Title

Agreement of high-definition oscillometry at two cuff locations with invasively measured arterial blood pressures in anaesthetised cheetahs.

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Abstract

Objectives To evaluate the agreement between high-definition oscillometry (HDO) used on the metatarsus or tail base with invasive arterial blood pressures measured in the dorsal pedal artery in anaesthetised cheetahs.

Study Design Prospective clinical study.

Animals A group of 13 captive adult cheetahs.

Methods Cheetahs were immobilised with medetomidine (32-45 μg kg^{-1}) and tiletamine/zolazepam (0.93-1.39 mg kg^{-1}) administered intramuscularly and anaesthesia was maintained with either isoflurane in oxygen or continuous propofol infusion. Invasive blood pressure was measured via a 20 gauge intra-arterial catheter in the dorsal pedal artery in the metatarsus and used as a reference method for pressures simultaneously estimated using HDO on the contralateral metatarsus and tail base. Bland-Altman plots (for repeated measurements) and criteria defined by the American College of Veterinary Internal Medicine (ACVIM) were used to compare agreement according to the anatomical location of the cuff, the anaesthetic maintenance agent and magnitude of the blood pressure.

Results A total of 147 paired measurements were obtained with HDO on the metatarsus and 135 on the tail. Agreement with invasive pressures was better when HDO was used on the tail (rather than on the metatarsus) with all ACVIM criteria being met. Mean bias (a positive bias meaning that HDO overestimated the invasively measured pressures) ± standard deviation of differences for systolic, diastolic, and mean arterial pressures were -7.0 ±13.9 mmHg, 4.2 ±12.1 and 4.6 ±11.2 respectively for HDO on the tail, and -11.9 ±15.1 mmHg, 2.8 ±16.5 and 2.1 ±13.2 respectively for HDO on the metatarsus. Agreement was better during isoflurane anaesthesia than propofol, and at lower blood pressures than at higher.

Conclusions and clinical relevance When used on the tail base of anaesthetised cheetahs, HDO met the ACVIM validation criteria for a noninvasive device, as compared to invasively measured pressures in the dorsal pedal artery.

Keywords *Acinonyx jubatus*, anaesthesia, blood pressure, cheetah, felid, oscillometry.

Introduction

With declining numbers of wild cheetahs (*Acinonyx jubatus*) (Durant et al. 2015), captive populations have become increasingly important for the perpetuation of the species (Marker 2002). Cheetahs in captivity are prone to certain chronic conditions, such as systemic amyloidosis and glomerulosclerosis, which, although not well understood, may be associated with hypertension (Munson 1993; Munson et al. 1999). Thus far it has not been possible to accurately measure the arterial blood pressure of cheetahs to determine the prevalence of hypertension or the role it might play in these diseases. In addition, it is often necessary to immobilise cheetahs for clinical procedures or transportation, and blood pressure is a key index of cardiovascular status during anaesthesia (Heard 2007; Grubb et al. 2020).

The gold standard method for blood pressure measurement in veterinary medicine involves the placement of an intra-arterial catheter (Waddell 2000). This is invasive, technically difficult, and impractical to perform in the field or in conscious animals. Noninvasive devices are a more practical option and, of these, high-definition oscillometry (HDO) offers some particular advantages. After application of the cuff, the device is essentially automated removing the problems of inter-observer differences and operator experience associated with the Doppler ultrasonographic method (Brown et al. 2007; Chetboul et al. 2010). Also, the HDO device, by virtue of its size and portability, is convenient for use in the field. Unlike conventional oscillometry which measures only MAP and then calculates the other values using an algorithm and the oscillogram, HDO analyses arterial wall oscillations to estimate systolic (SAP), diastolic (DAP) and mean arterial pressures (MAP) (Ogedegbe & Pickering 2010; Egner 2015).

In our previous study, HDO in cheetahs performed favourably, but the small sample size precluded validation (Sant Cassia et al. 2015). The aim of this study was therefore to build on those results using a larger number of study animals and to investigate the impact of the anatomical location of the HDO cuff on agreement with the invasive method. We hypothesised that owing to discrepancies in blood pressure measured in different arteries in the body (Kroeker & Wood 1955), HDO used on the metatarsus would agree more closely with invasive blood pressures (IBP) measured in the contralateral dorsal pedal artery than would HDO used on the tail.

Materials and methods

This study was approved by the Animal Ethics Committee of the University of Pretoria V014-14 and the Research Ethics and Scientific Committee of the National Zoological Gardens of South Africa (NZG/P13/11). A Research/Collecting Permit was obtained from the Namibian Ministry of Environment and Tourism (permit no. 2013/2015).

A convenience sample of 13 healthy captive cheetahs (eight males and five females, aged between 2 and 13 years, and weighing 31.5 - 50.6 kg), housed at the AfriCat Foundation in Namibia, were anaesthetised for annual health examinations and procedures including abdominal ultrasound, gastroscopy, dentistry, and castration. Within the constraints of available equipment and time, the maximum number of study animals was used.

The methods used were similar to our previous study (Sant Cassia et al. 2015), but a brief description and modifications are outlined here.

Briefly, animals were immobilised in a random order determined on the first day (names drawn from a hat), with a combination of medetomidine (32-45 μg kg^{-1}; Kyron Laboratories, RSA) and tiletamine/zolazepam (0.93-1.39 mg kg^{-1} Zoletil; Virbac, RSA) administered via intramuscular remote injection (darting). Following orotracheal intubation, animals were connected to an anaesthetic machine via a Bain breathing system (Mapleson's D; Intersurgical, UK). Oxygen was provided at 3 L $minute^{-1}$ and side-stream capnography (Cardiocap 5; Datex-Ohmeda, Finland) was used for monitoring. Anaesthesia was maintained with either isoflurane (Forane; Abbot Laboratories, RSA) in 100% oxygen (delivered by a precision, out-of-circuit vaporiser (OHMEDA Isotec MK 3; BOC Healthcare, UK) or continuous intravenous propofol infusion at 0.1 mg kg^{-1} $minute^{-1}$ (Propoven 50mL; Fresenius Kabi, RSA), allocated on an alternating basis as part of their inclusion in another study (Buck et al. 2017).

Intravenous fluids (lactated Ringer's solution) were administered at 5 mL kg^{-1} $hour^{-1}$, via an 18 gauge catheter (Jelco; Smiths Medical Ltd, RSA) placed aseptically in the medial saphenous vein. Animals undergoing surgical procedures were administered morphine intramuscularly (0.2 mg kg^{-1} Morphine Sulphate; Fresenius Kabi, RSA) and meloxicam subcutaneously (0.3 mg kg^{-1} Metacam; Boehringer Ingelheim, RSA). At the end of the anaesthesia the medetomidine was antagonised with atipamezole (200 μg kg^{-1} Antisedan; Zoetis, RSA) via intramuscular injection, and the animal extubated.

IBP was measured in each cheetah via aseptic catheterisation of the dorsal pedal artery in the metatarsus (the dependent pelvic limb in left lateral recumbency) with a 32mm 20-gauge over-the-needle catheter (Jelco; Smiths Medical Ltd, RSA) following a standard technique (Waddell 2000). Semi-rigid tubing, primed with heparinised saline (1 IU mL^{-1}), connected the catheter via a strain gauge pressure transducer to a multiparameter monitor (Cardiocap 5). The transducer was maintained at the level of the right atrium (in dorsal recumbency, a sandbag slightly elevated the hindquarters), zeroed to atmospheric pressure, and calibrated daily at 50, 150 and 200 mmHg using a handheld aneroid manometer (Durashock Hand Aneroid; Welch Allyn, NY, USA). The same transducer was used for each animal, owing to financial constraints. The catheter and tubing were periodically flushed using a bag of heparinised saline (pressurised to 300 mmHg) to maintain patency and remove air bubbles. Intermittent fast flush tests were performed and visually inspected to confirm appropriate damping within the system.

Blood pressure was simultaneously estimated noninvasively using two identical HDO devices, which internally calibrate, Vet HDO MD Equine (S+B medVET GmbH, Germany). The manufacturer's cuffs (8 cm in width) were placed on the contralateral dorsal pedal (metatarsus of the non-dependent pelvic limb) and coccygeal (tail base) arteries in each cheetah, level with the right atrium (in dorsal recumbency, a sandbag slightly elevated the hind quarters) and according to the manufacturer's instructions such that a little finger should just fit underneath. Given the density of burrs in the coat, for standardisation, a patch of fur overlying the relevant arteries was clipped (and the circumference of the limb/tail measured) prior to the fitting of each cuff. Both devices were initiated simultaneously every 3 to 5 minutes and the current position of the cheetah (dorsal or lateral recumbency) was noted.

To facilitate simultaneous comparison of invasive and noninvasive pressures, the multiparameter monitor displaying the IBP was recorded on video for the 30-40 seconds that the HDO devices were operating, and audio prompts were used to define the start and end of the HDO cuff deflation.

HDO waveforms were analysed retrospectively, using the manufacturer's computer software (S+B medVET Memodiagnostics MDS Analyse Software Version 2.0.3.0), to determine the key period between systolic and diastolic measurements (the exact few seconds that pressures were being estimated by the device) and the timing of these relative to the start of the cuff deflation. This information, combined with the audio cues on the videos, was then used to establish the average IBP during that 5-10 second period (IBP was recorded every 1/10 of a second and then averaged) for each of the tail base and metatarsal HDO devices, to provide as close to simultaneous measurements as possible.

The noninvasive pressures estimated by the HDO devices on the metatarsus and tail were thus each compared to the IBP measured in the contralateral dorsal pedal artery.

Statistical analysis

Whilst blinded to the HDO measurements, the IBP waveforms were reviewed using the video clips and any that showed evidence of overdamping (absence of a dicrotic notch and/or slurred upstroke) or underdamping (deep dicrotic notch and/or presence of oscillations during the diastolic phase) were rejected as unreliable.

Similarly, blinded to the IBP, HDO waveforms were inspected *post-hoc* for three key features: linear cuff deflation, a complete bell curve and absence of strong movement artefacts in the key period (between systolic and diastolic measurements). As advised by the manufacturer, and as in the previous study, if any one of these criteria were not met, that measurement set (i.e., the set of SAP, DAP and MAP) was rejected as unreliable.

Metatarsal and tail HDO results were treated as two separate data sets such that comparisons were purely between invasive and noninvasive measurements.

Mean difference (HDO minus IBP) and standard deviation (SD), taking into account that repeated measurements of a changing quantity were taken from each individual (Bland & Altman 2007), were used to assess bias and precision respectively. Percentages of HDO measurements falling within 5, 10 and 20 mmHg of the IBP, 95% limits of agreement (mean ± 1.96 SD) (Bland & Altman 2007), and their confidence intervals treated as a pair (Carkeet 2015) were calculated for each variable.

The difference between two simultaneous measurements (HDO minus IBP, such that a positive number indicates an overestimation by the HDO machine, and negative indicates an underestimation) was plotted against the mean of the two measurements (Bland & Altman 1986, 2007). These Bland-Altman plots were used to evaluate the agreement between invasive and noninvasive measurements for each of SAP, DAP and MAP, at each cuff location. Histograms showed an approximately normal distribution for the differences between measurements.

The data were further interrogated to determine the effect of various factors on agreement. Bland-Altman plots were used to detect patterns in agreement depending on the age, sex and weight of the cheetah, magnitude of the blood pressure, position of the cheetah at the time of each measurement and the maintenance agent used. The data set was divided into two groups according, separately, to the position of the cheetah, maintenance anaesthetic agent and magnitude of the IBP {[lower (< 180/120/140 for SAP/DAP/MAP respectively] or [higher (≥ 180/120/140)]}. The same statistical analyses were then performed, plus Welch's two sample t-tests to check the significance of any difference in bias. The impact of time on agreement was analysed by plotting the difference (HDO minus IBP) against time since darting, for each variable at each cuff location. Results in the text are presented as mean ± SD.

Results were compared with the validation criteria set out by the American College of Veterinary Internal Medicine (ACVIM) (Brown et al. 2007). In order to pass validation, the mean difference of paired measurements for SAP and DAP treated separately must be ±10 mmHg or less, with a SD of 15 mmHg or less; the correlation between paired measures for

SAP and DAP treated separately must be ≥ 0.9 across the range of measured blood pressures; 50% of all measurements for SAP and DAP treated separately must lie within 10 mmHg of the reference method and 80% within 20 mmHg (Brown et al. 2007). The same criteria were applied to MAP, although no provision was made for this variable in the ACVIM guidelines. Although correlation is not considered an appropriate measure of agreement (Bland & Altman 1986), it was included in the analysis to facilitate comparison with ACVIM criteria and other studies. Analyses were performed using R, version 4.0.4 (R Core Team 2021).

Results

All cheetahs completed the study. The HDO devices were tested over IBP ranges of 120-271 mmHg SAP, 68-168 mmHg DAP and 82-192 mmHg MAP. The mean circumference of the metatarsus of the cheetahs was 12.8 cm and that of the tail, 14.8 cm.

In the metatarsal comparison, 168 pairs of measurements were obtained. A total of seven HDO measurements were rejected owing to violation of the acceptance criteria, and 15 IBP measurements were rejected owing to overdamping, leaving a total of 147 pairs of reliable measurements (11 ± 3 measurements per cheetah; one measurement pair was rejected owing to problems with both the IBP and HDO waveforms). In the coccygeal comparison 162 pairs of measurements were obtained, with 15 HDO and 14 IBP measurements being rejected, leaving 135 reliable measurement pairs (10 ± 4 per cheetah; two measurement pairs were rejected owing to problems with both IBP and HDO). No IBP waveforms showed signs of underdamping. There was minimal variation, if any, in IBP over each measurement period.

HDO measurements on the tail agreed more closely with the IBP measurements measured in the dorsal pedal artery, than did the HDO on the contralateral metatarsus (Table 1). At each

Table 1. Agreement between high-definition oscillometry (HDO) used on either the metatarsus or tail base, and invasive blood pressures measured in the contralateral dorsal pedal artery, for systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP), in 13 anaesthetised cheetahs.

Statistical parameter	ACVIM criteria	Metatarsus n = 147			Tail base n = 135		
		SAP	DAP	MAP	SAP	DAP	MAP
Mean difference (mmHg)	≤10mmHg	-11.9	**2.8**	**2.1**	**-7.0**	**4.2**	**4.6**
SD of differences (mmHg)	≤15mmgHg	15.1	16.5	**13.2**	**13.9**	**12.1**	**11.2**
Correlation coefficient *	≥0.9	**0.90**	0.83	0.89	**0.93**	**0.94**	**0.95**
≤ 5mmHg (%) †		30.6	35.4	32.0	25.9	35.6	43.0
≤ 10mmHg (%) †	≥50%	**54.4**	**62.6**	**65.3**	**50.4**	**60.0**	**65.2**
≤ 20mmHg (%) †	≥80%	77.6	75.5	**86.4**	**85.9**	**89.6**	**89.6**
Lower limit of agreement [95% confidence interval]		-41 [-46,-38]	-30 [-34,-26]	-24 [-27,-21]	-34 [-38,-31]	-20 [-23,-17]	-17 [-20,-15]
Upper limit of agreement [95% confidence interval]		18 [15,22]	35 [32,40]	28 [25,32]	20 [17,24]	28 [25,31]	26 [24,30]

n = number of readings

* Pearson's correlation coefficient. All significant to $p < 0.001$

† Percentage of HDO readings within 5,10 and 20mmHg of the direct value

ACVIM, American College of Veterinary Internal Medicine; SD, standard deviation; **bold**, results meet ACVIM criteria location MAP was the variable which showed the best agreement, and SAP the poorest. At both locations SAP was on average underestimated by the HDO device and DAP, and MAP were overestimated, as evidenced by the mean differences.

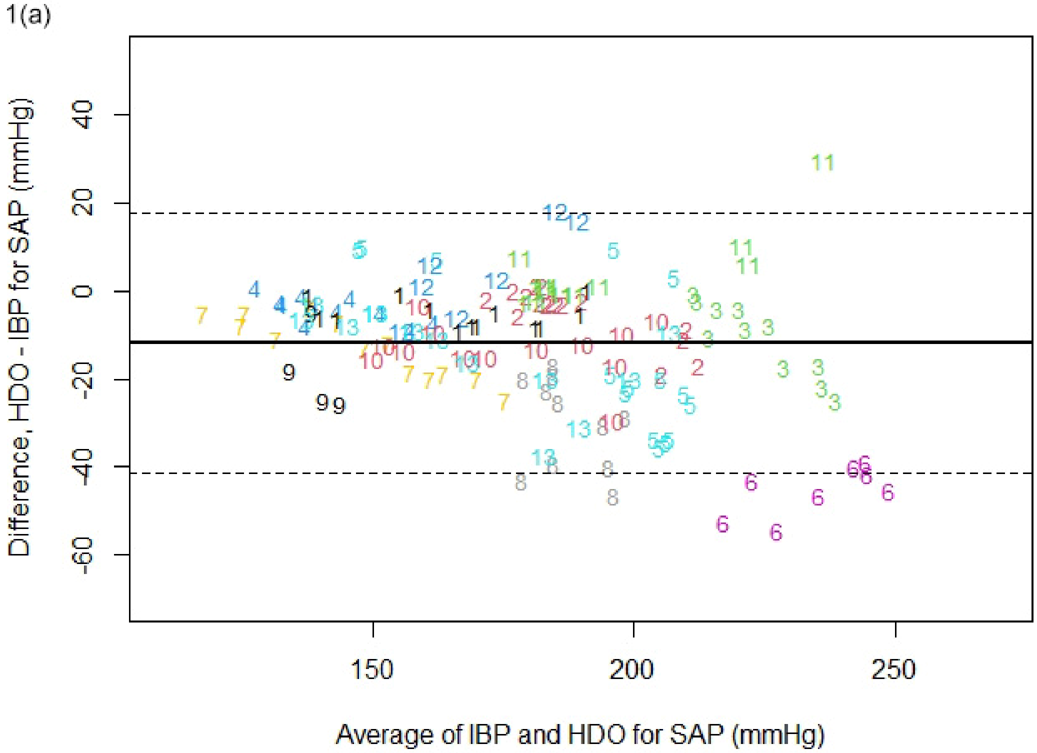
The Bland-Altman plots (Figs 1 & 2) show poorer agreement at higher SAP and MAP on the pelvic limb, whereas HDO overestimated higher pressures and underestimated lower pressures for DAP and MAP. No association was found between age, weight or sex of cheetahs and agreement. However there appeared to be some correlation with the choice of maintenance agent, with isoflurane anaesthesia in general resulting in better agreement than propofol.

The data divided according to the maintenance agent (Table 2) show that, with the cuff on the metatarsus, agreement was better during isoflurane anaesthesia for all variables. On the tail again agreement was better during isoflurane anaesthesia for DAP and MAP but better during propofol anaesthesia for SAP. However, it was also clear that blood pressures during propofol anaesthesia were significantly higher than during isoflurane anaesthesia (mean values of 210/133/156 mmHg for SAP/DAP/MAP with propofol, *versus* 167/103/122 with isoflurane, $p < 0.001$ in all cases).

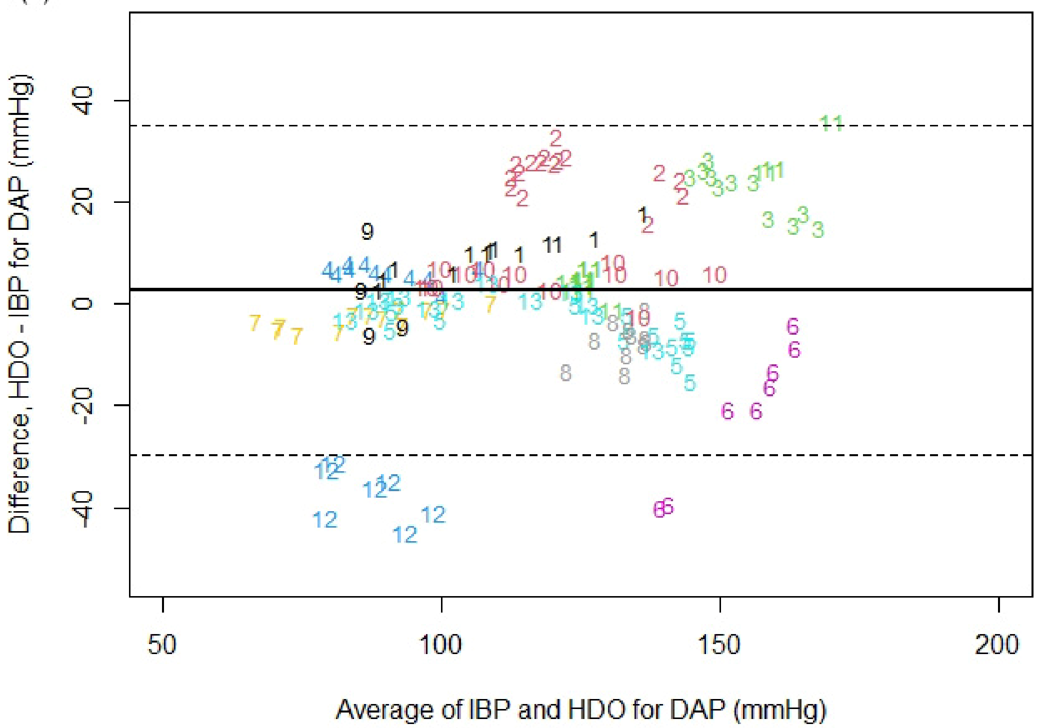
Whilst blood pressures were in general high, measurements < 180/120/140 mmHg (for invasive SAP/DAP/MAP) were designated "lower", and ≥ 180/120/140 mmHg were designated "higher", and the data were analysed again. For the metatarsus, agreement was significantly ($p < 0.001$) better at lower SAP (-6.2 ± 8.43) than higher (-16.0 ± 17.6). However, agreement was similar for lower and higher DAP (low 3.0 ± 17.2 *versus* high 2.6 ± 16.5; $p = 0.87$), and MAP (3.5 ± 11.8 *versus* 0.6 ± 15.1, $p = 0.18$). On the tail, agreement was significantly better at lower than higher DAP (-0.1 ± 10.1 *versus* 9.5 ± 12.9, $p < 0.001$) and

Figure 1a), b) and c). Bland-Altman plots showing agreement between high-definition oscillometry (HDO) used on the metatarsus and invasive blood pressure (IBP) measured in the contralateral dorsal pedal artery, for each of systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP) in 13 anaesthetised cheetahs. The difference between the HDO and IBP measurements (HDO - IBP, such that a positive number indicates an overestimate, and a negative an underestimate) is plotted against the average of the HDO and IBP measurements. Each point represents one measurement pair, with the number denoting the individual cheetah from which the measurements were taken. Horizontal lines indicate the mean difference (bias; solid line) and 95% limits of agreement (dashed lines).

1(a)

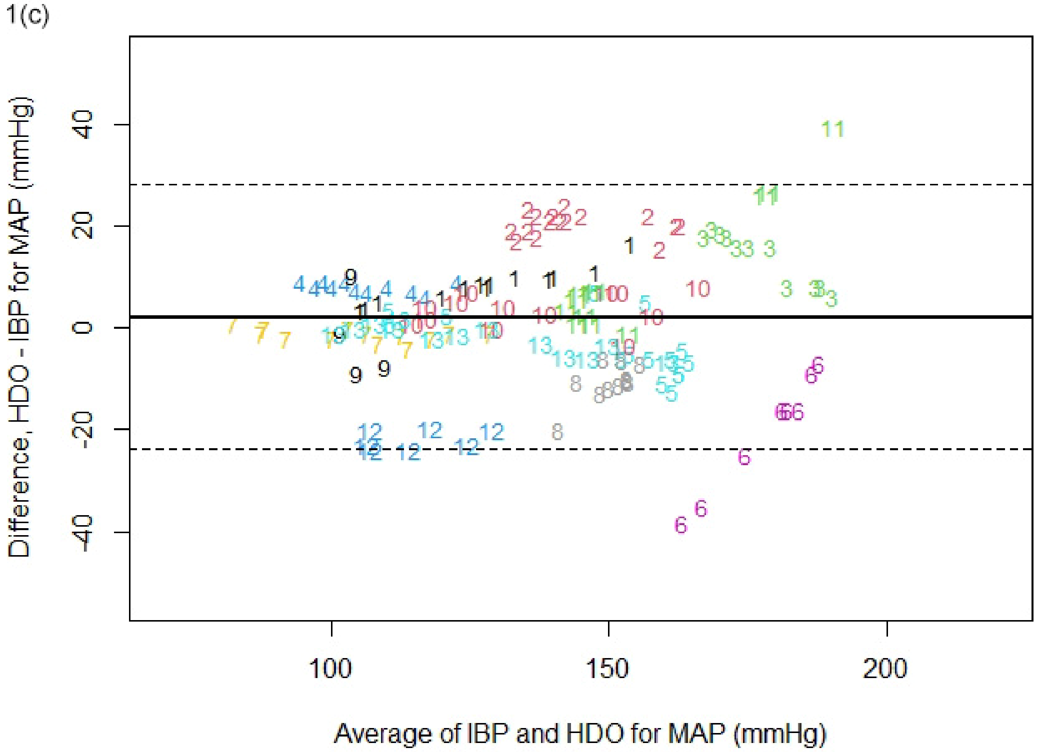


1(b)



Difference, HDO - IBP for DAP (mmHg)
Average of IBP and HDO for DAP (mmHg)

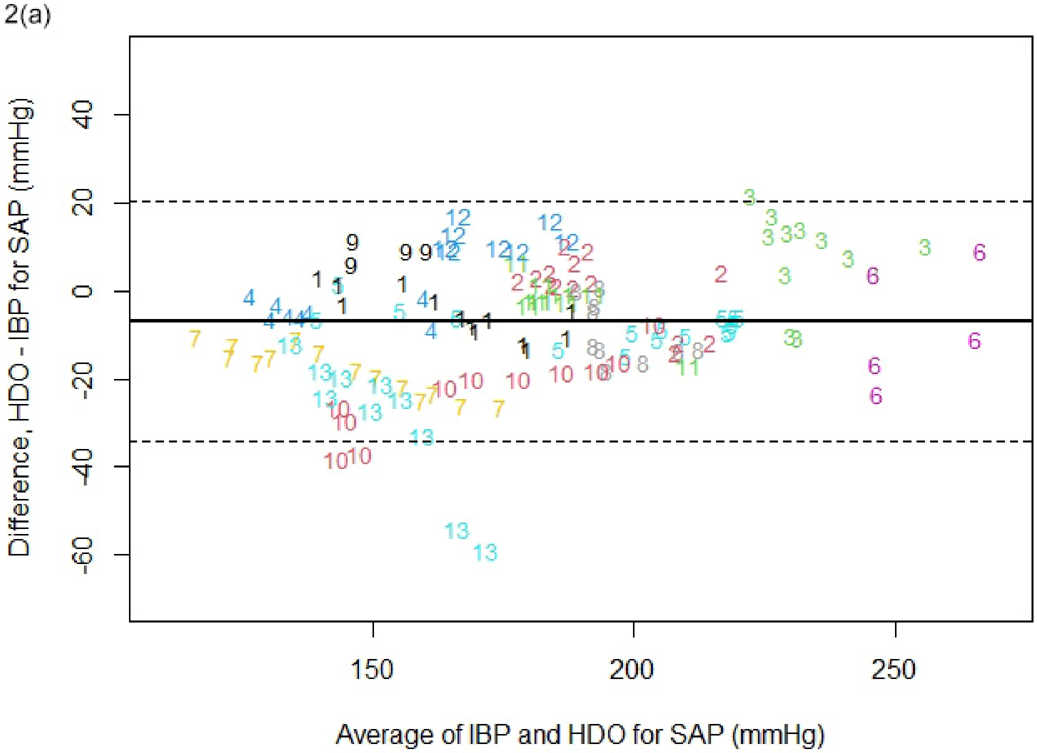
1(c)



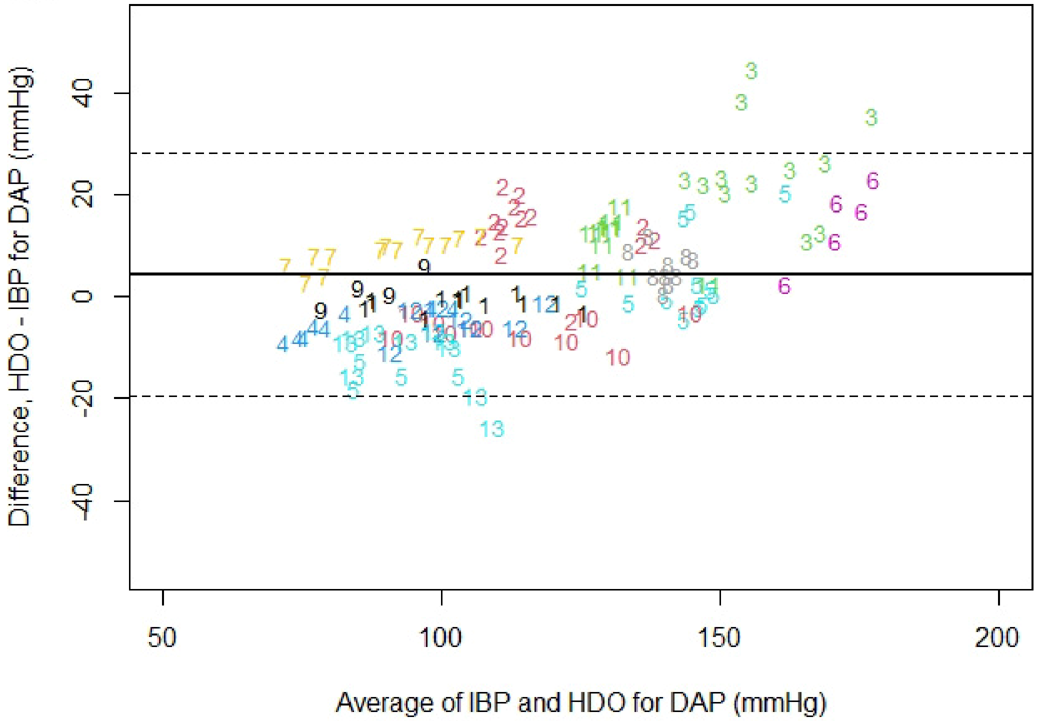
Difference, HDO - IBP for MAP (mmHg)
Average of IBP and HDO for MAP (mmHg)

Figure 2a), b) and c). Bland-Altman plots showing agreement between high-definition oscillometry (HDO) used on the tail base and invasive blood pressure (IBP) measured in the dorsal pedal artery, for each of systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP) in 13 anaesthetised cheetahs. The difference between the HDO and IBP measurements (HDO - IBP, such that a positive number indicates an overestimate, and a negative an underestimate) is plotted against the average of the HDO and IBP measurements. Each point represents one measurement pair, with the number denoting the individual cheetah from which the measurements were taken. Horizontal lines indicate the mean difference (bias; solid line) and 95% limits of agreement (dashed lines).

2(a)

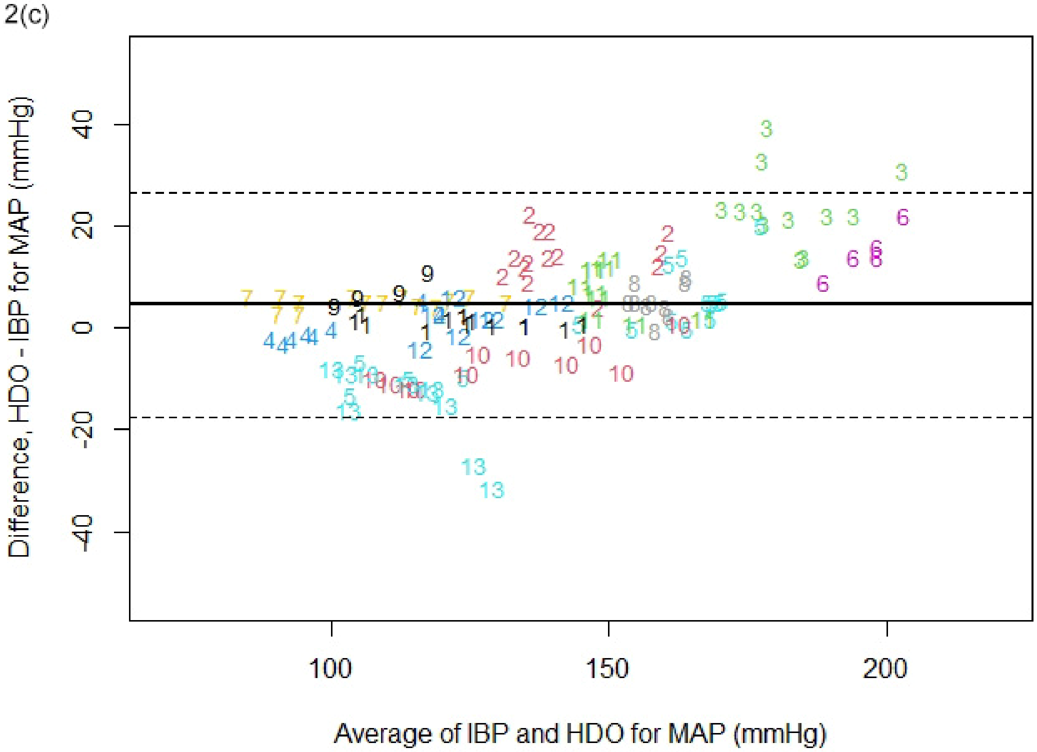


2(b)



Difference, HDO - IBP for DAP (mmHg)
Average of IBP and HDO for DAP (mmHg)

2(c)



Difference, HDO - IBP for MAP (mmHg)
Average of IBP and HDO for MAP (mmHg)

Table 2. Agreement between high-definition oscillometry (HDO) used on either the metatarsus or tail base, and invasive blood pressures measured in the contralateral dorsal pedal artery, for systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP), in 13 anaesthetised cheetahs maintained with either isoflurane in oxygen or continuous propofol infusion.

Statistical parameter	ACVIM criteria	ISOFLURANE			PROPOFOL		
		Metatarsus n = 86			Metatarsus n = 61		
		SAP	DAP	MAP	SAP	DAP	MAP
Mean difference (mmHg)	≤10mmHg	**-7.3**	**1.0**	**1.9**	-18.4	**5.3**	**2.4**
SD of differences (mmHg)	≤15mmgHg	**10.6**	**14.3**	**10.6**	18.6	20.6	17.5
Correlation coefficient [*]	≥0.9	**0.92**	0.86	**0.91**	0.80	0.57	0.70
≤ 5mmHg (%) [†]		33.7	47.7	47.7	26.2	18.0	9.8
≤ 10mmHg (%) [†]	≥50%	**65.1**	**79.1**	**84.9**	39.3	39.3	37.7
≤ 20mmHg (%) [†]	≥80%	**91.9**	**88.4**	**91.9**	57.4	57.4	78.7
Lower limit of agreement [95% confidence interval]		-28 [-31,-25]	-27 [-31,-24]	-19 [-22,-16]	-55 [-62,-50]	-35 [-43,-27]	-32 [-38,-27]
Upper limit of agreement [95% confidence interval]		14 [11,17]	29 [26,33]	23 [20,26]	18 [13,25]	46 [40,53]	37 [32,43]
Statistical parameter	ACVIM criteria	ISOFLURANE			PROPOFOL		
		Tail base n = 78			Tail base n = 57		
		SAP	DAP	MAP	SAP	DAP	MAP
Mean difference (mmHg)	≤10mmHg	-10.2	**-0.6**	**-0.4**	**-2.7**	10.7	11.3
SD of differences (mmHg)	≤15mmgHg	15.6	**8.9**	**8.6**	**10.6**	**13.5**	**11.2**
Correlation coefficient [*]	≥0.9	0.78	**0.90**	**0.91**	**0.93**	0.89	**0.93**
≤ 5mmHg (%) [†]		23.1	41.0	53.8	29.8	28.1	28.1
≤ 10mmHg (%) [†]	≥50%	44.9	**76.9**	**80.8**	**57.9**	36.8	43.9
≤ 20mmHg (%) [†]	≥80%	78.2	**98.7**	**97.4**	**96.5**	77.2	78.9
Lower limit of agreement [95% confidence interval]		-41 [-46,-37]	-18 [-21,-16]	-17 [-20,-15]	-23 [-28,-20]	-16 [-21,-12]	-11 [-15,-7]
Upper limit of agreement [95% confidence interval]		20 [17,25]	17 [15,20]	17 [14,19]	18 [15,22]	37 [33,42]	33 [30,38]

n = number of readings

* Pearson's correlation coefficient. All significant to $p < 0.001$

† Percentage of HDO readings within 5,10 and 20mmHg of the direct value

ACVIM, American College of Veterinary Internal Medicine; SD, standard deviation; **bold**, results meet ACVIM criteria

MAP (-0.7 ± 9.5 *versus* 9.4 ± 11.7, $p < 0.001$), but there was no significant difference for SAP (-8.4 ± 14.4 *versus* -5.9 ± 14.1, $p = 0.28$).

The body position of the cheetah at the time of each measurement did not significantly influence agreement, apart from for SAP measured using a metatarsal cuff for which lateral positioning resulted in a significantly smaller bias (lateral -9.3 ± 13.1 *versus* dorsal -22.7 ± 16.2, $p < 0.001$). Plots of the difference (HDO minus IBP) against time since drug administration revealed no clear change in agreement over time, apart from for SAP measured at the metatarsus for which agreement tended to improve over time for most cheetahs

Discussion

The HDO device used on the tail unexpectedly provided better agreement with invasive pressures measured via intra-arterial catheter in the dorsal pedal artery, than did HDO used on the contralateral pelvic limb. Agreement was generally better during isoflurane anaesthesia and at lower blood pressures.

It was hypothesised that the HDO positioned on the pelvic limb would agree more closely with the invasive pressures measured in the contralateral pelvic limb, than would the HDO on the tail. This is because blood pressure is different when measured in different arteries because of both distal pulse amplification (Kroeker & Wood 1955) and branching which creates turbulence and resistance affecting the pressure (Davis et al. 2003; da Cunha et al. 2017). In fact, the tail cuff produced better agreement, meeting all ACVIM criteria across all three variables. The phenomenon of inter-arm differences in blood pressure is well documented in human medicine (Clark et al. 2006) and, while this has not been demonstrated in veterinary medicine, it may be that such differences between contralateral limbs confounded the agreement in this study. Also, as the tail is a more cylindrical appendage than the more angular metatarsus, this may result in better contact between the cuff and the skin and thus better transmission of the pulse wave to the sensor. Indeed, the manufacturer advises that the HDO machine be used on the tail (in cats, dogs, and horses) although they provide no data to support this recommendation.

For many noninvasive blood pressure devices, cuff width:limb circumference is important for accurate measurements although recommendations vary between 25% (Tearney et al. 2016) and 40-60% (Sawyer et al. 1991), depending on the species and the study, whilst 30-40% is the commonly cited ratio for domestic cats and dogs (Acierno et al. 2018). Precise cuff width is reportedly not a critical factor for HDO (Egner et al. 2007) and the manufacturer produces only four cuff sizes for use in cats, dogs and horses, simply advising that the fit should allow a little finger to be inserted between the cuff and the limb. The equine cuff, with a width of 8 cm, was used in this study because the more powerful pump in the equine device was needed to repeatedly inflate the cuff to 300 mmHg. This width represents approximately 54% of the circumference of the cheetah's tail, and 62% of the circumference of the metatarsus. Given that 62% is slightly outside the usual recommendations, and agreement was poorer when the device was used on the metatarsus, it is possible that cuff width may be a factor in the accuracy of HDO, despite the manufacturer's advice (Duke-Novakovski et al. 2017). However, a consistent underestimation of both SAP and DAP, as would be expected with an oversized cuff (Sprafka et al. 1991), was not seen in this study and, in addition, the appropriate ratio for cuff width has not been determined in cheetahs.

Agreement between HDO and IBP was generally better during isoflurane anaesthesia than with propofol. To cause a discrepancy in agreement, any effects of the maintenance agents would have to impact one method differentially. Pharmacological agents may affect the resistance and compliance of vessels and therefore the arterial wall oscillations used by HDO to estimate blood pressure. These changes may affect the values obtained by HDO to a greater extent than those measured via the invasive method (Duke-Novakovski et al. 2017; van Zeeland et al. 2017). Although isoflurane and propofol both produce dose-dependent vasodilation and decreases in systemic vascular resistance (Grimm & Lamont 2007; van Zeeland et al. 2017), their effects are not equal. Blood pressure is often better maintained by propofol than by isoflurane (Keegen & Greene 1993; Deryck et al. 1996; Kleinschmidt et al. 2018), whereas systemic vascular resistance has either been higher with propofol or the same (Keegen & Greene 1993; Deryck et al. 1996). Agreement of HDO values derived from the tail *versus* invasively measured facial artery pressures was better in horses maintained with isoflurane than those maintained with a constant rate infusion of xylazine, ketamine and guaifenesin (Duke-Novakovski et al. 2017). This was thought to be attributable partially to the lower blood pressures seen with isoflurane, and the possibility that arterial wall stiffness, produced by xylazine, reduced the precision of the HDO machine.

Whilst normal blood pressure ranges have not yet been established in cheetahs, compared to generally accepted thresholds in other species (Brown et al. 2007; Acierno et al. 2018) the arterial pressures measured in this study were often very high. All cheetahs were hypertensive at the start of anaesthesia, almost certainly as a result of the combination of drugs used for immobilisation (Deem et al. 1998; Stegmann & Jago 2006), but then pressures decreased as anaesthesia continued. For most variables there was no obvious improvement in agreement over time, apart from for SAP in the metatarsal comparison. However, the data divided according to higher or lower pressures showed that the HDO device performed better at lower blood pressures or there was minimal difference. Direct comparison with other studies is difficult owing to their use of different thresholds and statistics. However, the results of this study, like those in other species, found that HDO showed poor agreement at extremes of the scale (Rysnik et al. 2013; van Zeeland et al. 2017), as have conventional oscillometry and the Doppler ultrasound method (Garofalo et al. 2012). These studies found a tendency for noninvasive devices to underestimate high and overestimate low pressures across most variables (Garofalo et al. 2012; Rysnik et al. 2013; van Zeeland et al. 2017). In contrast, we found that, when used on the tail, HDO was more likely to overestimate high pressures, but when used on the metatarsus SAP was underestimated to a greater degree at high pressures, with DAP and MAP not showing a clear bias. Also in the cheetah, both Doppler ultrasound and conventional oscillometry underestimated lower and overestimated higher blood pressures, apart from DAP which was underestimated by oscillometry across the pressure range (Sadler et al. 2013).

Comparing the tail cuff results of the present study with those from our previous study (Sant Cassia et al. 2015), the range of blood pressures observed was similarly wide, although in general slightly higher in the present study probably owing to the use of a propofol infusion in some individuals. SAP agreement was again the poorest of the three variables, but mean bias was better in the present study, bringing it within the ACVIM threshold of ± 10mmHg. Similar levels of precision and limits of agreement were seen when compared with the previous study.

In cheetahs, conventional oscillometry and Doppler sphygmomanometry, both used on the tail, showed good agreement with IBP in the dorsal pedal artery (Sadler et al. 2013). Compared with HDO in the present study, conventional oscillometry showed lower bias for SAP and MAP (although higher for DAP), and higher precision across all variables (Sadler et al. 2013). The better agreement seen may be due to the different oscillometric technology or may be reflective of the lower blood pressures reported in that study or the uniformity of the anaesthetic protocol used.

With the HDO cuff applied to the tail, the results of the present study met the ACVIM validation criteria (Brown et al. 2007). Despite this, it is noteworthy that the device still yielded very wide limits of agreement. No specification for this is made in the validation criteria but the limits of agreement are wide enough to have clinical implications.

To the authors' knowledge, since the criteria were defined in 2007, only one other study has been able to validate a noninvasive blood pressure device (da Cunha et al. 2016). That study compared two conventional oscillometric devices with IBP in anaesthetised dogs, the results of which met both the ACVIM and the more stringent Association for the Advancement of Medical Instrumentation guidelines for validation of blood pressure devices (Brown et al. 2007; American National Standards 2008). Aside from testing different oscillometric technologies in a target species, the very standardised canine population and narrow range of blood pressures observed probably contributed to the better agreement in that study.

The most significant limitation of this study was the inability to calculate the natural frequency and damping coefficient of the intra-arterial system, because of equipment constraints. In addition, although the HDO devices internally calibrate, there was no means of verifying this and the manufacturer does not provide any data on expected measurement error between devices. We were able to improve upon the methodology of our previous study (Sant Cassia et al. 2015) by performing calibration and visual analysis of fast flush tests and the invasive wave form for each measurement. No evidence of underdamping was found, but some individual measurements were rejected because of overdamping. Had this been a systematic problem across all measurements, then an accurate HDO would have effectively appeared to overestimate an overdamped invasive SAP. In fact, SAP was in general underestimated by the HDO machine.

In addition, although our ultimate goal is to measure the blood pressure of conscious cheetahs, animals in this study were anaesthetised. Since the results of this study cannot be extrapolated to conscious animals, further validation testing would be needed. However, an intra-arterial catheter would be difficult to maintain in a conscious cheetah which would increase the risk of complications and bring into doubt the accuracy of the IBP measurements under these circumstances.

In conclusion, when used on the tail base of anaesthetised cheetahs, according to the manufacturer's instructions, HDO has met the validation criteria for a noninvasive device, as compared to invasively measured pressures in the dorsal pedal artery. The device produced more accurate and precise results when used on the tail than when used on the metatarsus.

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Authors' contributions:

ESC: data collection, statistical analysis and preparation of manuscript

AT: study design, data collection and preparation of manuscript

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