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Original Article

Non-invasive blood pressure measurement in ferrets (*Mustela putorius furo*) using high definition oscillometry

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ABSTRACT

This study was conducted to validate the use of high definition oscillometry (HDO) for non-invasive blood pressure (NIBP) measurements in ferrets and to establish reference ranges for NIBP in minimally sedated, healthy, young adult ferrets (<4 years of age). The bias, limits of agreement and correlation for HDO compared to direct arterial blood pressure (DABP) measurement were established in 14 anaesthetised ferrets. Measurements were performed at the forelimb, hind limb and tail under hypo- (<110 mmHg), normo- (110–170 mmHg) and hypertensive (>170 mmHg) conditions. Although HDO correlated well with DABP ($r > 0.90$), it showed significant proportional bias, whereby HDO generally underestimated DABP with hyper- and normotensive conditions, and overestimated DABP with hypotensive conditions. Measurements obtained from the hind limb showed higher bias than those obtained from the tail or forelimb ($P < 0.001$). Based on the above, and for practical reasons, the tail was selected as the preferred site of cuff placement in ferrets. Subsequently, a cross-over study was performed in 10 ferrets to establish the minimum dose of butorphanol and midazolam needed to successfully obtain NIBP in 100% of cases. Using this dose (0.2 mg/kg IM, each), reference intervals for NIBP from 63 healthy, young adult ferrets were established at 95–155 mmHg (systolic), 69–109 mmHg (mean) and 51–87 mmHg (diastolic) arterial pressures.

Introduction

Renal and endocrine diseases commonly cause hypertension and are reported frequently in ferrets (Chen, 2010). Thus, reliable non-invasive measurement of arterial blood pressure (ABP) is necessary in this species. Although direct arterial blood pressure (DABP) measurement is considered to be the gold standard for reliable blood pressure (BP) measurement (Wagner and Brodbelt, 1997; Pachtinger, 2013), arteries are inaccessible in ferrets for this purpose. Non-invasive BP (NIBP) measurement is therefore the only feasible alternative in ferrets. Thus far, NIBP measurements in ferrets have mainly been performed using the Doppler technique (Olin et al., 1997; Lichtenberger and Ko, 2007; DeCubellis, 2010). However, this technique only allows measurement of systolic arterial pressure (SAP).

High definition oscillometry (HDO) allows measurement of SAP, mean arterial pressure (MAP) and diastolic arterial pressure (DAP), and might provide a useful alternative to the Doppler technique. HDO has been evaluated previously in dogs, cats, horses, cheetahs and monkeys (Schmelting et al., 2009; Meyer et al., 2010; Petrič et al., 2010; Wernick et al., 2010; Martel et al., 2013; Rysnik et al., 2013; Seliškar et al., 2013; Mietsch and Einspanier, 2015; Sant Cassia et al., 2015; Tünsmeyer et al., 2015), but not ferrets.

The success and reliability of NIBP measurement are influenced by the conditions under which the measurement is obtained, cuff site and width:limb circumference ratio, BP (in cases of severe hypotension), use of pharmacological agents, and the position and compliance of the subject (Valtonen and Eriksson, 1970; Binns et al., 1995; Hall et al., 2001; Brown et al., 2007; Egner et al., 2007). These factors need to be taken into account when developing a standardised protocol for measuring NIBP in ferrets.

In ferrets, measurement of NIBP can especially be challenging due to their activity levels. Fixation or sedation is therefore

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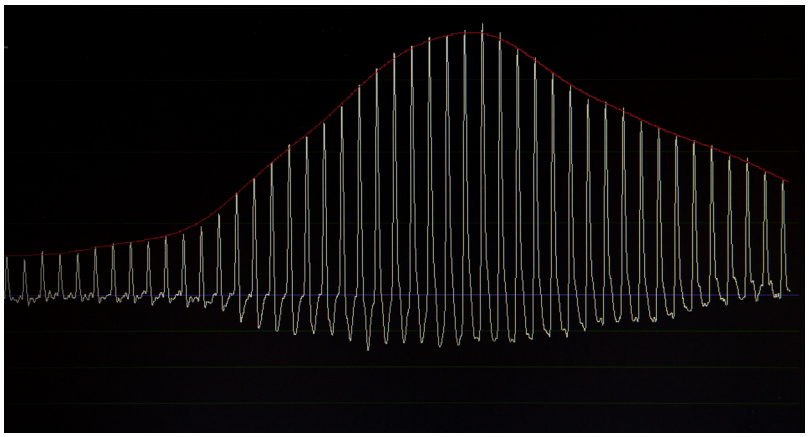

Fig. 1. Successful measurement of blood pressure using high definition oscillometry, showing optimal representation of arterial opening behaviour during blood pressure measurement as indicated by an initial slight, followed by a more dominant increase in height:relaxation of the arterial wall ratio (systolic arterial pressure) up to a maximum (close to mean arterial pressure) due to turbulence caused by an increase in blood flow, a subsequent decrease in amplitude size due to a change from turbulent to laminar blood flow (diastolic arterial pressure) and finally a complete opening of the artery.

required, although these techniques influence BP (Gasthuys et al., 1990; Farah et al., 2004). In ferrets, 'scruffing' (a method of restraint whereby the loose skin around the neck of the ferret is grasped and held firmly) results in a certain state of relaxation (Ball, 2006), but the applicability of this technique for BP measurement is unknown. Alternatively, low dosages of the short-acting sedatives midazolam and butorphanol can be given simultaneously, as these have a limited effect on BP (Egner et al., 2007; see Appendix: Supplementary material) and are considered safe, even in the critical patient (Lichtenberger et al., 2009). However, currently no information is available on the preferred technique or dose to allow BP measurement in ferrets.

In view of the lack of knowledge of BP measurement using HDO in ferrets, the aims of the current study were to determine: (1) the accuracy (bias)[4] and precision[5] of NIBP measurement with an HDO device under hypo-, normo- and hypertensive conditions; (2) the best location to measure NIBP in ferrets; (3) the lowest dosages of midazolam and butorphanol needed to sedate ferrets in order to successfully obtain NIBP measurements; and (4) reference values for standardised NIBP measurement with an HDO device in minimally sedated, healthy, adult ferrets.

Materials and methods

Ethical approval

The studies were approved by the Institutional Animal Care and Use Committee for Biomedical Studies of Utrecht University (study 1: DEC2008.III.08.085, date of approval 27 August 2008; studies 2 and 3: DEC2012.III.06.060, date of approval 11 July 2012). Owners of ferrets in study 3 were informed of the study design and asked to sign an informed consent declaring their approval to participate in the study.

Non-invasive blood pressure measurement

NIBP measurements were performed using a VET HDO monitor (Memodiagnostic MD_15/90 Pro, S + B medVET), which relies on HDO for rapid and sensitive measurement of pulse-wave related arterial wall oscillations. High speed high sensitivity hardware with a 32 bit processor and a high speed electronic valve enables the system to analyse incoming signals 8–12 times per microsecond. The SAP, MAP and DAP are subsequently measured by analysing different characteristics of the pulse waves (e.g. area under the curve, steepness, morphology and interstroke intervals).

The smallest cuff size (C1 cuff; length 11.5 cm, width 4 cm) was used for all measurements, with cuff placement performed by the same individual throughout the entire experiment. Although cuff width:limb circumference (W:L) ratio does not influence measurements for HDO significantly (Egner et al., 2007), W:L ratios were determined for the C1 cuff. For this purpose, limb circumference measurements were taken in 54 (21 male, 33 female) ferrets at three locations, i.e. just distal to the elbow, proximal to the hock and at the base of the tail; the W:L ratio ranged from 56 to 143% (see Appendix: Supplementary material).

Primary analysis of the NIBP measurements was performed using MDSoftware (version 2.0.3.0; 2011; S + B medVET). In addition, all BP readings were independently evaluated by two researchers blinded for the conditions under which the measurements were taken. Any measurements that contained gross artefacts and/or did not follow the characteristic pattern (Fig. 1) were excluded from further analyses.

Study 1: Intra-arterial versus non-invasive blood pressure measurement

Animals

Fourteen 4.5 year old, male research ferrets (mean ± standard deviation, SD, body weight 1.4 ± 0.2 kg; range: 0.9–1.6 kg), which had participated in an unrelated study and needed to be euthanased, were used in this study. In four ferrets, the tail had been missing since birth, whereas two other ferrets only had a tail stump, hindering placement of the cuff. Prior to the procedure, all ferrets were fasted for 4 h and physically examined to ensure they were healthy.

Anaesthesia and instrumentation

Ferrets were premedicated using a combination of ketamine (5 mg/kg, IM; Narketan, Vétoquinol), midazolam (0.5 mg/kg, IM; Dormicum, Roche) and butorphanol (0.5 mg/kg, IM; Morphasol, AniMedica). Anaesthesia was induced and maintained with IV propofol (bolus of 1–3 mg/kg followed by continuous rate infusion at 0.15–0.3 mg/kg/min, dosed to effect; PropoVet, Abbott Laboratories). All ferrets received 100% oxygen (flow 0.8 L/min) via a non-cuffed endotracheal tube (Sheridan, inner diameter 2.5–3.0 mm, Teleflex Medical).

Once the ferrets were in a deep anaesthetic plane, a 24 G intra-arterial catheter (Abbocath-T, Hospira) was placed in the common carotid artery. The catheter was connected to an air bubble free, fluid-filled, pressurised, disposable pressure transducer (Argon DTX Plus, Argon Medical Devices) via a three-way stopcock and connected to a Datascope 3000 monitor. After zeroing the system to atmosphere with the transducer at the level of the right atrium, a square wave test confirmed appropriate harmonic characteristics of the connected system. To avoid clotting, the catheter was flushed intermittently with 0.9% NaCl.

Blood pressure measurement

NIBP measurements were performed with the cuff placed on the forelimb just below the elbow (FL), the hind limb just above the hock (HL) and the base of the tail (T) under hypotensive (SAP < 110 mmHg), normotensive (SAP 110–170 mmHg) and hypertensive (SAP > 170 mmHg) conditions. These threshold values for hypo-, normo- and hypertensive conditions were based on threshold values used in cats (Martel et al., 2013) and previously published normotensive ranges for ferrets (Lichtenberger and Ko, 2007), where SAP ranged from 80 to 120 mmHg when

[4] Accuracy refers to the closeness of a measured value to a standard or known value, i.e. similarity between the indirect and direct blood pressure measurement (the last one representing the actual blood pressure).

[5] Precision refers to the closeness of two or more measurements to each other, i.e. similarity in outcomes of consecutive blood pressure measurements.

Table 1
Agreement between direct arterial and indirect systolic (a) and diastolic (b) arterial pressure values measured at the forelimb, hind limb and tail with high definition oscillometry (HDO) in anaesthetised male ferrets.[a]

Location	Pressure group[b]	Bias (mmHg)	Limits of agreement (mmHg)		% of paired measurements within 10 mmHg	% of paired measurements within 20 mmHg
			Lower	Upper		
Systolic arterial pressure (SAP) values						
Forelimb	High (n = 77/10)[c]	20.6 ± 12.4	−3.7	44.8	18.3	62.2
	Normal (n = 129/13)[d]	135.3 − 0.81 × MBP ± 12.8	−0.81 × MBP + 110.3	−0.81 × MBP + 160.4	55.6	81.4
	Low (n = 130/13)[d]	3.9 − 0.26 × MBP ± 11.8	−0.26 × MBP − 19.1	−0.26 × MBP + 27.0	30.8	74.6
	Overall[d]	−39.8 + 0.29 × MBP ± 14.5	0.29 × MBP − 68.3	0.29 × MBP − 11.4	36.9	74.1
Hind limb	High (n = 90/11)[d]	163.9 − 0.72 × MBP ± 17.9	−0.72 × MBP + 128.8	−0.72 × MBP + 199.1	12	39.1
	Normal (n = 88/11)[d]	94.7 − 0.61 × MBP ± 16.5	−0.61 × MBP + 62.4	−0.61 × MBP + 127.0	31.4	68.6
	Low (n = 135/14)[d]	17.7 − 0.55 × MBP ± 15.9	−0.55 × MBP-13.6	−0.55 × MBP + 48.9	11.1	34.1
	Overall[d]	−56.4 + 0.33 × MBP ± 22.0	0.33 × MBP − 99.4	0.33 × MBP − 13.3	16.9	45.0
Tail	High (n = 37/4)[d]	120.4 − 0.50 × MBP ± 7.1	−0.50 × MBP + 106.4	−0.50 × MBP + 134.4	27	73
	Normal (n = 80/9)	−11.5 ± 12.5	−35.9	12.9	46.9	77.8
	Low (n = 58/7)	−21.7 ± 9.9	−41.1	-2.4	13.8	43.1
	Overall[d]	−39.8 + 0.21 × MBP ± 14.0	0.21 × MBP − 67.2	0.21 × MBP − 12.3	31.8	61.9
Diastolic arterial pressure (DAP) values						
Forelimb	High (n = 77/10)[c]	35.8 ± 16.4	3.6	68.0	0	25.6
	Normal (n = 129/13)[d]	−11.5 + 0.32 × MBP ± 13.0	0.32 × MBP − 37.1	0.32 × MBP + 14.0	28.2	66.1
	Low (n = 130/13)	−11.5 ± 9.9	−30.8	7.8	49.2	85.4
	Overall[d]	−36.5 + 0.57 × MBP ± 13.2	0.57 × MBP − 62.5	0.57 × MBP − 10.6	29.5	63.7
Hind limb	High (n = 90/11)[d]	−43.3 + 0.80 × MBP ± 19.3	0.80 × MBP − 81.2	0.80 × MBP − 5.4	0	6.5
	Normal (n = 88/11)	24.0 ± 17.2	−9.7	57.6	23.3	36.0
	Low (n = 135/14)	−15.7 ± 13.4	−42.0	10.7	14.8	70.4
	Overall[d]	−55.2 + 0.87 × MBP ± 17.3	0.87 × MBP − 89.0	0.87 × MBP − 21.4	12.8	33.2
Tail	High (n = 37/4)[d]	−60.9 + 0.82 × MBP ± 6.7	0.82 × MBP − 74.1	0.82 × MBP − 47.7	0	5.4
	Normal (n = 80/9)	18.4 ± 11.5	−4.1	40.9	37	61.7
	Low (n = 58/7)[d]	9.0 − 0.56 × MBP ± 6.2	−0.56 × MBP − 3.2	−0.56 × MBP + 21.2	20.7	94.8
	Overall[d]	−42.2 + 0.65 × MBP ± 10.7	0.65 × MBP − 63.1	0.65 × MBP − 21.2	23.9	60.8

MBP, mean blood pressure (average of direct blood pressure and indirect blood pressure as determined by HDO).
[a] Negative values represent overestimation, whereas positive values represent underestimation of the actual BP. Only valid measurements were included in the analysis.
[b] Pressure group: low, mean SAP < 110 mmHg; normal, mean SAP = 110–170 mmHg; high, mean SAP > 170 mmHg.
[c] Numbers refer to the number of measurements and number of animals, respectively.
[d] Significant proportional bias present, following which regression based methods were used to determine bias and limits of agreement.

measured non-invasively, whereby the NIBP was presumed to underestimate DABP by 30 mmHg. Originally, it was the intention to randomise the order in which hypotension (L), normotension (N) and hypertension (H) were induced. However, ferrets became hypotensive after routine induction with propofol. To decrease the BP to the desired level, extra boluses of propofol were administered to further decrease BP, whereas colloidal plasma (5 mL/h IV; Hemohes 6%, Braun Medical) and norepinephrine (8–12 μg/min IV; Norepinephrine CF 1 mg/mL, Centrafarm) were gradually administered to effect to create normotensive and hypertensive states, respectively. At each peripheral measurement site (FL/HL/T), five measurements each of BP state (H/N/L), NIBP and DABP were simultaneously recorded at 1 min intervals.

Statistical analysis

Statistical analysis was performed using SPSS Statistics (version 21.0, IBM), R-Studio version 0.97.551 and R version 3.0.1 (R Development Core Team[6]). Results were analysed separately for each location and BP state, only including valid measurements. Data were expressed as mean ± SD, with P values < 0.05 considered to be statistically significant. Prior to analysis, histograms and normality plots were prepared to confirm whether the distributional assumptions for parametric analysis were met.

As recommended by the American College of Veterinary Internal Medicine (ACVIM) consensus panel for validation of devices measuring NIBP (Brown et al., 2007), bias for SAP and DAP was calculated by subtracting the individual measurements for NIBP from corresponding DABP, with positive bias reflecting underestimation of DABP and negative bias reflecting overestimation of DABP (Binns et al., 1995). Additionally, the level of agreement between NIBP and DABP was assessed according to Bland and Altman (2007). Differences between paired observations were plotted against the means of both values and limits of agreement were calculated as the mean difference ± 1.96 SD or, in the case of proportional bias, using the regression based method (Bland and Altman, 1999). The percentage of paired measurements lying within a difference of <10 mmHg and <20 mmHg were calculated for the two methods. Linear regression curves were built for calculations of correlation coefficient (r) between the two methods for SAP and DAP for each location.

To determine whether location had a significant effect on the bias of the measurements, a linear mixed model was performed, with mean bias for SAP and DAP as the dependent variable, and arterial BP, location and their interaction, and measurement number, as independent variables. The preferred location for NIBP was determined as the location which resulted in the least bias and highest correlations for the paired measurements.

Study 2: Minimum sedative dose needed for adequate non-invasive blood pressure measurement

Animals

Ten healthy, female, neutered research ferrets (age: 2.5 years; body weight: 809 ± 59 g) were used in this blinded cross-over study. All ferrets were deemed to be healthy on the basis of the results of a physical examination prior to entering the study.

Study design

Each ferret was subjected to five methods of restraint/sedation for measurement of NIBP in separate sessions, performed 1 week apart. The order in which the different methods were applied was randomised using computerised random numbers.[7]

Prior to restraint or sedation, ferrets were fasted for a period of 4 h and acclimatised to the examination room for 30 min. Subsequently, the ferrets were

[6] See: www.r-project.org (accessed 17 March 2016).

[7] See: www.random.org (accessed 17 March 2016).

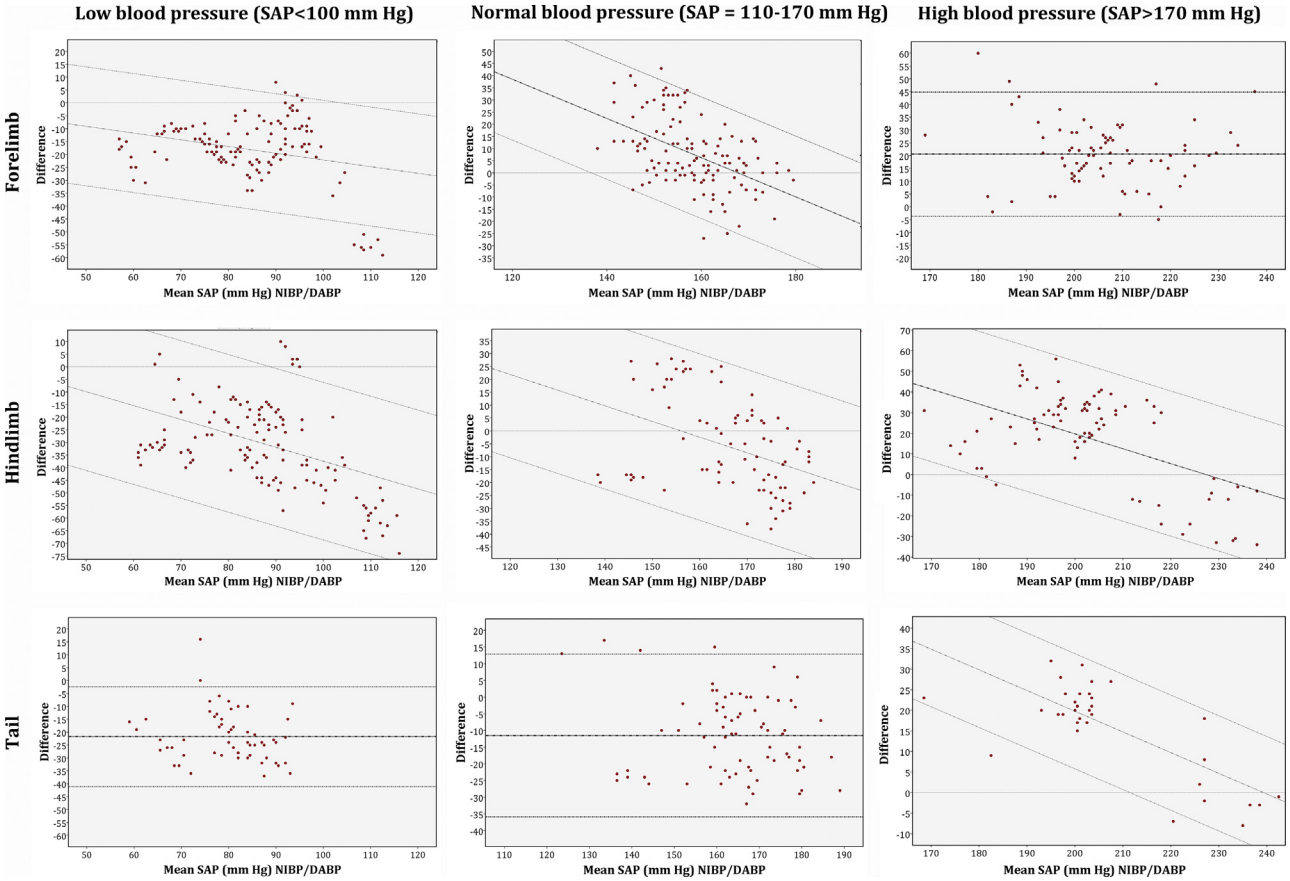

Fig. 2. Bland Altman plots of agreement for systolic arterial pressure (SAP; a) and diastolic arterial pressure (DAP; b) measured directly in the carotid artery (DABP) and using high definition oscillometry (HDO) for low (SAP < 110 mmHg), normal (SAP = 110–170 mmHg) and high (SAP > 170 mmHg) arterial blood pressures measured in ferrets ($n = 14$). Arterial blood pressures were measured at three locations: forelimb, hind limb and tail. Mean difference (bias; –··–·) and limits of agreement (mean bias ± 1.96SD; –·–·–·) are included in all plots. Positive and negative bias reflect under- and over-estimation of the actual blood pressure, respectively.

'scruffed' or given a combination of midazolam and butorphanol IM in one of four different dosages (0.05, 0.1, 0.15 or 0.2 mg/kg), with equivalent dosages used for both drugs (time, t = 0). At t = 5 min, the ferrets were placed on a heating blanket, after which the cuff was placed around the base of the tail, based on the results of study 1. Two attempts to measure NIBP were subsequently made every 5 min for a total of 60 min or until no further measurements were possible due to non-compliance of the animal. In addition, depth of sedation was evaluated at t = 10, t = 30 and t = 60 min using previously published subjective and objective evaluation criteria (Leppanen et al., 2006; see Appendix: Supplementary material), as well as the time until the ferret fully recovered from sedation (i.e. subjective sedation score 1). During sedation, ferrets were closely monitored for changes in vital parameters (respiratory rate, pulse, rectal temperature) and/or occurrence of adverse effects.

Classification of blood pressure measurements

The data were evaluated by two independent researchers blinded to the treatment. Measurements were classified as 'successful' when a good reading (Fig. 1) could be obtained. If no measurement could be obtained or the graph lacked the typical characteristics of a correct reading and/or contained gross artefacts, the measurement was classified as 'failed'. In cases where the two researchers did not unanimously classify an attempt as 'failed' or 'successful', the attempt was recorded as 'missing value' and excluded from further analysis.

Statistical analysis

Mean ± SD were calculated for sedation scores, temperature, respiration rate, pulse rate and BP at each time point and dose used. A linear mixed effects model was subsequently performed to analyse whether time and/or dosage had a significant effect on the aforementioned parameters. In addition, success rates for measurement at each time point and per 10 min period were determined as the percentages of successful attempts to measure NIBP compared to the total number of attempts made. To analyse the success rate of the different sedative/restraint techniques, a mixed effects logistic regression was performed on the data, with success rate as outcome variable, dosage and time as fixed effects, and measurement number as random effect.

Study 3: Determining reference intervals for NIBP in minimally sedated, healthy adult ferrets

Animals

Both research ($n = 36$) and privately owned ($n = 27$) adult ferrets were used to determine the reference intervals for NIBP. The research ferrets included three male (age 1.5 years; body weight 1613 ± 72 g) and 33 female (age 2.5 years; body weight 816 ± 99 g) animals. The group of privately owned ferrets consisted of 16 male (age 1.8 ± 1.4 years; body weight 1141 ± 200 g) and 11 female (age 1.2 ± 1.5 years; body weight 728 ± 143 g) animals. All ferrets were deemed to be healthy based on the results of a physical examination.

Study design

After the physical examination, ferrets were allowed to acclimatise to the environment for 30 min. Subsequently, butorphanol and midazolam (0.2 mg/kg each) were administered IM, based on results of study 2. NIBP was measured from 10 to 20 min post-injection until three good readings were obtained. Additionally, the depth of sedation was subjectively evaluated at t = 20 min (see Appendix: Supplementary material), as well as the time until full recovery from sedation. Throughout the sedation, the ferrets' vital parameters were closely monitored and any adverse effects were noted.

Statistical analysis

After averaging the three measurements for each ferret, reference intervals for SAP, MAP and DAP for the whole group and for each sex were calculated according to Clinical and Laboratory Standards Institute (CLSI) guidelines (Horowitz, 2010) using MedCalc Statistical Software version 13.0.2 (MedCalc Software BV[8]). For each sex, the 'robust' method was used, whereas the non-parametric percentile method or

[8] See: www.medcalc.org (accessed 17 March 2016).

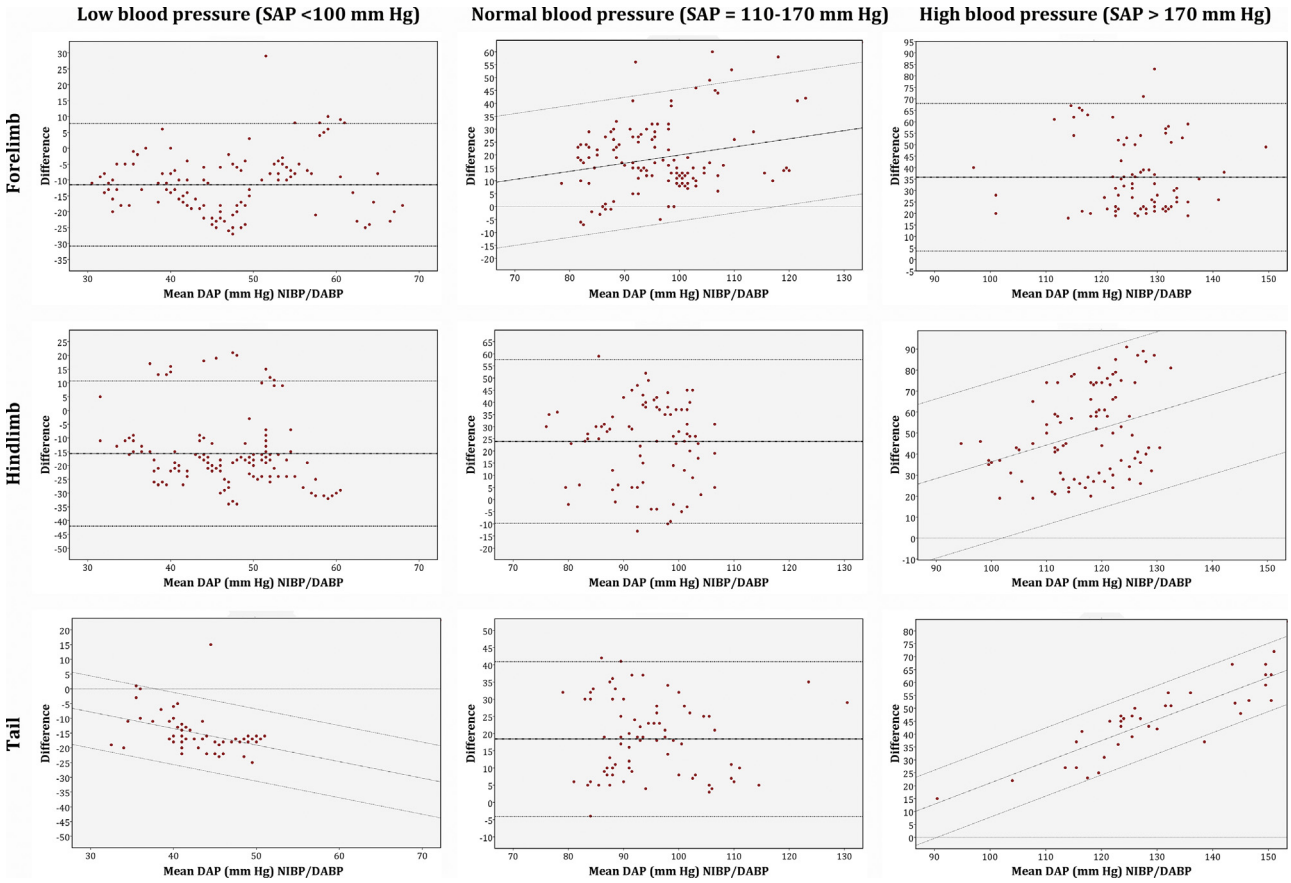

Fig. 2. (Continued)

method based on normal distribution were used for the whole group, after checking for normal distribution of data (Shapiro–Wilk test). A two-sided *t* test was performed to determine the presence of sex differences in NIBP values.

To determine the reproducibility of the BP measurement using HDO, the repeatability coefficient was calculated from 100 duplicate measurements collected within a time frame of 45 s, according to Bland and Altman (1999). In addition, intra-class correlation coefficients (ICCs) for the three measurements per ferret were calculated using a two-way random effects model for average measurements (ICC[2,k]), with ICC of <0.40 considered to reflect poor, 0.40–0.59 fair, 0.60–0.74 good, and >0.74 excellent reproducibility (Fleiss, 1981). In addition, within-subject variation was determined using the same three measurements to calculate the coefficients of variance (CVs) according to the formula CV = SD/mean × 100%.

Results

Intra-arterial versus non-invasive blood pressure measurement

Due to technical difficulties, 126 of the 1260 measurements were considered to be unreliable and were excluded from further analysis; 40 (3.2%) were due to failure of the Datascope to record direct BP and 86 (6.8%) were due to equipment failure or gross artefacts in the HDO measurements. The number of results was further decreased by the absence of a tail ($n = 6$; 180 measurements) and/or peri-anaesthetic death ($n = 4$; 130 measurements) due to procedural difficulties. However, the total number of measurements obtained per location and BP condition (range: 37–135) was considered to be sufficient to proceed with analysis (Table 1).

Mean ± SD values for bias, limits of agreement and percentage of measurements with bias <10 or <20 mmHg for HDO compared with DABP measurement for SAP and DAP under hypo-, normo- and hypertensive conditions at the three locations (forelimb, hind limb and tail) are presented in Table 1, with corresponding Bland Altman plots for SAP and DAP depicted in Fig. 2. Significant proportional bias was present for most conditions, whereby HDO generally underestimated DABP in hyper- and normotensive states, and overestimated DABP in hypotensive states (Table 1; Fig. 2). Standard deviation of the bias was <15 mmHg for all pressure ranges of SAP and DAP at the forelimb and tail, except for DAP at the forelimb in the higher pressure range. In contrast, SDs for hind limb measurements exceeded 15 mmHg under all conditions, except for DAP in the lower pressure ranges. Except for SAP at the forelimb under normotensive conditions, where 55.6% and 81.4%, of the paired measurements remained within a 10 and 20 mmHg range of each other, respectively, the difference between paired measurements exceeded 10 mmHg for >50% of the performed measurements (range 50.8–100%). For most of these locations, >20% of measurements also exceeded the 20 mmHg limit (range 22.2–94.6%), except for DAP at the forelimb and tail in the lower pressure range, where 85.4% and 94.8% of paired measurements, respectively, remained within 20 mmHg of each other. Correlation coefficients between HDO and DABP for SAP were >0.90 in all locations; for DAP, correlations were >0.90 for the tail and forelimb, but only 0.81 for the hind limb (Fig. 3). Results of a linear mixed model showed a significant effect of location ($P < 0.001$), arterial BP ($P < 0.001$) and of the interaction between these parameters ($P < 0.001$), but not of measurement number on bias for SAP and DAP. No significant differences in bias were present between the tail and forelimb (SAP: $t = -0.471$, $P = 0.638$; DAP: $t = 0.653$, $P = 0.514$). However, bias differed significantly between the tail and the hind limb, and between the forelimb and hind limb ($P < 0.001$ for SAP and DAP in both cases); it was estimated that the

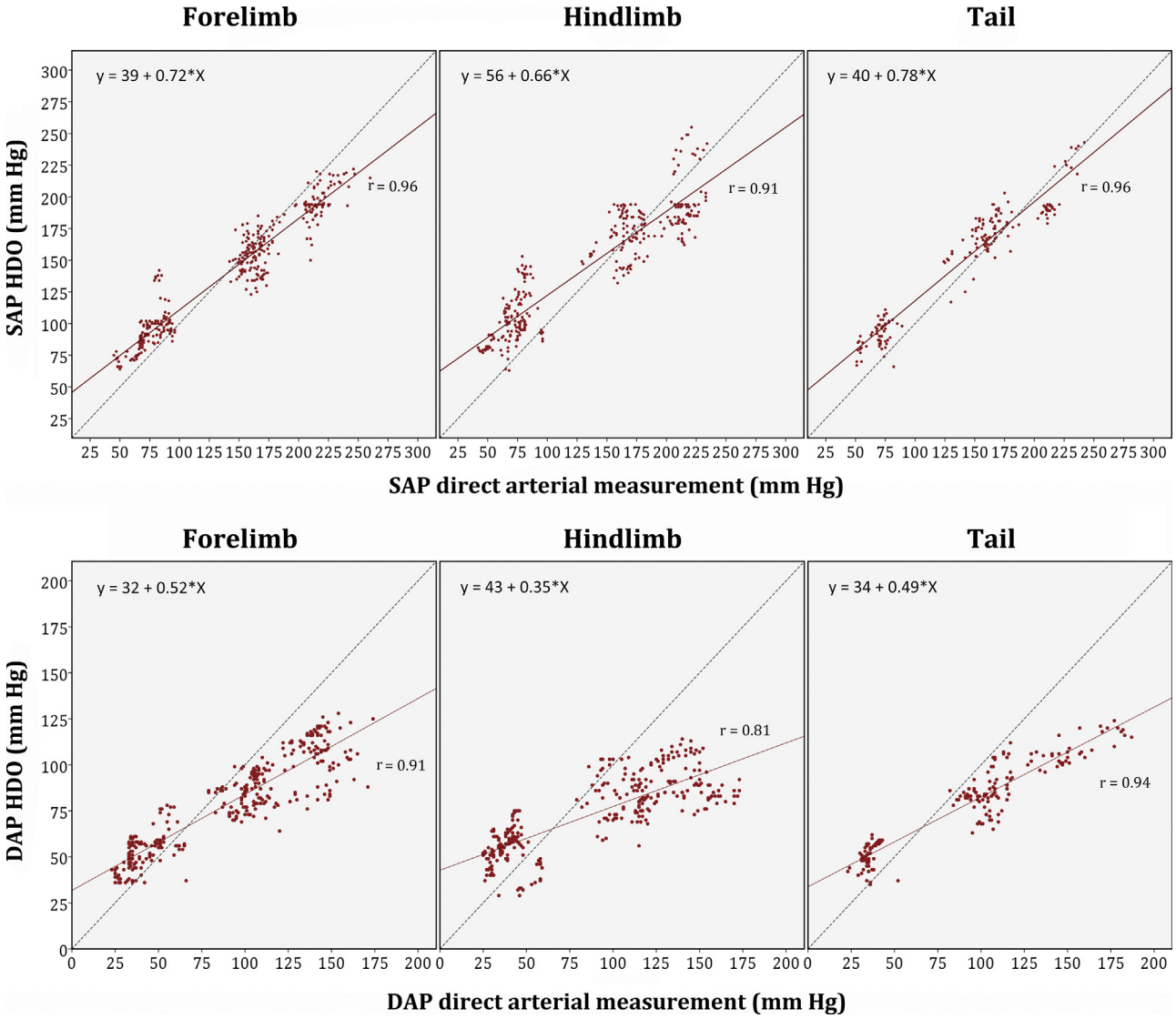

Fig. 3. Linear regression for systolic (SAP) and diastolic (DAP) arterial pressure measured by high definition oscillometry (HDO) compared to direct arterial blood pressure measurement (DABP) in three different locations (forelimb, hind limb and tail). The dotted dark grey line represents the line of equality (x = y) for comparison with the trend lines for the measurements obtained at each location. Pearson correlation coefficients (r) are included in the plots.

hind limb generally resulted in a bias of −18.0 (SAP) and −9.4 mmHg (DAP) compared to the tail, and −16.4 (SAP) and −10.8 mmHg (DAP) compared to the forelimb.

Minimum sedative dose needed for adequate NIBP measurement

Sedatives generally took effect in 5–10 min, after which sedation scores gradually declined (Table 2). Both time and dose affected sedation scores (Table 2). The time needed until full recovery from sedation (sedation score 1) was proportional to the dosage (0.05 mg/kg: 32 ± 16 min, range 10–60 min; 0.10 mg/kg: 53 ± 17 min, range 25–70 min; 0.15 mg/kg: 58 ± 13 min, range 20–75 min; 0.20 mg/kg: 75 ± 12 min, range 60–90 min).

Of the 1200 NIBP measurements that were recorded, 68 (5.7%) were classified as 'missing', 447 (37.2%) were classified as 'successful' and 683 (57.1%) were classified as 'failed'. Since two attempts failed due to equipment failure rather than uncooperative behaviour or graph abnormalities, these were excluded from further analysis. Logistic regression analysis of success rates of the attempts to measure NIBP showed a significant effect of time ($P < 0.001$) and dose ($P < 0.001$) on obtaining a successful measurement. A dose of 0.2 mg/kg resulted in significantly more successful attempts than all other dosages used (including scruffing; $P < 0.001$) and was the only dose able to achieve a sufficient plane of sedation to obtain NIBP in all ferrets (Table 3), resulting in 100% success from 10 to 20 min post-administration of sedatives (Table 3).

Neither the administered dose, nor time of measurement, affected actual values for SAP ($F = 0.874$, $P = 0.449$ for dose; $F = 0.025$, $P = 0.874$ for time), MAP ($F = 1.274$, $P = 0.279$ for dose; $F = 0.955$, $P = 0.329$ for time) or DAP ($F = 1.671$, $P = 0.155$ for dose; $F = 2.892$, $P = 0.089$ for time; Fig. 4). Over time, respiration and pulse rates remained relatively stable. However, the rectal temperature decreased slightly (0.31 ± 0.74 °C at a dose of 0.05 mg/kg; $P = 0.260$) to moderately (1.24 ± 0.7 °C at a dose of 0.20 mg/kg; $P < 0.001$) throughout the 60 min sedation period.

Reference intervals for non-invasive blood pressure measurement in minimally sedated, healthy ferrets

All ferrets were sufficiently sedated (subjective sedation score 2.4 ± 1.0 at t = 20 min) to allow three successful NIBP

Table 2
Mean ± standard deviation subjective and objective sedation scores of ferrets ($n = 10$) at the various time points (t = 10, t = 30 and t = 60 min) after receiving an intramuscular dose of midazolam and butorphanol.

	Subjective score				Objective score			
Dose (mg/kg)[a]	t = 10 min	t = 30 min	t = 60 min	*P* value for dose	t = 10 min	t = 30 min	t = 60 min	*P* value for dose
0.05	1.4 ± 0.7	1.3 ± 0.5	1.0	–	2.3 ± 2.9	0.9 ± 1.9	0	–
0.1	2.3 ± 1.3	2.3 ± 0.7	1.0	0.003[c]	4.9 ± 1.8	5.0 ± 2.6	0.5 ± 0.8	0.003[c]
0.15	2.7 ± 1.3	2.5 ± 1.1	1.2 ± 0.4	<0.001[c]	7.0 ± 4.6	4.5 ± 3.3	0.9 ± 1.2	<0.001[c]
0.2	3.6 ± 0.5	3.1 ± 0.7	1.4 ± 0.5	<0.001[c]	11.3 ± 1.9	8.6 ± 3.7	2.5 ± 2.3	<0.001[c]
P value for time	<0.001[b]	0.001[b]	–		0.059	0.001[b]	–	

[a] Identical doses of butorphanol and midazolam were used.
[b] Significant difference compared to t = 60 min.
[c] Significant difference compared to lowest dose (0.05 mg/kg).

measurements to be taken within 10–20 min post-administration of sedatives. None of the ferrets showed any adverse effects and all recovered from sedation within 45–90 min post-injection. Reference intervals for NIBP were established as 95–155 mmHg (SAP), 69–109 mmHg (MAP) and 51–87 mmHg (DAP; Table 4). Males and females did not differ in NIBP values (SAP: $t = -0.246$, $P = 0.806$; MAP: $t = -0.089$, $P = 0.929$; DAP: $t = 0.079$, $P = 0.937$).

Repeatability coefficients for SAP, MAP and DAP using HDO were 14.5, 10.7 and 14.6, respectively. Intra-class correlation coefficients and within-ferret CVs for SAP, MAP and DAP were 0.82, 0.86 and 0.76 ($P < 0.001$), and 6.4 ± 4.0%, 6.8 ± 5.5% and 11.0 ± 8.0%, respectively.

Discussion

To validate the use of the HDO technique in ferrets, we measured NIBP and DABP simultaneously in anaesthetised ferrets under hyper-, normo- and hypotensive conditions, and subsequently determined bias, limits of agreement and correlations. We evaluated our results according to the validation criteria for NIBP measuring devices set by the ACVIM Hypertension Consensus Panel (Brown et al., 2007). According to these criteria, bias of a NIBP monitoring device should not exceed 10 mmHg, with a SD of <15 mmHg. Bias between HDO and DABP approximated 10 mmHg for some of the locations and pressure ranges (i.e. normotensive states at the tail and hypotensive states at the forelimb). However, for most other pressure ranges, as well as overall pressure, bias between HDO and DABP in ferrets was highly variable and proportional to the average BP, with a shift from a negative to a positive bias with increases in BP. We therefore concluded that HDO and DABP do not agree sufficiently to be interchangeable.

The maximum SD for NIBP measurements in ferrets obtained at the forelimb (except for DAP during hypertension) and at the tail for both individual pressure ranges, as well as the overall pressure range, met the criteria of the ACVIM guidelines, with values being comparable to those in cats (Cerejo et al., 2017) and lower than those in dogs and horses (Rysnik et al., 2013; Tünsmeyer et al., 2015). These findings suggest that BP measurements using the HDO device are highly reproducible, as was also demonstrated during study 3, in which the repeatability coefficient and ICCs for SAP, MAP and DAP showed excellent agreement between measurements. In addition, within-ferret CVs were relatively low, similar to those in dogs and macaques (Schmelting et al., 2009; Chetboul et al., 2010), thereby underlining the high reproducibility and thus precision of the measurements.

It has been reported that W:L circumference ratio does not significantly influence the reliability of measurements with the HDO monitor (Egner et al., 2007). Nevertheless, cuff size might have played a role in inaccuracy of the results. This hypothesis is supported by findings in common marmosets, where BP measurements at the tail (W:L ratio 85–102%) were less accurate than those at the thigh (W:L ratio 46–55%; Mietsch and Einspanier, 2015). In dogs and cats, W:L ratios of 30–40% (Brown et al., 2007) to 40–60% (Hall et al., 2001) are recommended to enable accurate BP measurement. However, W:L ratios for the C1 cuff used in this study exceeded 60% in the majority of ferrets, thus potentially preventing accurate measurements being obtained.

In our study, NIBP generally underestimated DABP, except under hypotensive conditions, during which NIBP overestimated DABP. These findings are similar to those found in dogs, cats and horses (Wernick et al., 2010; Martel et al., 2013; Rysnik et al., 2013; Seliškar et al., 2013; Tünsmeyer et al., 2015). This discrepancy between DABP and NIBP measurement might be explained in part by the inaccuracy of the device (Wernick et al., 2010), but might also be the result of the technique used to measure NIBP. With the HDO technique, arterial wall oscillations rather than actual BP is measured. At higher BP and/or heart rates, amplifications and distortions of the arterial wall will be smaller (Warner, 1957), resulting in lower resonance and thus underestimation of DABP. This phenomenon could explain the shift from a negative to a positive bias seen in the ferrets in our study, as well as in dogs, cats and rabbits (Ypsilantis et al., 2005; Martel et al., 2013; Rysnik et al., 2013).

However, oscillations of the arterial wall are also dependent on resistance and compliance of the vessels, both of which may be influenced by drugs, such as those administered in this study. As examples, propofol (used to induce hypotension in this study) decreases peripheral vascular resistance (Robinson et al., 1997), whereas norepinephrine (used to induce hypertension) increases peripheral vascular resistance (Wilkinson et al., 2001). As a result, vascular resistance and compliance could have been altered, thereby potentially inducing bias between the central and peripheral measurements. The hypo- and hypertensive states of the ferrets in this study therefore are not necessarily a true representation of these clinical haemodynamic states, with bias and precision of the device in real life conditions potentially differing from those in our study.

Table 3
Success rate (in % of total measurements performed at a specific time point) of NIBP blood pressure measurements in ferrets ($n = 10$) at 5 min intervals after scruffing or sedation with different dosages of midazolam and butorphanol.

Dose (mg/kg)[a]	Time (min)[b]											
	5	10	15	20	25	30	35	40	45	50	55	60
Scruffing	0	0	5	5	0	0	0	0	0	0	0	0
0.05	15	25	35	20	45	15	5	5	15	10	10	0
0.1	40	70	75	80	80	65	55	50	45	50	25	10
0.15	45	55	85	80	70	55	65	35	35	35	30	10
0.2	55	100[c]	100	100	90	85	40	80	50	25	25	40

NIBP, non-invasive blood pressure.
[a] Identical doses of butorphanol and midazolam were used.
[b] Time points after administration of sedatives (t = 0). For each ferret and dose, two attempts were made to measure NIBP at each time point.
[c] Excluding two measurements in one ferret that could not be obtained due to equipment failure.

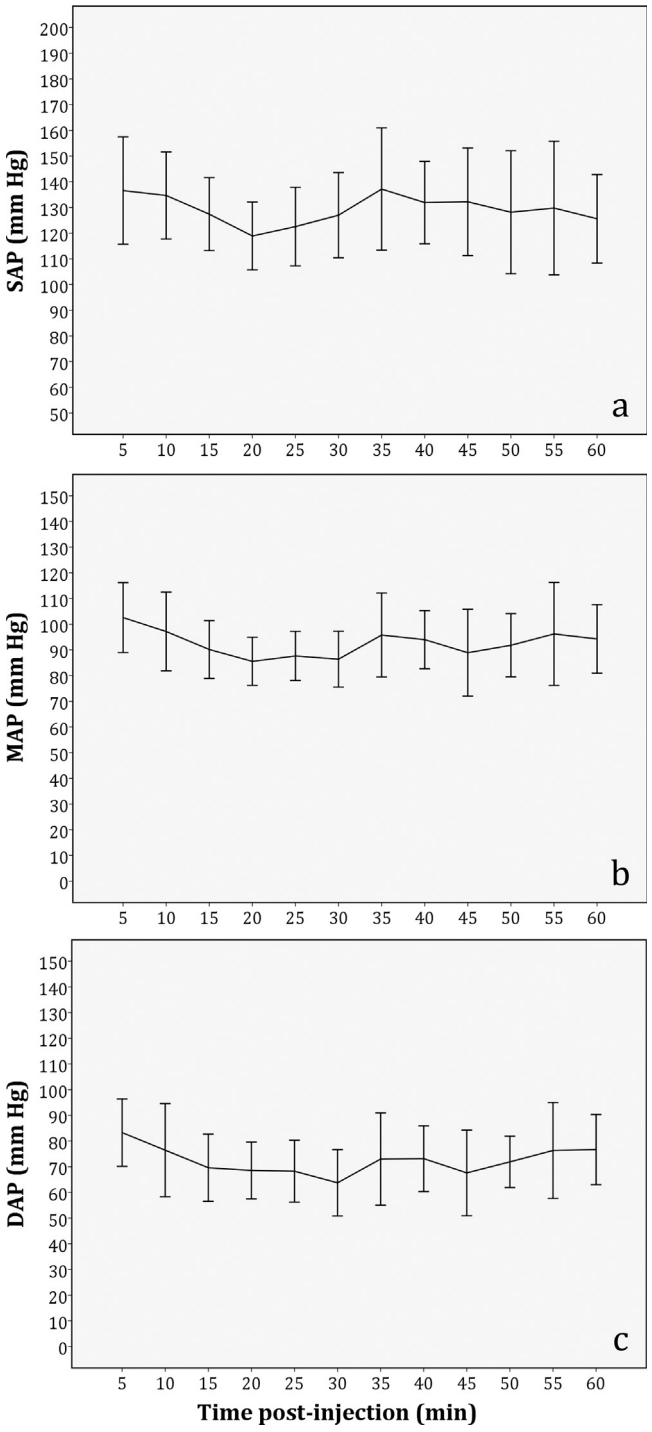

Fig. 4. Changes (mean ± standard deviation) in systolic arterial pressure (SAP) (a), mean arterial pressure (MAP) (b) and diastolic arterial pressure (DAP) (c) over a 60-min period for ferrets sedated with 0.2 mg/kg butorphanol and 0.2 mg/kg midazolam.

Bias for SAP was relatively lower (i.e. less positive or more negative) compared to the bias for DAP. This relative greater overestimation of SAP versus relative greater underestimation of DAP might be explained in part by the location where BP measurement took place. Since SAP increases and DAP decreases as a pressure pulse moves peripherally (Gorback, 1988), and DABP and NIBP measurements respectively took place in the common carotid artery and extremities, peripheral NIBP measurements using HDO may lead to a relative greater overestimation of SAP and a relative greater underestimation of DAP. However, in dogs, an overestimated SAP and underestimated DAP were also seen when the DABP and NIBP were measured at a similar distance from the heart (i.e. the distal pedal artery and tail, respectively; Rysnik et al., 2013). It therefore remains unclear whether location of BP measurement is the only factor that resulted in relative over- and underestimation of SAP and DAP, or whether other factors might also play a role.

Cuff site variably affects BP measurement in different species, with no differences reported between forelimb and hind limb cuff placement in dogs (McMurphy et al., 2006), whereas significant differences were found between different locations in marmosets (Mietsch and Einspanier, 2015), rabbits (Ypsilantis et al., 2005) and cats (Binns et al., 1995). Similar to the studies in cats and rabbits, cuff site influences accuracy of BP measurement in ferrets, with hind limb measurements displaying higher bias, wider limits of agreement and lower correlation coefficients than forelimb and tail measurements. As a result, the hind limb is less suitable for NIBP measurement in ferrets. Measurements at the forelimb and tail overall resulted in similar findings, although results from tail measurements were based on fewer measurements than results from the forelimb, since ferrets were missing a tail. Therefore, the choice for the preferred location to measure NIBP will be mainly based on personal preferences and practicality. Since cuff placement was easiest on the tail, and bias between HDO and DABP at this location was consistent and independent of the BP in the normotensive range, the tail was chosen as the preferred site for cuff placement for the subsequent studies.

Ideally, NIBP is measured in a non-sedated animal that is gently restrained in a quiet area without distractors present (Brown et al., 2007). Unfortunately, most ferrets are too lively to tolerate these measurements without sedation. Therefore, we chose midazolam and butorphanol to sedate ferrets, since this combination has little effect on BP (Egner et al., 2007). A dose of 0.2 mg/kg IM for both midazolam and butorphanol allowed NIBP measurement from 10 to 20 min post-injection in all ferrets. Animals subsequently awoke within 90 min post-injection, with no side-effects seen other than a slight to moderate decrease in body temperature ($1.2 \pm 0.7\,^{\circ}C$). However, this temperature decrease could be minimised by using an active warming device (e.g. heating blanket).

NIBP decreased slightly in the first period following injection of the sedatives. In dogs, a similar decrease in BP has been observed during the first 20 min post-injection of a butorphanol-midazolam combination (Kojima et al., 1999), with intramuscular doses of 0.2 mg/kg each decreasing SAP by 15 mmHg (Novellas et al., 2007). Since we could not measure NIBP in unsedated ferrets, it was not possible to determine whether midazolam and butorphanol affected BP at the dosages used in our study. Evaluation of BP in conscious, 'scruffed' ferrets was considered as an alternative, even though handling and restraint can significantly increase BP in rats (Irvine et al., 1997; Baturaite et al., 2005). However, these attempts were also unsuccessful in most instances, thereby limiting our ability to compare NIBP values of awake, restrained and sedated ferrets.

On the basis of the results of studies 1 and 2, we designed a standardised protocol to measure NIBP and establish reference intervals for SAP, MAP and DAP in young adult, healthy, minimally sedated ferrets. The reference intervals in young ferrets in our study were equivalent to those previously found in awake dogs (Chetboul et al., 2010), awake cats (Paepe et al., 2013), anaesthetised rabbits (Ypsilantis et al., 2005), and awake humans (Borow and Newburger, 1982). Nevertheless, it should be emphasised that values obtained in individual ferrets may only be compared to these reference intervals if the sedation protocol, measurement site and BP device and cuff are identical to the one

Table 4
Means, standard deviations and reference intervals for non-invasive blood pressure (NIBP, mmHg) obtained with a high definition oscillometry (HDO) monitor[a] and C1 cuff in healthy, young adult (<4 years of age) ferrets ($n = 63$) 10–20 min after IM administration of midazolam (0.2 mg/kg) and butorphanol (0.2 mg/kg).

	Mean	Standard deviation	Reference interval[c]
All ferrets ($n = 63$)[b]			
SAP	125	15	95–155
MAP	89	10	69–109
DAP	69	7	51–87
Male (Hobs) ($n = 19$)			
SAP	124	17	87–161
MAP	89	10	66–110
DAP	69	9	50–88
Female (Jills) ($n = 44$)			
SAP	125	15	95–156
MAP	89	10	68–109
DAP	69	9	49–86

SAP, systolic arterial pressure; MAP, mean arterial pressure; DAP, diastolic arterial pressure.
[a] Memodiagnostic MD_15/90 Pro, S + B medVET.
[b] All data were normally distributed.
[c] According to Clinical and Laboratory Standards Institute (CLSI) standards (Horowitz, 2010).

used in this study (Brown et al., 2007). Additionally, BP in older ferrets is likely to be higher, because of their increased risk for diseases associated with an elevated BP (e.g. renal disease, hyperadrenocorticism; Safar, 1990; Paepe et al., 2013). Only ferrets younger than 4 years were included in our study, which limits the extrapolation of reference intervals to older ferrets. Similarly, borderline BP measurements should be interpreted with caution, since these are especially subject to incorrect classification due to over- and underestimation of DABP in hypo- and hypertensive states, respectively.

Conclusions

HDO allowed for precise although though less accurate BP measurement in (normotensive) ferrets, with forelimb and tail measurements resulting in the least bias, when compared to DABP. A minimum dose of 0.2 mg/kg of butorphanol and midazolam each allowed for successful NIBP measurement in ferrets 10–20 min post-injection. Using this protocol, reference intervals for SAP, MAP and DAP were established for young adult ferrets. However, due to bias between DABP and HDO being highly variable and proportional to the actual BP, difficulties arise with extrapolating NIBP findings to an actual blood pressure, thereby hindering validation of the device for clinical purposes other than monitoring of BP changes in a single animal over time.

Conflict of interest statement

Dr B. Egner is married to the developer of the HDO-monitor and owner of S + B medVET. On occasion, Dr Egner is also an unpaid consultant for this company (and other companies). Dr Egner's contributions to this study have been focussed solely on the correct use of the monitor and classification of the readings for study 2. To avoid biased interpretation of the results, data analysis was performed blinded, whereby Dr Egner had no access to any other details or information regarding the study.

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Appendix: Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tvjl.2017.10.019.

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