jugularis* in all animals (VTX $n = 6$; CONTROL $n = 4$) to measure additional cardiovascular variables including mean, systolic and diastolic pulmonary artery pressure (MPAP, SPAP, DPAP), pulmonary artery occlusion pressure (PAOP) and cardiac output (CO); these variables were not measured during the first trial round. The *V. jugularis* was surgically exposed for better visualisation, and an 8.5F introducer sheath (Intro-Flex-Percutaneous sheath introducer kit, Edwards Lifesciences Austria GmbH, Austria) was inserted into it. A 7.5F thermodilution catheter (Edwards Swan-Ganz CCOmbo

Thermodilution Catheter: 7.5F x 110 cm, Edwards Lifesciences Austria GmbH, Austria) was passed through the introducer sheath and advanced into a distal branch of the pulmonary artery. When the balloon at the tip of the catheter was inflated, it 'wedged' the pulmonary artery. The adjustment of the correct position was controlled by continuous monitoring of pressure tracings from the distal port. The pressure transducer was fixed at the level of the scapulohumeral joint and connected to a patient-side pressure monitor (IntraTorr; IntraVitals, UK). Simultaneous ECG readings were observed for any arrhythmias caused by the catheter passing through the right ventricle. The Swan Ganz catheter was connected to a Vigilance Monitor (Vigilance II CCO/SvO2/CEDV Monitor, 220v, Edwards Lifesciences Austria GmbH, Austria) enabling continuous CO monitoring based on thermodilution principles.

For continuous recording of HR, MAP, SAP, DAP and for collection of blood samples for blood gas analysis, a 22-gauge catheter (Vasofix Safety, Ø 0,9 x L 45 mm, B. Braun Austria GesmbH, Maria Enzersdorf, Austria) was inserted in a femoral artery. The catheter was flushed with heparinised saline (Heparin 5000 I.E./ml, Gilvasan Pharma GmbH, Austria) and secured in place. It was connected via a fluid filled arterial line to an electronic strain-gauge transducer with non-compliant tubing. The transducer itself was attached to a multiparameter monitor (PM-8000 Express, Mindray Medical Germany GmbH, Darmstadt, Germany), that measured HR, MAP/SAP/DAP and continuous lead II ECG. The transducer was pre-calibrated and zeroed to atmospheric air pressure and secured at the level of the sternum and the scapulohumeral joint (level of the heart base) before each experiment.

Tissue oxygen saturation (StO_2) was obtained using near-infrared spectroscopy. An approximately 4×3 cm site was shaved over the two areas analysed: *M. flexor carpi radialis* (right medial forearm, StO_{2F}) and *M. gracilis* (right medial thigh, StO_{2H}). Non-invasive contact probes with regional oximetry sensors (O3 adult adhesive sensor, O3 MOC-9 module, Masimo Corporation, CA, USA) were secured to the skin over the muscle areas. A multiparameter monitor (root with non-invasive blood pressure and temperature monitoring; Radical-7; Phasein ISA; Masimo Corporation, CA, USA), calibrated with CO_2, was used for continuous measurements of the variables StO_{2F} and StO_{2H}, as well as end-tidal carbon dioxide ($PE'CO_2$), respiratory rate (RR), peripheral oxygen haemoglobin saturation (SpO_2).

Femoral artery blood samples were drawn with a heparinised 1 ml syringe (HS Einmalspritzen 1 ml, Covetrus AT GmbH, Austria) and analysed immediately using a portable blood gas analyser (i-STAT 1 Portable Clinical Analyser; Abbott GmbH, Germany). Blood gas cartridges (i-STAT CG4+ Cartridge, ABBott GmbH, Germany) were used to measure arterial oxygen partial pressure (PaO_2), carbon dioxide partial pressure ($PaCO_2$), total carbon dioxide (tCO_2), arterial pH (pH), lactate (Lac), base excess (BE), bicarbonate (HCO_3) and arterial oxygen haemoglobin saturation (SaO_2). The values were corrected for the animal's body temperature. The catheter was flushed with 2 ml heparinised saline (Heparin 5000 I.E./ml, Gilvasan Pharma GmbH, Austria) after each collection.

Rectal temperature (RT) was measured with a digital thermometer (HS Digital Veterinary Thermometer, Covetrus AT GmBH, Austria).

The following three reflexes were tested: palpebral (naso-ventral canthus of the eye) and perineal (perianal skin) reflex by tactile stimulation (up to three times within 10 seconds), as well as pedal withdrawal in response to clamping the interdigital space. Reflex responses were scored with 0 = absent; 1 = reflex could be induced only by repeated stimulus; 2 = present but attenuated reflex response; 3 = normal reflex response.

Procedures and measurements

The animals were trained to access a walled corral located within the enclosure. To leave the corral, the animals had to pass through a corridor in which a wooden box trap was placed. Once the animal entered the box trap, it was closed and transported to the clinic within 10 min. To minimise stress during handling and anaesthetic induction, positive reinforcement training was used to familiarise animals with this loading procedure in advance.

At the clinic animals were weighed using a scale placed underneath the box trap. Timing started (time 0, start of anaesthesia) at injection of MTZ, and animals were moved back into the box trap.

Ten minutes after injection of MTZ, the box trap was partly opened to evaluate reflexes and assess the plane of anaesthesia. When an adequate level of anaesthesia was obtained (no response to respective stimuli), the wild boar received eye ointment applied to the cornea to avert drying (Vit-A-Vision, Omnivision GmbH, Puchheim, Germany), was blindfolded and then transported to the anaesthetic table. The wild boar was placed in dorsal recumbency, and the trachea was intubated (HS Endotracheal Tube, inner diameter 5–7 mm, length 24–30 cm Murphy, Covetrus AT GmbH, Austria) and connected to a semi-open breathing system. Oxygen (100 %; 2 L min^{-1}), and IV isotonic fluids (Isotonic sodium chloride solution 0.9 % ad us. vet., B. Braun GmbH, Austria) were administered to all individuals until the end of anaesthesia. It took approximately 15 min to place all the monitoring equipment. Baseline values (MAP, SAP, DAP, MPAP, SPAP, DPAP, MPAOP, CO, HR, RR, $PE'CO_2$, SpO_2, RT, NIRS, blood gas variables) were measured 25–35 min after anaesthesia start. Values were measured in specifically determined time intervals thereafter. The values MAP, SAP, DAP, MPAP, SPAP, DPAP, HR, ECG were recorded at 10 s-intervals for 2 min, 60 s-intervals for the subsequent 8-min and 5-min intervals for the remaining 20 min. The values MPAOP, CO, $PE'CO_2$, RR, RT, SpO_2, StO_{2F} and StO_{2H} were recorded at 5-min intervals for 30 min. Arterial blood samples were taken at baseline and 5 min after treatment for arterial blood gas analyses.

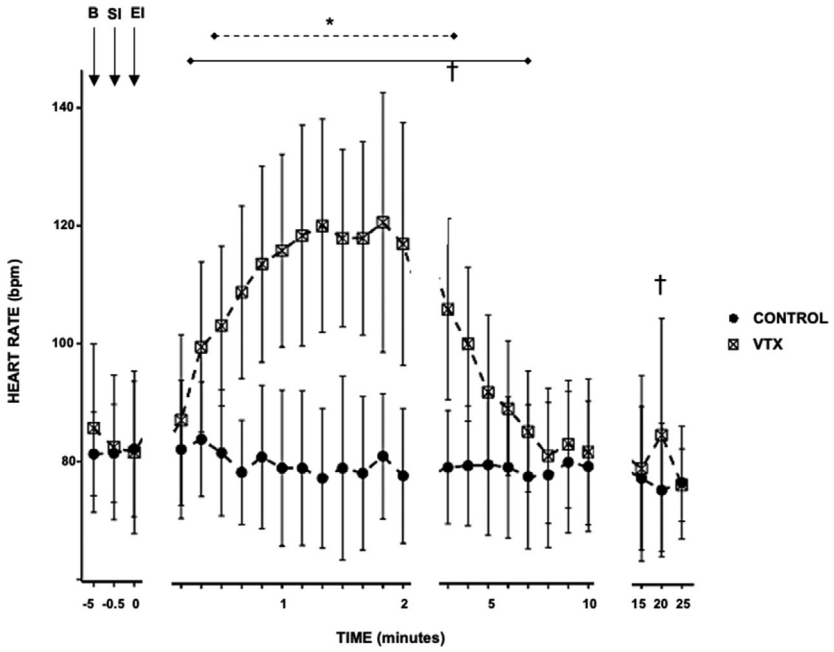

FIGURE 1 Mean of the heart rate (beats minute^{-1}) in wild boar anaesthetised with medetomidine (0.1 mg kg^{-1}) and tiletamine/zolazepam (2.5 mg kg^{-1}) IM. Baseline was assessed 25–35 min after anaesthesia start. Five minutes after baseline vatinoxan (0.1 mg kg^{-1}, $n = 10$) or an equivalent amount of saline ($n = 8$) was injected IV. Gaps in the time line (x-axis) represent changes in time intervals. Error bars indicate the standard deviation. * VTX group significantly different (*post-hoc* test, $p < 0.05$) from baseline. †Significantly different (*post-hoc* test, $p < 0.05$) from control. Arrows represent: B = baseline (5 min before vatinoxan/saline injection), SI = start injection of vatinoxan/saline, EI = end injection of vatinoxan/saline

The total anaesthesia duration was approximately 60 min. At the end of the assessment period, all instruments and monitoring equipment were removed.

During the first trial animals were marked with ear tags for identification purposes. Finally, medetomidine was antagonised by the administration of atipamezole (Antisedan, Vetoquinol GmbH, Germany), dosed at 5 μg for each μg of medetomidine IM. Animals were moved back to their enclosure within the box traps and kept separated from other individuals. They were observed until completely recovered.

As soon as data collection was completed in the second trial, anaesthetised animals were euthanised by injection of T61 IV (1 ml per 10 kg, T61, active compound: embutramide, MSD Animal Health, Austria).

Sample size and statistical analysis

The blinded data acquisition was done by the same investigator (JE) throughout the project. Statistical evaluation is based on data from 12 animals. Power analysis for two independent study groups receiving different treatment and continuous (means) primary endpoints was based on data previously obtained in our laboratory and suggested that 10 animals plus two back-up animals would permit the detection of a 24% difference in MAP with a standard deviation (SD) of 19 mm Hg between VTX and CONTROL treatment, with an alpha level of 0.05 and a power of 0.95.

Statistical analyses were performed by use of R (R version 3.4.1).[19]

A plot and a histogram of the residual data were used to check for normal distribution in the data. Levene's test (car package)[20] was used to test for homoscedasticity between treatments. No deviation from normal distribution or homoscedasticity was found. To adjust for repeated measurements and to avoid pseudo-replication, differences between treatments were tested with a repeated measures analysis of linear mixed effects models (lmer, nlme package)[21] with multiple comparisons (VTX *versus* CONTROL). By including ID as a random effect, we accounted for repeated measurements within the individuals. Changes in cardiopulmonary variables were analysed with a post hoc test (Tukey Honestly Significant Difference) over-time within treatments (change from baseline) and between treatments, as well as at selected time points for time x treatment interaction effects (lsmeans package).[22] Concerning continuous ECG-readings we used binomial generalized linear mixed models with the lme4 package[23] to determine whether treatment, time, trial round and an interaction of those variables influenced the presence of arrhythmias. Regarding the reflex scoring system, a generalized linear mixed model (data were non-parametric) was used to assess differences between treatments (lme4 package).[23] Data are reported as mean ± SD. Statistical significance was set at $p < 0.05$.

RESULTS

Animals

Data of 12 animals were included in the study. However, data of two animals of one respective trial round were excluded. One individual showed insufficient response to anaesthetic drugs. The second animal developed cardiac irregularities (supraventricular and ventricular extra-systoles, ventricular fibrillation) during the placement of the Swan-Ganz catheter.

Heart rate, cardiac output and index, ECG

A significant effect of treatment time interaction (lmer: $p < 0.0001$, degrees of freedom(df) = 25, f-value = 10.123) was found for HR. VTX treatment led to an increase in HR from baseline after 30 s, which remained above baseline values for 3 min (Figure 1, Table 1). The CONTROL treatment did not lead to a change in HR from baseline.

TABLE 1 Changes in cardiovascular variables in wild boar before and after IV administration of 0.1 mg kg^{-1} vatinoxan (VTX) or saline (equal amount of ml vatinoxan; Control). Drugs were injected at time 0. Data are means ± standard deviation

		Time (minutes)										
Variable	**Treatment (*n*)**	**-5 (baseline)**	**0**	**1**	**2**	**3**	**4**	**5**	**10**	**15**	**20**	**25**
HR (beats $minute^{-1}$)	Control (8)	81 ± 7	82 ± 11	79 ± 13	78 ± 11	79 ± 10	80 ± 10	80 ± 12	79 ± 11	78 ± 12	76 ± 11	77 ± 10
	VTX (10)	86 ± 14	82 ± 12	116 ± 16*,†	117 ± 20*,†	106 ± 15*,†	100 ± 13*,†	92 ± 13*,†	82 ± 12	79 ± 16	85 ± 20†	76 ± 6
SAP (mm Hg)	Control (8)	167 ± 10	170 ± 7	168 ± 8	167 ± 8	169 ± 10	167 ± 9	167 ± 9	165 ± 9	162 ± 9	160 ± 11	159 ± 10
	VTX (10)	176 ± 24	168 ± 21	136 ± 18*,†	134 ± 20*,†	136 ± 20*,†	138 ± 21*,†	138 ± 20*,†	144 ± 20*,†	142 ± 22*,†	146 ± 18*,†	143 ± 19*,†
MAP (mm Hg)	Control (8)	140 ± 10	142 ± 8	137 ± 11	137 ± 9	139 ± 10	137 ± 10	137 ± 9	135 ± 10	131 ± 9	128 ± 11	125 ± 11
	VTX (10)	146 ± 24	137 ± 23	103 ± 18*,†	102 ± 19*,†	105 ± 19*,†	107 ± 19*,†	107 ± 18*,†	115 ± 16*,†	115 ± 18*,†	118 ± 17*	114 ± 17*
DAP (mm Hg)	Control (8)	127 ± 12	128 ± 9	122 ± 13	122 ± 10	124 ± 11	122 ± 11	122 ± 10	119 ± 11	115 ± 10	112 ± 13	108 ± 13
	VTX (10)	131 ± 25	122 ± 24	86 ± 20*,†	86 ± 20*,†	89 ± 19*,†	92 ± 19*,†	93 ± 19*,†	101 ± 16*,†	102 ± 17*,†	104 ± 19*	99 ± 18*
MPAP (mm Hg)	Control (4)	25 ± 1.5	25 ± 1.1	24 ± 1.4	24 ± 2.1	23 ± 0.8	23 ± 1.5	23 ± 1.3	23 ± 1.1	23 ± 1.8	22 ± 1.8	22 ± 1.1
	VTX (6)	26 ± 3.7	27 ± 5.9	22 ± 4.6*	20 ± 3.0*	20 ± 3.2*	19 ± 3.9*	20 ± 3.3*	21 ± 2.6*	20 ± 3.1*	20 ± 3.6*	19 ± 3.8*
CO (L min^{-1})	Control (4)	2.6 ± 0.7	2.6 ± 0.7	NA	NA	NA	NA	2.8 ± 0.9	2.9 ± 0.8	3.0 ± 0.7	3.2 ± 0.6	NA
	VTX (4)	2.6 ± 0.4	2.5 ± 0.5	NA	NA	NA	NA	2.9 ± 0.8	2.9 ± 0.6	2.8 ± 0.4	2.7 ± 0.4	NA
MPAOP (mm Hg)	Control (4)	17 ± 2	16 ± 2	NA	NA	NA	NA	15 ± 2	15 ± 2	15 ± 3	15 ± 3	12 ± 3*
	VTX (5)	18 ± 3	9 ± 4*,†	NA	NA	NA	NA	8 ± 1*	12 ± 4*	11 ± 4*	12 ± 4*	12 ± 3*

Abbreviations: CO, cardiac output; DAP, diastolic arterial pressure (invasive); HR, heart rate; IV, intravenous; MAP, mean arterial pressure (invasive); MPAOP, mean pulmonary artery occlusion pressure; MPAP, mean pulmonary artery pressure; NA, not available; SAP, systolic arterial pressure (invasive).

*Significantly different from baseline (−5 minutes) (*post hoc* test, $p < 0.05$).

†Significantly different from control at this time point (*post hoc* test, $p < 0.05$).

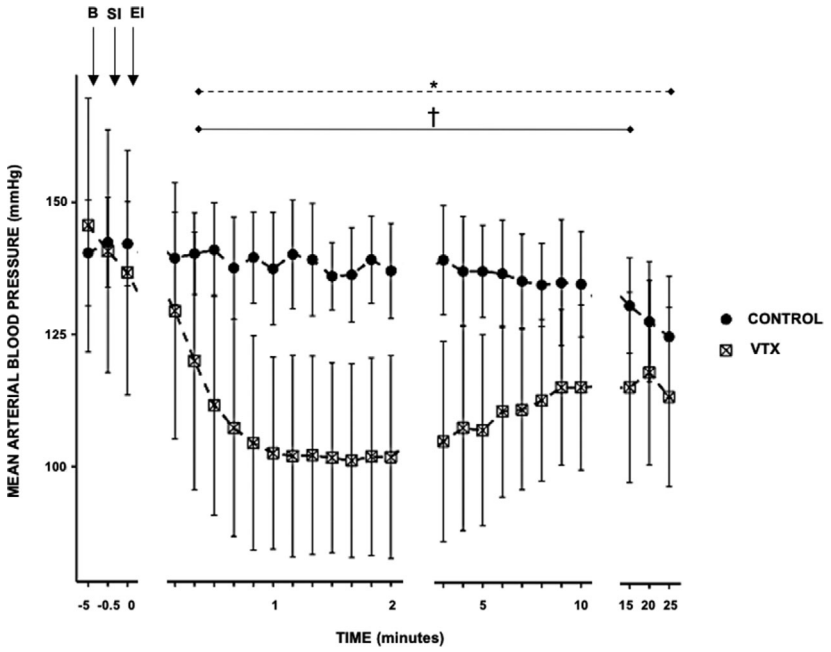

FIGURE 2 Mean of the mean arterial blood pressure (mm Hg) in wild boar anaesthetised with medetomidine (0.1 mg kg^{-1}) and tiletamine/zolazepam (2.5 mg kg^{-1}) IM. Baseline was assessed 25–35 min after anaesthesia start. Five minutes after baseline vatinoxan (0.1 mg kg^{-1}, $n = 10$) or an equivalent amount of saline ($n = 8$) was injected IV. Gaps in the time line (X-axis) represent changes in time intervals. Error bars indicate the standard deviation. * VTX group significantly different (*post-hoc* test, $p < 0.05$) from baseline. †Significantly different (*post-hoc* test, $p < 0.05$) from Control. Arrows represent: B = baseline (5 min before vatinoxan/saline injection), SI = start injection of vatinoxan/saline, EI = end injection of vatinoxan/saline

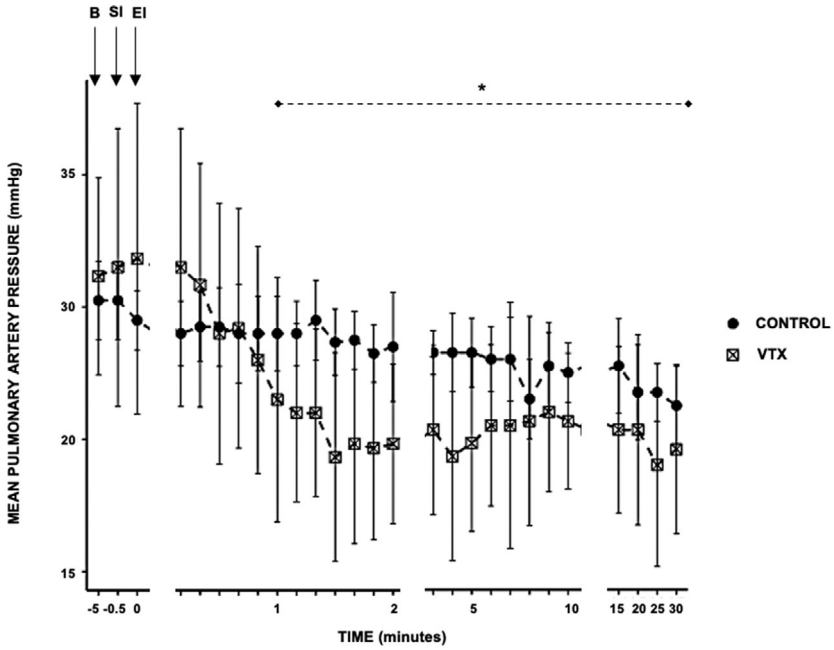

FIGURE 3 Mean of the mean pulmonary artery pressure (mm Hg) in wild boar anaesthetised with medetomidine (0.1 mg kg^{-1}) and tiletamine/zolazepam (2.5 mg kg^{-1}) IM. Baseline was assessed 25–35 min after anaesthesia start. Five minutes after baseline vatinoxan (0.1 mg kg^{-1}, $n = 6$) or an equivalent amount of saline ($n = 4$) was injected IV. Gaps in the time line (x-axis) represent changes in time intervals. Error bars indicate the standard deviation. * VTX group significantly different (*post-hoc* test, $p < 0.05$) from baseline. †Significantly different (*post-hoc* test, $p < 0.05$) from control. Arrows represent: B = baseline (5 min before vatinoxan/saline injection), SI = start injection of vatinoxan/saline, EI = end injection of vatinoxan/saline

No difference within and between treatments was found for CO (Table 1) or the occurrence of arrythmias.

Arterial blood, pulmonary artery and occlusion pressures

A significant effect of treatment time interaction (lmer: $p < 0.0001$, df = 25, f-value = 4.200, 4.395, 3.256, respectively) was found for MAP, DAP and SAP. A decrease from baseline in MAP/DAP/SAP occurred 20 s after VTX administration and remained below baseline values until the end of anaesthesia (Table 1, for MAP see Figure 2). The MAP and DAP values showed differences between treatments from 20 s until 15 min after treatment. The SAP values showed differences between treatments 20 s after treatment until the end of anaesthesia.

A significant effect of treatment time interaction (lmer: $p < 0.0001$, df = 6, f-value = 10.789) was found for MPAOP (Table 1).

A significant effect of treatment time interaction ($p = 0.001$, $p = 0.01$, $p = 0.0006$, df = 26, f-value = 2.190, 1.839, 2.307 respectively) was found for MPAP/DPAP/SPAP. The MPAP values decreased from baseline 1 min after VTX treatment and remained below baseline values until the end of anaesthesia (Figure 3, Table 1). There was no difference between treatments at any time point. DPAP values showed a decline from baseline 70 s after VTX treatment and remained below baseline values until the end of anaesthesia. There was no difference between treatments for DPAP at any time point. SPAP decreased from baseline after 1 min and remained—except for 5 time points in between—below baseline values until the end of anaesthesia. There was a difference between

TABLE 2 Changes in vital variables in wild boar before and after IV administration of 0.1 mg kg^{-1} vatinoxan (VTX) or saline (equal amount of ml vatinoxan; Control). Drugs were injected at time 0. Data are mean ± standard deviation

		Time (minutes)							
Variable	**Treatment (*n*)**	**-5 (baseline)**	**0**	**5**	**10**	**15**	**20**	**25**	**30**
RR (breaths $minute^{-1}$)	Control (10)	51 ± 13	53 ± 8	53 ± 8	51 ± 10	51 ± 9	51 ± 9	53 ± 9	56 ± 15
	VTX (10)	56 ± 12	55 ± 9	53 ± 8	53 ± 11	56 ± 9	55 ± 8	55 ± 8	55 ± 8
$PE'CO_2$ (mm Hg)	Control (10)	56 ± 3	53 ± 3	53 ± 3	51 ± 3*	50 ± 2*	50 ± 3*	48 ± 4*	50 ± 3*
	VTX (10)	52 ± 5†	54 ± 6	49 ± 4†	49 ± 3*,†	47 ± 5*,†	49 ± 3*	48 ± 4*	50 ± 3*
SpO_2 (%)	Control (10)	96 ± 3.5	97 ± 2.2	97 ± 1.9	97 ± 1.0	98 ± 0.7	96 ± 1.9	96 ± 2.9	97 ± 2.3
	VTX (10)	96 ±1.8	97 ± 1.8	96 ± 2.0	95 ± 2.2†	96 ± 1.9†	96 ± 1.4	96 ± 1.9	97 ± 0.4
RT (°C)	Control (10)	39.6 ± 0.9	39.3 ± 0.6	39.3 ± 0.6	39.2 ± 0.6	39.2 ± 0.6	39.0 ± 0.6	39.0 ± 0.6	38.8 ± 0.5
	VTX (10)	39.5 ± 0.9	39.3 ± 0.8	39.3 ± 0.7	39.1 ± 0.7	39.0 ± 0.7	39.1 ± 0.6	38.8 ± 0.5	38.8 ± 0.5
StO_{2F} (%)	Control (7)	64 ± 7	64 ± 6	64 ± 8	66 ± 8	66 ± 8	66 ± 8	67 ± 8	66 ± 8
	VTX (8)	64± 4	66 ± 3	65 ± 3	65 ± 3	65 ± 3	65 ± 3	64 ± 3	65 ± 3
StO_{2H} (%)	Control (6)	72 ± 7	73 ± 6	74 ± 7	73 ± 6	73 ± 6	73 ± 6	73 ± 6	73 ± 6
	VTX (6)	70 ± 5	70 ± 6	69 ± 7†	68 ± 7†	69 ± 6†	66 ± 8†	70 ± 7	69 ± 7

Abbreviations: IV, intravenous; $PE'CO_2$, end-tidal CO_2; SpO_2, peripheral oxygen haemoglobin saturation measured by pulse oximetry; RT, rectal temperature; StO_{2F}, O3 regional oximetry measured at the *M. flexor carpi radialis* by near-infrared spectroscopy; RR, respiratory rate; StO_{2H}, O3 regional oximetry measured at the *M. gracilis* by near-infrared spectroscopy.
*Significantly different from baseline (−5 minutes) (*post hoc* test, $p < 0.05$).
†Significantly different from Control at this time point (*post hoc* test, $p < 0.05$).

treatments for SPAP at the time-points 100 s and 4 min after treatment. The CONTROL treatment did not lead to differences from baseline for MPAP/DPAP/SPAP.

Respiratory indices and tissue oxygen saturation

For $PE'CO_2$ there was a significant difference between treatments at baseline, and 5 min after treatment lasting for a further 10 min, with lower $PE'CO_2$ values observed with the VTX treatment (Table 2).

A significant effect of treatment was detected for SpO_2 after 10–15 min, with lower values for the VTX treatment (Table 2). No difference within and between treatments was found for RR and StO_{2F} (Table 2).

For StO_{2H} a significant effect of treatment was observed (Table 2) after 5–20 min, with lower values with the VTX treatment.

Arterial blood gases

VTX treatment caused a significant increase from baseline for pH and BE (Table 3).

For Lac there was a difference between treatments 5 min after treatment, with vatinoxan leading to higher values (Table 3).

No difference within and between treatments was detected for $PaCO_2$, tCO_2, HCO_3, PaO_2, SaO_2 (Table 3).

The variables pH, PaO_2, $PaCO_2$ and Lac are measured by cartridge sensors. The values for HCO_3, tCO_2, SaO_2 and BE are calculated according to a preassigned algorithm/calculation of the I-stat device. Blood gases were corrected for body temperature, but not for FIO_2.

TABLE 3 Changes in arterial blood gas values in wild boar 5 min before and after IV administration of 0.1 mg kg^{-1} vatinoxan (VTX; $n = 10$) or saline (equal amount of ml vatinoxan; Control; $n = 8$). Drugs were injected at time 0. Data are mean ± standard deviation

		Time (minutes)	
Variable	**Treatment**	**-5 (baseline)**	**5**
pH	Control	7.38 ± 0.02	7.39 ± 0.02
	VTX	7.37 ± 0.05	7.41 ± 0.04*
$PaCO_2$ (mm Hg)	Control	51 ± 2.5	51 ± 2.9
	VTX	48 ± 8.2	48 ± 5
PaO_2 (mm Hg)	Control	176 ± 44	180 ± 48
	VTX	174 ± 45	168 ± 39
tCO_2 (mmol/L)	Control	31 ± 1	32 ± 1
	VTX	28 ± 4	31 ± 2
BE (mmol L^{-1})	Control	6 ± 1.7	6 ± 1.7
	VTX	2 ± 5†	5 ± 3*
HCO_3^- (mmol L^{-1})	Control	29.9 ± 1.3	30.6 ± 1.3
	VTX	27.1 ± 4.2	29.4 ± 2.3
SaO_2 (%)	Control	99 ± 2	99 ± 2
	VTX	99 ± 2.3	99 ± 2.0
Lac (mmol L^{-1})	Control	2 ± 0.8	1.7 ± 0.4
	VTX	2.4 ± 1.0	2.2 ± 0.9†

Abbreviations: BE, base excess; HCO_3^-, concentration of hydrogen carbonate (bicarbonate); IV, intravenous; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; SaO_2, percentage arterial haemoglobin oxygen saturation; Lac, lactate concentration; tCO_2, total carbon dioxide.
*Significantly different from baseline (−5 minutes) (*post* hoc test, $p < 0.05$).
†Significantly different from control at this time point (*post* hoc test, $p < 0.05$).

Rectal temperature

No significant effect of treatment or time was found for RT (Table 2).

Reflexes

No difference between treatments was found for palpebral, perianal or pedal withdrawal reflexes. The recovery from anaesthesia after atipamezole administration was smooth and rapid without differences between treatments.

DISCUSSION

The combination of MTZ induced hypertension and potential bradycardia in the wild boars. The IV VTX significantly increased HR and reduced arterial blood pressure without causing hypotension. While the effect on the reduction of blood pressure lasted until the end of the anaesthesia, HR returned to baseline values within 3 min of injection of VTX.

As physiological reference values for HR in unsedated wild boars are not available, resting HR and cut-off points for bradycardia and tachycardia were calculated according to the formula ($241 * BW^{-0.25}$),[24] where a rate of more than 20 % below or above that value was considered brady- or tachycardic. Calculated reference ranges were comparable to conscious domestic juvenile pigs (Table S1).

The duration of action of VTX on HR in our study was short compared to other studies. For example, in dogs significant alleviations of the dexmedetomidine[8,9] and medetomidine-induced decrease[10,25]in HR were detected for a duration of 40–90 min when VTX was co-administered. In contrast to other studies in cats (0.6 mg kg^{-1} IV),[16] dogs (0.25 mg kg^{-1} IV)[8] and sheep (0.25 mg kg^{-1} IV),[26] we used a relatively low dose of VTX (0.1 mg kg^{-1} IV). A previous study in red deer, where the same low dose of VTX (0.1 mg kg^{-1} IV) was used, also showed a relatively short duration of action, with the effects on HR subsiding after 15 min.[18] It has been demonstrated in many species sedated with (dex)medetomidine that the duration of cardiovascular effects of VTX can be dose-dependent.[9,13,17,25,27] Therefore, the short effect of VTX on HR might be attributed to the low VTX dose, or the dose ratio between the alpha-2-adrenergic agonist and antagonist in the current study.[25,28] However, comparable doses in horses (0.15 mg kg^{-1} IV), administered 10 min after detomidine (0.02 mg/kg IV), led to an increase in HR that was sustained for 90 min after VTX administration.[29] A study in markhors, another non-domestic species, showed no dose-dependent effects of VTX on HR (0.117-0.297 mg kg^{-1} of VTX).[17] We therefore speculate that a higher dose of VTX may have led to more profound and longer lasting cardiovascular effects. However, our results demonstrate that also a relatively low dose of VTX effectively alleviated the major cardiovascular disturbances induced by medetomidine.

Apart from dose, the wide range of reported duration of effects of VTX on HR may also be attributed to a species-specific sensitivity. Plasma half live of VTX was longer in horses (140–170 min)[30] compared to dogs (40–60 min).[31]

Differences in the pharmacokinetics between the intramuscularly administered medetomidine and the intravenous bolus of VTX, which would result in different plasma concentration profiles could be another reason for the short effect of VTX on HR in this study. In dogs, the plasma concentration of VTX decreased rapidly after IV administration,[31] while the concentration of medetomidine administered intramuscularly in dogs did not change substantially between 30 and 90 min.[25] Therefore, in our study, the concentration of VTX necessary to out-compete medetomidine at the receptor sites may have occurred for only a short duration.

However, whereas HR increased only momentarily, VTX administration led to an alleviation of hypertension, which lasted until the end of the monitoring period. As a shorter effect of vatinoxan on HR than on blood pressure appears unlikely, the recurring decrease of HR might be caused by a central sympatholytic effect[4] of medetomidine, which vatinoxan is not expected to affect.

Cats anaesthetised with isoflurane (end-tidal isoflurane concentration: 1.4 - 1.5 %) and receiving a target-controlled infusion of DMED (plasma DMED concentration of 10 ng mL^{-1}) showed significant changes in ABP after VTX administration, irrespective of the dose used.[32] After administration of 0.03 and 0.06 mg kg^{-1} VTX, blood pressure decreased by >40 %. However, compared to the marked change in ABP, HR increased by only 7%. Similarly to our study, VTX was administered after the alpha-2-adrenergic agonist, and the animals were under the additional influence of an anaesthetic component (in this case isoflurane). Isoflurane is known to depress baroreceptor-mediated sympathetic activity,[33] which might have contributed to the mild changes in HR compared to blood pressure after VTX in isoflurane anaesthetised cats. A study investigating the impact of ketamine on the baroreceptor reflex in rabbits during mechanical ventilation suggested an inhibitory effect of ketamine on the vagal (HR) component of the baroreceptor reflex.[34] In markhors anaesthetised with medetomidine and ketamine, significant changes in blood pressure were observed after VTX administration.[17] However, no statistically significant changes in HR were detected, which was attributed to the small sample size ($n = 8$). Nevertheless, the presence of ketamine in this study might have had an influence of unknown degree on the baroreceptor mediated reflex after vatinoxan administration. Based on these findings a potential effect of TZ leading to a less pronounced effect of vatinoxan on HR compared to ABP should be further considered in the present study.

Although studies in other species sedated with medetomidine, such as sheep[11] and dogs,[10,25] have shown a significant increase of CO by VTX, no effect of VTX was detected on CO and CI in the current study. However, in contrast to HR, which was assessed every 10 s after VTX administration CO was measured

only every 5 min in our study. At the first measurement of CO, 5 min after VTX administration, HR had already decreased to the bradycardic baseline values. Therefore, it is likely that immediate and short-term responses to VTX on CO were not detected in this study. Furthermore, the small sample size concerning variables measured by the Swan Ganz catheter (CO, PAP, MPAOP) might have limited detecting the effects of VTX in this study.

However, we did observe significant decreases in pulmonary artery pressure and pulmonary artery occlusion pressure following VTX administration. This finding agrees with previous studies in for example dogs[10] and cats.[35]

No difference was detected in RR between treatments. Slightly elevated $PE'CO_2$ was measured in both treatments at baseline. While $PE'CO_2$ slightly decreased in both treatments throughout monitoring period, values were lower after VTX.

Both treatments showed SpO_2 values within marginally acceptable limits (95%–97 %), which is in line with SpO_2 measurements of studies conducted in conscious domestic pigs (Table S1). VTX led to a significant decrease in SpO_2 10 min after administration lasting for 5 min. This finding was unexpected and not confirmed by SaO_2 values. However, blood gas samples were drawn only 5 min after VTX administration. To our knowledge no other studies have shown similar effects of VTX. VTX administered alone markedly improved cardiac index, and thereby oxygen delivery, in various domestic animals sedated with (dex)medetomidine.[9,11,36] More detailed studies on the pulmonary effects of VTX when medetomidine is used in wild boars are desirable.

Whereas PaO_2, $PaCO_2$, HCO_3 and SaO_2. Lac, HCO_3^-, SaO_2, pH and PaO_2 were within clinically acceptable ranges in both treatments, and no effect of VTX treatment could be detected, $PaCO_2$ and BE were elevated. However, no hypoxemia or severe hypercapnia was detected in the animals, which was defined as a partial pressure of arterial carbon dioxide or end-tidal carbon dioxide above 55 mm Hg.[37] Furthermore, BE values were comparable to studies in awake pigs (Table S1). After VTX, BE and pH increased significantly from baseline. This change might indicate an effective compensation of respiratory acidosis with the VTX treatment.

Oxygen delivery, consumption and extraction ratios were not measured in the current study. However, near-infrared spectroscopy was used to evaluate StO_2 at the capillary level, which was low compared to, for example, dogs,[38] pigs[39] and humans.[40] Medetomidine-induced hypertension and lower heart rate may have influenced the tissue perfusion and thereby StO_2. Concerning StO_{2H}, a significant difference between treatments occurred after 5 min, lasting for 20 min, with lower values observed in the VTX treatment. Blood haemoglobin concentrations have a marked impact on StO_2 readings in pigs.[39] Studies in sheep and dogs showed lower haemoglobin concentrations when the alpha-2-adrenergic agonist was combined with VTX.[12,13,41]

All animals showed a sufficient level plane of anaesthesia, and no difference was detected between treatments. However, the additional anaesthetic effects of tiletamine and zolazepam used in the study does not allow interpretation of the impact of VTX on the level or duration of the medetomidine-induced sedation.

CONCLUSION

We found that IV administration of vatinoxan effectively reversed medetomidine-induced hypertension and increased heart rate, in MTZ anaesthetised wild boars. However, the effect of vatinoxan on heart rate subsided after a short period of time compared to the long-lasting effect on blood pressure. Vatinoxan has the potential to reduce cardiovascular anaesthetic side effects, especially hypertension, in non-domestic boars immobilized with MTZ.

ACKNOWLEDGEMENTS

We would like to thank Vetcare Ltd, Finland for providing vatinoxan. This work was supported by the Vetmed Success scholarship of the University of Veterinary Medicine Vienna to JE and funding from the Humboldt foundation to JN. We also thank Renate Hengsberger for helping in preparing the MS.

AUTHOR CONTRIBUTIONS

Conceptualization of the study: Gabrielle Stalder, Ulrike Auer, Johanna Painer and Marja Raekallio. *Performed experiments and data sampling*: Joy Einwaller, Johanna Painer, Ulrike Auer, Leith C. R. Meyer, Gabrielle Stalder, Julia Nowack and Sebastian Vetter. *Statistical analysis*: Joy Einwaller and Julia Nowack. *Data interpretation*: Joy Einwaller, Marja Raekallio, Leith C. R. Meyer, Ulrike Auer, Anna Haw, Gabrielle Stalder and Johanna Painer. *Funding acquisition, resources*: Gabrielle Stalder, Johanna Painer and Ulrike Auer. *Writing – original draft*: Joy Einwaller, Gabrielle Stalder and Anna Haw. *Review and editing*: All authors.

CONFLICT OF INTEREST

The authors declare no competing financial interests as well as no conflict of interests. Vetcare, Finland, provided vatinoxan the study. However, the company played no role in the study design or in the data collection, analysis and interpretation. None of the authors has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the manuscript.

ORCID

Gabrielle Stalder https://orcid.org/0000-0002-8901-1181

REFERENCES

1. Enqvist K, Arnemo JM, Lemel JP, Truve J. Medetomidine/tiletamine-zolazepam and medetomidine/butorphanol/tiletamine-zolazepam: a comparison of two anesthetic regimens for surgical implantation of intraperitoneal radiotransmitters in free-ranging juvenile European Wild Boars (*Sus scrofa scrofa*). Florida: American Association of Zoo Veterinarians; 2000.
2. Barasona JA, López-Olvera JR, Beltrán-Beck B, Gortázar C, Vicente J. Trap-effectiveness and response to tiletamine-zolazepam and medetomidine anaesthesia in Eurasian wild boar captured with cage and corral traps. BMC Vet Res. 2013;9:107.
3. Sutherland-Smith M Suidae and Tayassuidae (Wild Pigs, Peccaries). In: Miller RE, Fowler ME, editors. *Fowler's zoo and wild animal medicine*. St Louis, MO: Saunders; 2015. p. 568–84
4. Murrell JC, Hellebrekers LJ. Medetomidine and dexmedetomidine: a review of cardiovascular effects and antinociceptive properties in the dog. Vet Anaesth Analg. 2005;32(3):117–27.
5. Langer SZ, Massingham R, Shepperson NB. Presence of Postsynaptic α_2-Adrenoreceptors of Predominantly Extrasynaptic Location in the Vascular Smooth Muscle of the Dog Hind Limb. Clin Sci. 1980;59(s6):225s–8s.
6. Bryant CE, Clarke KW, Thompson J. Cardiopulmonary effects of medetomidine in sheep and in ponies. Res Vet Sci. 1996;60(3):267–71.
7. Nishimura R, Kim H-Y, Matsunaga S, Hayashi K, Tamura H, Sasaki N, et al. Cardiopulmonary Effects of Medetomidine-Midazolam and Medetomidine-Midazolam-Atipamezole in Laboratory Pigs. J Vet Med Sci. 1994;56(2):359–63.
8. Honkavaara JM, Raekallio MR, Kuusela EK, Hyvärinen EA, Vainio OM. The effects of L-659,066, a peripheral α2-adrenoceptor antagonist, on dexmedetomidine-induced sedation and bradycardia in dogs. Vet Anaesth Analg. 2008;35(5):409–13.
9. Honkavaara JM, Restitutti F, Raekallio MR, Kuusela EK, Vainio OM. The effects of increasing doses of MK-467, a peripheral alpha$_2$-adrenergic receptor antagonist, on the cardiopulmonary effects of intravenous dexmedetomidine in conscious dogs. J Vet Pharmacol Therap. 2011;34(4):332–7.
10. Rolfe NG, Kerr CL, Mcdonell WN. Cardiopulmonary and sedative effects of the peripheral α_2-adrenoceptor antagonist MK 0467 administered intravenously or intramuscularly concurrently with medetomidine in dogs. Am J Vet Res. 2012;73(5):587–94.
11. Adam M, Huuskonen V, Raekallio MR, Casoni D, Mykkänen AK, Lappalainen AK, et al. Cardiopulmonary effects of vatinoxan in sevoflurane-anaesthetised sheep receiving dexmedetomidine. Vet J. 2018;238:63–9.
12. Adam M, Raekallio MR, Keskitalo T, Honkavaara JM, Scheinin M, Kajula M, et al. The impact of MK-467 on plasma drug concentrations, sedation and cardiopulmonary changes in sheep treated with intramuscular medetomidine and atipamezole for reversal. J Vet Pharmacol Therap. 2018;41(3):447–56.
13. Adam M, Raekallio MR, Salla KM, Honkavaara JM, Männikkö S, Scheinin M, et al. Effects of the peripherally acting α2-adrenoceptor antagonist MK-467 on cardiopulmonary function in sheep sedated by intramuscular administration of medetomidine and ketamine and reversed by intramuscular administration of atipamezole. Am J Vet Res. 2018;79(9):921–32.
14. Salla K, Restitutti F, Vainionpää M, Junnila J, Honkavaara J, Kuusela E, et al. The cardiopulmonary effects of a peripheral alpha-2-adrenoceptor antagonist, MK-467, in dogs sedated with a combination of medetomidine and butorphanol. Vet Anaesth Analg. 2014;41(6):567–74.
15. Pakkanen SAE, Raekallio MR, Mykkänen AK, Salla KM, De Vries A, Vuorilehto L, et al. Detomidine and the combination of detomidine and MK-467, a peripheral alpha-2 adrenoceptor antagonist, as premedication in horses anaesthetized with isoflurane. Vet Anaesth Analg. 2015;42(5):527–36.
16. Pypendop BH, Honkavaara J, Ilkiw JE. Cardiovascular effects of dexmedetomidine, with or without MK-467, following intravenous administration in cats. Vet Anaesth Analg. 2017;44(1):52–62.
17. Sainmaa S, Mykkänen AK, Adam M, Jantunen N, Vainio O, Raekallio MR. Intravenous vatinoxan in markhors (*Capra falconeri heptneri*) immobilized with intramuscular medetomidine and ketamine—A preliminary dose screening study. J Zoo Wildlife Med. 2019;50:159–66.
18. Einwaller J, Painer J, Raekallio M, Gasch K, Restitutti F, Auer U, et al. Cardiovascular effects of intravenous vatinoxan (MK-467) in medetomidine–tiletamine–zolazepam anaesthetised red deer (*Cervus elaphus*). Vet Anaesth Analg. 2020;47(4):518–27.
19. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2017.
20. Fox J, Weisberg S. *An R companion to applied regression*. Los Angeles; London: Sage Publications; 2019.
21. Pinheiro J, Bates D, Debroy S, Sarkar D, R Development Core Team. Linear and nonlinear mixed effects models. 2017. http://CRAN.R-project.org/package=nlme. Accessed 5 June 2020.
22. Lenth RV. Least-squares means: the R package lsmeans. J Stat Softw. 2016;69(1):1–33.
23. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw. 2014;23:1215–25.
24. Heard DJ. Monitoring. In zoo animal & wildlife. In: West G, Heard DJ, Caulkett N, editors. *Immobilization and Anesthesia*. Ames, Iowa: Blackwell; 2007. p. 81–91.
25. Restitutti F, Kaartinen MJ, Raekallio MR, Wejberg O, Mikkola E, Del Castillo JRE, et al. Plasma concentration and cardiovascular effects of intramuscular medetomidine combined with three doses of the peripheral alpha$_2$-antagonist MK-467 in dogs. Vet Anaesth Analg. 2017;44(3):417–26.
26. Raekallio MR, Honkavaara JM, Vainio OM. The effects of L-659,066, a peripheral α_2-adrenoceptor antagonist, and verapamil on the cardiovascular influences of dexmedetomidine in conscious sheep. J Vet Pharmacol Therap. 2010;33(5):434–8.
27. Honkavaara J, Pypendop B, Turunen H, Ilkiw J. The effect of MK-467, a peripheral α_2-adrenoceptor antagonist, on dexmedetomidine-induced sedation and bradycardia after intravenous administration in conscious cats. Vet Anaesth Analg. 2017;44(1):42–51.
28. Kaartinen J, Del Castillo JRE, Salla K, Troncy E, Raekallio MR, Vainio OM. Haemodynamic interactions of medetomidine and the peripheral alpha-2 antagonist MK-467 during step infusions in isoflurane-anaesthetised dogs. Vet J. 2014;202(2):353–60.
29. Tapio HA, Raekallio MR, Mykkänen A, Mama K, Mendez-Angulo JL, Hautajärvi H, et al. Effects of MK-467 hydrochloride and hyoscine butylbromide on cardiorespiratory and gastrointestinal changes induced by detomidine hydrochloride in horses. Am J Vet Res. 2018;79(4):376–87.
30. De Vries A, Pakkanen SAE, Raekallio MR, Ekiri A, Scheinin M, Taylor PM, et al. Clinical effects and pharmacokinetic variables of romifidine and the peripheral α2-adrenoceptor antagonist MK-467 in horses. Vet Anaesth Analg. 2016;43(6):599–610.
31. Honkavaara J, Restitutti F, Raekallio M, Salla K, Kuusela E, Ranta-Panula V, et al. Influence of MK-467, a peripherally acting α_2-adrenoceptor antagonist on the disposition of intravenous dexmedetomidine in dogs. Drug Metab Dispos. 2012;40(3):445–9.
32. Martin-Flores M, Sakai DM, Honkavaara J, Campoy L, Portela DA, Gleed RD. Hemodynamic effects of MK-467 following intravenous administration to isoflurane-anesthetized cats concurrently receiving dexmedetomidine. Am J Vet Res. 2018;79(7):711–7.
33. Sellgren J, Biber B, Henriksson BÅ, Martner J, Pontén J. The effects of propofol, methohexitone and isoflurane on the baroreceptor reflex in the cat. Acta Anaesth. Scand. 1992;36(8):784–90.
34. Mcgrath JC, Mackenzie JE, Millar RA. Effects of ketamine on central sympathetic discharge and the baroreceptor reflex during mechanical ventilation. Br J Anaesth. 1975;47(11):1141–7.

35. Siao KT, Pypendop BH, Honkavaara J, Ilkiw JE. Hemodynamic effects of dexmedetomidine, with and without MK-467, following intramuscular administration in cats anesthetized with isoflurane. Vet Anaesth Analg. 2017;44(5):1101–15.
36. Enouri SS, Kerr CL, Mcdonell WN, O'sullivan ML, Neto FJT. Effects of a peripheral α_2-adrenergic receptor antagonist on the hemodynamic changes induced by medetomidine administration in conscious dogs. Am J Vet Res. 2008;69(6):728–36.
37. Brodbelt DC, Flaherty D, Pettifer GR. Anesthetic risk and informed consent. In: Grimm KA, Lamont LA, Tranquilli WJ, Greene SA, Robertson SA, editors. *Veterinary anesthesia and analgesia: the fifth edition of lumb and jones*. Hoboken, New Jersey: John Wiley & Sons; 2015. p. 11–22.
38. Hall KE, Powell LL, Beilman GJ, Shafer KR, Skala VK, Olmstead EA. Measurement of tissue oxygen saturation levels using portable near-infrared spectroscopy in clinically healthy dogs. J Vet Ermerg Crit Care. 2008;18(6):594–600.
39. Myers D, Mcgraw M, George M, Mulier K, Beilman G. Tissue hemoglobin index: a non-invasive optical measure of total tissue hemoglobin. Crit Care. 2009;13(Suppl 5):S2.
40. Buono MJ, Miller PW, Hom C, Pozos RS, Kolkhorst FW. Skin blood flow affects *In Vivo* near-infrared spectroscopy measurements in human skeletal muscle. Jpn J Physiol. 2005;55(4):241–44.
41. Salla K, Bennett RC, Restitutti F, Junnila J, Raekallio M, Vainio O. A comparison in dogs of medetomidine, with or without MK-467, and the combination acepromazine-butorphanol as premedication prior to anaesthesia induced by propofol and maintained with isoflurane. Vet Anaesth Analg. 2014;41(2):163–73.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Einwaller J, Meyer LCR, Auer U, Raekallio M, Nowack J, Haw A, et al. Cardiovascular effects of intravenous vatinoxan in wild boars (*Sus scrofa*) anaesthetised with intramuscular medetomidine-tiletamine-zolazepam. *Vet Rec*. 2021;e835. https://doi.org/10.1002/vetr.835