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Blood Pressure Reference Intervals for Ketamine-sedated Rhesus Macaques (*Macaca mulatta*)

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Appropriate calculation and use of reference intervals have widespread clinical and research implications. Unfortunately, reference intervals for blood pressure in one of the most commonly used NHP species, rhesus macaques (*Macaca mulatta*), have never been calculated. Although anesthetic drugs and noninvasive methods of blood pressure measurement both have known effects on blood pressure values, their use provides the safest, fastest, and most widely used approach to clinical evaluation and blood pressure collection in this species. We analyzed noninvasive blood pressure measurements from 103 healthy, ketamine-sedated, adult (age, 8 to 16 y) rhesus macaques, representing both sexes, with various body condition scores by using 2 types of sphygmomanometers at 3 different anatomic locations. Reference intervals were calculated for each device, in each location, thus establishing normative data beneficial to clinical veterinarians assessing animal health and encouraging researchers to use noninvasive methods. Age, body condition score, sex, type of sphygmomanometer, and location of cuff placement were all found to influence blood pressure measurements significantly, providing important information necessary for the appropriate interpretation of noninvasive blood pressure values in rhesus macaques.

Abbreviations: BCS, body condition score; DAP, diastolic arterial pressure; HDO, high-definition oscillometry; MAP, mean arterial pressure; PR, pulse rate; RI, reference interval; SAP, systolic arterial pressure; SO, standard oscillometry

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A reference interval (RI) can be a crucial human and veterinary medical management tool when it is calculated and used appropriately.[22] RI are generated from the reference values that fall between 2 reference limits, usually the central 95%.[9] According to the National Committee for Clinical Laboratory Standards, development of an RI should start with the target measurements, obtained with consistent and reproducible methods, from a large number (120 being the preferred minimum) of healthy subjects.[9,22] However, the utility of RI as a predictor of measurements within a population still depends on their correct use and includes identification of possible variables in that population that may alter results.

As in human medicine, blood pressure (BP) in veterinary species can be affected by age,[14,15] comorbidity,[4,27] method of measurement,[29,30,32,37,39,38]pharmaceuticals,[6,23,41] and cuff placement.[3,40] The Veterinary Blood Pressure Society and the American Heart Association Council on High Blood Pressure Research have published guidelines for measuring BP in animals,[4,27] both of which require unanesthetized and minimally restrained subjects. Unfortunately, following these guidelines for obtaining BP can be very difficult—even dangerous—with some species of NHP, including adult rhesus macaques (*Macaca mulatta*).[34] Chemical restraint is a widely used practice in both research and clinical settings to maintain the safety of animals and personnel. To increase the utility of BP RI in this species, values should be obtained under a consistent sedation regimen. Ketamine is one of the most commonly used anesthetics in NHP medicine, despite being known to potentially increase both BP and heart rate.[6,7,12,23,24,38]

Similarly, a consistent method of BP measurement ought to be used. A variety of methods can be used to measure BP, including direct catheterization, which is the 'gold standard,' and indirect methods, such as Doppler ultrasound, manual sphygmomanometry, standard oscillometry (SO), and high-definition oscillometry (HDO).[13] Indirect, or noninvasive, BP measurements are the most useful in clinical medicine because of their ease of use, speed, and relative affordability.[13,35] The difficulty, expense, and rarity of direct BP measurement in the clinical setting make its use less practical for establishing RI. Doppler ultrasound and manual sphygmomanometry are subjective and therefore inappropriate for calculating RI. Blood pressure measurements from oscillometric sphygmomanometers generate precise systolic, diastolic, and mean arterial pressure (SAP, DAP, MAP, respectively) measurements and a pulse rate (PR). Standard oscillometry devices retrospectively calculate SAP and DAP from the MAP, or the strongest oscillation, and use a preprogrammed 3 mm Hg/s cuff deflation rate, regardless of PR.[13] Alternatively, HDO devices are capable of detecting the SAP and DAP amplitudes of each individual pulse wave and of deflating the cuff synchronously with the PR, thus culminating in a more precise calculation of MAP.[13,29,32,37] Agreement has been found between invasive (direct or telemetric) and HDO BP measurements in cats,[29] dogs,[30,37] horses,[39] cynomolgus macaques,[38] common marmosets,[32] and rhesus macaques.[24]

Although rhesus macaques are one of the most commonly used NHP species in biomedical research,[5,28] RI for BP in healthy adults have yet to be established. Multiple publications address

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BP values for a small number of pregnant and infant,[23] anesthetized,[21,26] and unanesthetized rhesus macaques.[16] Similarly, BP values for other NHP species, such as common marmosets (*Callithrix jacchus*),[19,31,32] chimpanzees (*Pan troglodytes*),[14,15] baboons (*Papio hamadryas*),[41] and cynomolgus macaques (*Macaca fascicularis*)[6,7,12,33,38] have also been made available. The aim of the current study was to calculate RI from the indirect BP measurements of a large number of healthy, sedated, adult rhesus macaques, to mimic clinical and research applications. We hypothesized that age, sex, BCS, sphygmomanometer, and cuff location would not significantly influence measurements of SAP, DAP, MAP and PR measurements.

Materials and Methods

Animals. This study involved 103 apparently healthy, adult rhesus macaques housed indoors at the California National Primate Research Center (Davis, CA). The absence of abnormalities on annual physical examinations, as well as normal activity and mentation, were used as inclusion criteria for healthy animals. Animals were selected according to age, sex and BCS to ensure balanced representation within the sample population; 55 of the 103 animals were males, and 48 were nonpregnant females. Of the selected animals, 30 were 8 to 10 y old, 27 were 10 to 12 y old, 26 were 12 to 14 y old, and 20 were 14 to 16 y old. On the day of BP measurement, animals were weighed (range, 4.5 to 19.3 kg), and their BCS were evaluated according to a validated system.[10,11] Macaques were considered lean when they had a BCS of 2 or lower; this study included 29 lean animals. In addition, 39 animals with optimal BCS (that is, 2.5 and 3.5) were selected. All animals with a BCS of 4.0 or greater were considered overweight, and this study included 18 overweight animals. In addition, selected animals were required to have a tail length of at least 3 in., to allow for adequate cuff placement. After the completion of data collection, macaques were followed for at least 1 y; their data were excluded when cardiac, vascular, renal, or pulmonary disease was diagnosed.

All macaques were provided species-appropriate environmental enrichment, fed chow twice daily (LabDiet Monkey Diet 5047, Purina Laboratory, St Louis, MO), supplemented with fruits and vegetables, and offered water free choice by using automatic watering devices. Animals underwent biannual physical examinations as part of routine care. This study was approved by the IACUC of the University of California–Davis. Animals were maintained in accordance with the USDA Animal Welfare Act and Regulations and the *Guide for the Care and Use of Laboratory* Animals.[1,2,20] The animal care and use program of the University of California–Davis is USDA-registered, maintains a Public Health Services Assurance, and is fully accredited by AAALAC.

BP measurements. Data was collected in the morning hours between 14 February 2012 and 6 May 2016. All animals were sedated by using ketamine (10 mg/kg IM) and, once fully sedated, were delivered to a procedure room. Data collection may have been delayed by as long as 17 min after sedation, depending on the distance of an animal's home cage from the procedure room. The time it took to collect all measurements lasted no more than 39 min but varied due to sphygmomanometer speed and animal movement, thus requiring repetition of data collection.

The 2 noninvasive sphygmomanometers were a SO veterinary device (Cardell model 9401, Sharn Veterinary, Tampa, FL) and an HDO veterinary device (Vet-HDO-Monitor, S+B MedVET, Babenhausen, Germany), both of which were factory-calibrated. The HDO sphygmomanometer used manufacturer-supplied software (Memodiagnostics MDS Analyze Software version 2.0.3.0, S+B medVET) that had an artifact recognition algorithm and displayed the pulse wave on a monitor to allow for real-time evaluation.

Macaques were randomly assigned to undergo left or right-sided measurements, and either the upper arm (brachial artery), lower leg (medial tibial artery), or proximal tail (coccygeal artery) was chosen randomly for the first and second location of BP measurements for each device. While animals were in lateral recumbency (left-sided for right-sided measurements, and right-sided for left-sided measurements), a set of at least 7 recordings were taken from each device, at each location. Both devices supported the acquisition of SAP, DAP, MAP, and PR. Care was taken to ensure that both machines were used with the most appropriate cuff size for each animal, because inappropriately large or small cuffs have been shown to affect readings in other species.[3] For SO measurements, Sharn blood pressure cuffs (Midmark, Torrance, CA) were available in sizes 1 to 5, 8, and 10. The cuff size was determined by measuring with the width of the cuff around the circumference of the limb, and the one that was closest to covering 40% of the limb or tail circumference was used for SO.[13] For HDO measurements, cuffs of sizes C1, D1, and D2 were selected according to the manufacturer's instructions, wrapped circumferentially around the appendage, and placed at the level of the heart, with each device measuring BP at different sites. Consistency in cuff selection and placement were maintained by using the same 3 personnel to obtain measurements. For all animals, limb and tail sizes fell within the acceptable range for one of the cuff size options for each machine. Animals were not disturbed during measurements from either machine. When an animal showed visible movement during measurement, or when the HDO software detected an artifact, the data were neither recorded nor included in the RI calculations. After completion of BP measurements at the first location (for example, SO on the arm and HDO on the leg), both devices were then moved to one of the remaining 2 locations (for example, SO on the leg and HDO on the tail) and readings repeated; the devices were then moved once more for the final location readings (for example, SO on the tail and HDO on the arm). Every animal experienced at least 7 readings for each parameter, from both SO and HDO devices, in 3 locations (arm, leg, and tail); totaling 6 sets or 42 measurements per animal.

Health status verification. Apparently healthy, adult rhesus macaques (n = 103) were sedated with ketamine for BP measurements on the arm, leg, and tail by using noninvasive SO and HDO devices. Following completion of data collection, all animals were prospectively followed for at least one year. Medical records were assessed for any health concerns that may have a significant effect on blood pressure (that is, cardiac, vascular, renal or pulmonary disease). By 2 y after data collection, 49 animals had been euthanized for various reasons, and necropsy reports were reviewed to verify health status. Four animals diagnosed with either left ventricular hypertrophy, cardiomyositis with arteritis, or chronic nephritis were excluded from analysis. In addition, one animal, still living, was noted to have mitral valve endocardiosis, which was confirmed by echocardiography; this macaque was excluded from the study also.

Statistical analysis. Aggregation of data was achieved by maintaining measurements that were reported together (that is, SAP, DAP, MAP, and PR). Only the data correlating with the middle 3 SAP values, that is the median and its adjacent values, were included in the reference values. When duplicate SAP values arose (for example, 50 and 50), then the middle

Table 1. Reference intervals for systolic arterial pressure (SAP; mm Hg), diastolic arterial pressure (DAP; mm Hg), and mean arterial pressure (MAP; mm Hg) for adult rhesus macaques by using standard oscillometric (SO) and high-definition oscillometric (HDO) devices

		SO			HDO		
		SAP	DAP	MAP	SAP	DAP	MAP
Arm	Upper limit	163	102	124	176	108	129
	Median	119	61	86	118	57	77
	Lower limit	78	34	52	74	19	38
Leg	Upper limit	179	103	134	195	121	147
	Median	133	68	96	132	64	88
	Lower limit	96	32	57	93	23	52
Tail	Upper limit	177	100	124	187	110	128
	Median	130	67	90	130	73	93
	Lower limit	90	34	54	91	28	57

3 MAP values (that is, the median and its adjacent values) were cross-referenced to determine which duplicate (and its associated data) was included ultimately. Again, when duplicates arose within the MAP values, the middle 3 DAP values were cross-referenced to determine data inclusion. The final 3 values for each animal, from each device and in each location, were averaged. All statistical analyses were performed by using statistical software (MedCalc Software, Ostend, Belgium). Nonparametric percentile methods were used to calculate RI for both devices and for all 3 measurement locations. The Shapiro–Wilks omnibus goodness-of-fit test rejected the assumption of a normal (Gaussian) distribution for SO leg SAP (W = 0.9666 and $P = 0.0142$), SO arm and tail MAP (W = 0.9657 and $P = 0.0152$, W = 0.9669 and $P = 0.0183$, respectively) and DAP (W = 0.9329 and $P = 0.0001$, W = 0.9524 and $P = 0.0019$, respectively), HDO arm SAP and MAP (W = 0.9650 and $P = 0.0121$, W = 0.9638 and $P = 0.0100$, respectively), and HDO arm and tail DAP (W = 0.9530 and $P = 0.0018$, W = 0.9708 and $P = 0.0401$, respectively), where W is the Shapiro–Wilk test statistic.

An exact Freidman test was used to measure variation within an individual's data by measurement location to determine whether the distribution of measurements was the same for all locations. Relationships between blood pressure and age or BCS were compared by using Spearman correlations. Significant differences based on sex was determined by using Mann–Whitney analysis (95% confidence intervals, 2 tails). A P value of 0.05 was considered statistically significant for all analyses.

Results

RIs and variation by device and location. Each SO or HDO reading generated values for SAP, DAP, MAP, and PR. RI from each macaque's average of their middle 3 readings were calculated for SAP, DAP and MAP at each location and for both devices (Table 1) SAP and MAP were significantly different among locations for both the SO ($P < 0.0001$ for both parameters), and HDO ($P < 0.0001$ for both parameters; Figure 1) devices. DAP measurements differed significantly ($P < 0.0001$) by location only when measured with the HDO device. PR did not differ between locations or devices.

Variation by age, BCS, and sex. Age affected BP measurement across locations and devices (Figure 2). Comparisons revealed significant and positive age-associated correlations between the SO-derived SAP, MAP, and DAP on the arm, leg, and tail (Table 2). The HDO device yielded significant positively correlated age-related differences between the arm SAP, MAP, and DAP and the leg SAP (Table 2). PR did not differ according to animal age for either device at any location.

Similarly, BCS was found to have a significant and positive correlation between the SO-derived SAP and MAP and the HDO-obtained SAP, MAP, and DAP measurements from the arm (Table 2). In addition, BCS led to significant difference when SO was used to measure SAP and DAP on the leg and SAP on the tail; these correlations again were positive (Table 2). Figure 3 illustrates the trend of increasing BP with increasing BCS, with the exception of HDO SAP measurements on the arm of animals with ideal BCS which saw a decreased BP. PR did not differ according to BCS for any device or location.

Significant differences according to animal sex were found for SO between SAP, MAP, and DAP when measured on the arm as well as between SAP and MAP when measured on the leg. HDO measurements differed for the arm MAP and DAP and leg MAP and DAP. Tail measurements differed according to sex only for the SO-derived MAP and DAP. In addition, sex was the only variable that significantly affected PR, with females at consistently higher rates regardless of location or device (all $P < 0.0001$; Figure 4).

Discussion

BP measurements can provide important physiologic data for both investigators and clinical veterinarians. Researchers often use invasive telemetry devices to obtain BP data, due to the difficulty handling unanesthetized, adult rhesus macaques and the known variable effects sedatives have on blood pressure. Similarly, when clinical disease provides an indication for BP measurement, clinical veterinarians have few options for capturing an accurate value, and appropriately calculated RI for comparison with that value are unavailable. To our knowledge, this study represents the first attempt to generate noninvasive BP RI from a large number of healthy, ketamine-sedated, adult rhesus macaques. Importantly, we considered the potential for clinical and research applications in the design of this study, by using the most common sedation for noninvasive procedures.

Both sedation and the stress of unanesthetized restraint dramatically affect BP measurements in a variety of animal species.[3,6,15,23,33,35,37-39,41] We chose chemical restraint for our study because it is the safest and most common method used for BP measurement in this species. Indeed, routine physical examinations are often performed under the same chemical restraint protocol that we used in this study, making the BP RI presented

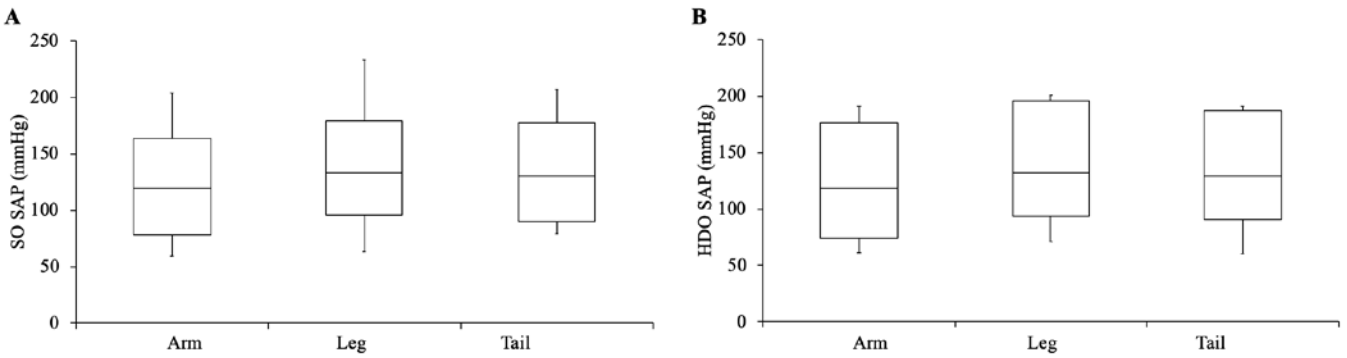

Figure 1. Box plot distribution, with reference intervals and medians, for systolic arterial pressure (SAP) from the (A) standard oscillometric (SO) device and (B) high-definition oscillometric (HDO) device, showing a statistically significant ($P < 0.001$) difference between locations of measurement.

here relevant for screening animals at routine exams. Similarly, noninvasive methods for measuring BP are fast, require minimal technical skill, and are economically practical, thereby making them the most appropriate for establishing BP RI. Following recommendations laid out by the National Committee for Clinical Laboratory Standards, we used nonparametric methods—those that do not infer 'normal' (Gaussian) distribution patterns, to calculate RI.[9]

The first variable that we examined—the type of noninvasive sphygmomanometer—did not significantly affect BP and PR measurements. This finding was not altogether surprising, given that both devices use the detection of an oscillometric pulse wave to calculate BP measurements. Whereas the SO device runs on an 8-bit processor, which limits pulse detection during cuff deflation, the 32-bit processor in the HDO device makes it capable of instantaneous valve adjustment according to the pressure detected in the cuff during the deflation phase.[13,33] Previous work has found that SO devices are accurate within an 80- to 160-mm Hg window only,[13] which largely encompasses the measured values in this study.

A second variable, the location of BP measurement, caused significant differences in the BP values and subsequently the RI. In general, within the same animal, BP measurements from the arm (brachial artery) tended to be lower than those from the leg (medial tibial artery) and tail (coccygeal artery). This finding might be explained by the larger muscle mass in the arm, thus suppressing oscillometric waves between the brachial artery and the cuff, compared with the leg and tail arteries. Previous studies have found tail BP measurements to be more precise than those of the limbs (radial and medial tibial arteries) when measured indirectly in dogs[3] and cats.[40] The Veterinary Blood Pressure Society recommends cuff placement on either a limb or tail.[4] Alternatively, BP may truly differ between peripheral vessels, given that they differ from central arteries,[25] especially when influenced by ketamine sedation.[6,23,41]

Other significant variables, such as age and BCS, increased overall BP measurements in adult rhesus macaques as the variables themselves increased. This pattern is consistent with previous findings in chimpanzees[15] and humans,[8,17,1836] despite being confounded by comorbidities in those species. This result could represent possible health complications that have not yet been elucidated in rhesus macaques or the difference in the sensitivity of the devices used in these studies. Furthermore, animal sex altered the BP significantly in our study; however, sex was proposed to be confounded by body weight in a similar study in chimpanzees[15] and is certainly a possibility in the sexually dimorphic rhesus macaque. More surprisingly, sex significantly influenced PR but not by any other variable in our animals. To

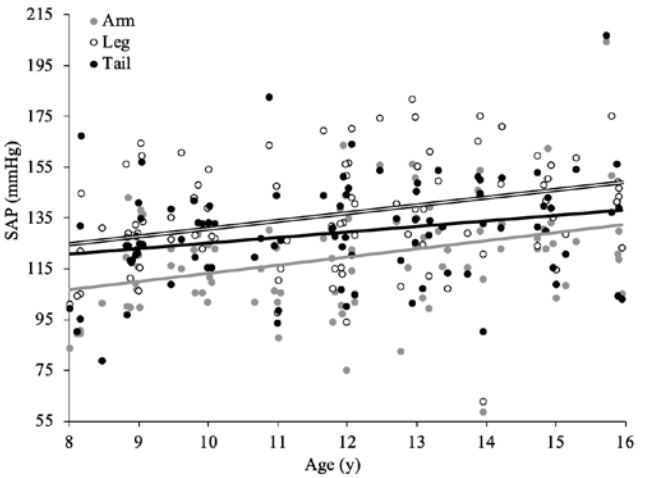

Figure 2. Arm, leg, and tail systolic arterial pressures (SAP), with linear trendlines, showing a significant ($P < 0.05$) difference by age.

our knowledge, this study represents the first time that PR was found to significantly differ between rhesus macaques according to sex, or more precisely, that an inverse relationship exists between males compared with females in the association of PR and body weight.

In clinical and research settings, ketamine sedation for noninvasive BP measurement is the fastest, safest and, therefore, the most likely application for BP RI. Limitations to this study include a lack of recovery time between measurements, which likely would have affected results depending on the individual subject's rate of ketamine metabolism. The lack of a direct arterial catheterization for comparison limits interpretation of these results as we could not determine the accuracy of particular techniques for measuring arterial blood pressure. These devices have previously been validated against direct BP monitoring in multiple veterinary species,[3,12,29,30,32,33,37-39,41] thereby prompting our investigation into their utility. Future research should be done to explore the RI of BP in rhesus macaques under different sedation regimens and to define hyper- and hypotensive pathologic states. Similarly, different positions of blood pressure measurement on the arm (brachium compared with antebrachium) is a potential area for future study. Furthermore, testing multiple methods of BP measurement during hypotensive states could determine whether particular methods might be better suited for BP monitoring during anesthesia. Our study has established RI for healthy, ketamine-sedated, adult rhesus macaques and confirmed that age, BCS, sex, and location of measurement can all significantly influence the BP measurement

Table 2. *P* values for systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP) measured by using standard oscillometric (SO) and high-definition oscillometric (HDO) devices

		SO			HDO		
		SAP	DAP	MAP	SAP	DAP	MAP
Arm	Age	$P < 0.0005$	$P < 0.0003$	$P < 0.0001$	$P < 0.0004$	$P < 0.0001$	$P < 0.0002$
	BCS	$P < 0.0002$	NS	$P < 0.0144$	$P < 0.0028$	$P < 0.0126$	$P < 0.0059$
	Sex	$P < 0.0019$	$P < 0.0003$	$P < 0.0018$	NS	$P < 0.0100$	$P < 0.0327$
Leg	Age	$P < 0.0009$	$P < 0.0010$	$P < 0.0002$	$P < 0.0162$	NS	NS
	BCS	NS	$P < 0.0476$	$P < 0.0484$	NS	NS	NS
	Sex	$P < 0.0208$	NS	$P < 0.0091$	NS	$P < 0.0098$	$P < 0.0247$
Tail	Age	$P < 0.0118$	$P < 0.0162$	$P < 0.0086$	NS	NS	NS
	BCS	$P < 0.0249$	NS	NS	NS	NS	NS
	Sex	NS	$P < 0.0139$	$P < 0.0183$	NS	NS	NS

NS, not significant

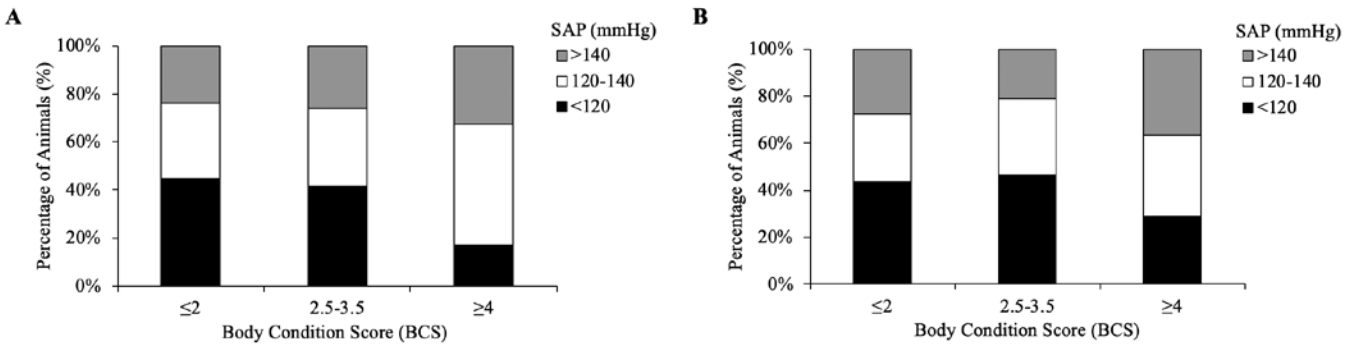

Figure 3. (A) Standard oscillometric and (B) high-definition oscillometric measurements of systolic arterial pressure (SAP) at the arm show a significant ($P < 0.05$) increase in SAP as body conditioning score (BCS) increases.

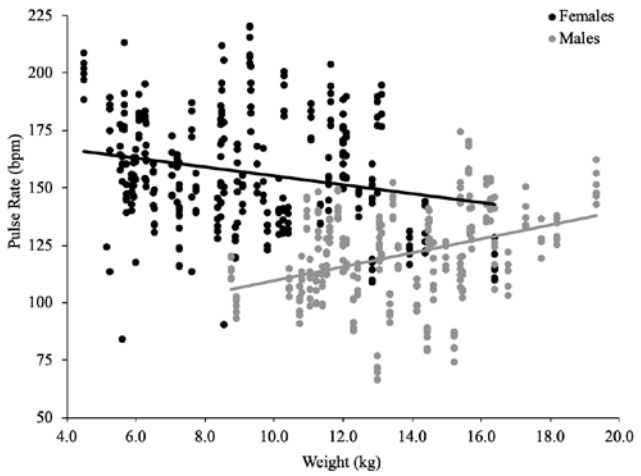

Figure 4. Pulse rate (PR; bpm) from all locations, with linear trendlines, showing significant ($P < 0.001$) differences between males and females by weight.

values obtained. When implementing a blood pressure screening program for macaques, we recommend standardizing the device and location of measurement.

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