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Standard Electrocardiographic Data from Capuchin Monkeys (*Cebus apella,* Linnaeus, 1758)

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Capuchin monkeys are a species of arboreal primate found in all South American countries. These monkeys have been highlighted for their potential for biomedical research due to their anatomic and physiologic similarities and genetic homology with humans. Here we characterized the electrocardiographic tracings from 12 healthy, young capuchin monkeys that were restrained with ketamine and midazolam. All 12 monkeys had normal sinus rhythms. Neither P-wave duration, PR interval, QT interval, nor P- or R-wave amplitude (in millivolts) differed between males and females. The P waves were small, monophasic, and positive in all animals. The QRS complex showed positive polarity in the D1, D2, aVL, aVF, V2, V4, and V10 derivations and negative polarity in the D3, aVR, and rV2 leads. The T wave exhibited a negative polarity only in the aVR derivation in all animals in the study, and no significant difference was present between sexes. The ST segment was isoelectric in both sexes and lacked reductions and elevations. The anesthetic protocol was well tolerated all of the monkeys and allowed for diagnostic-quality acquisition, measurement, and characterization of the electrocardiogram and establishment of the normal electrocardiographic parameters of chemically restrained capuchin monkeys.

Capuchin monkey (*Cebus apella,* Linnaeus, 1758) are a species of arboreal primate of short stature and diurnal habits. This species has a wide geographic distribution that covers most of the countries of South America.[16] From a cognitive perspective, capuchins are considered the most competent primates in America due to their ability to obtain food.[36]

Increasing deforestation has led to the destruction of the natural habitat of NHP and has caused them to migrate to other regions, which has made them vulnerable to predatory hunting and to withdrawal from nature. These factors in turn have led to numerous capuchins living in captivity. In this context, the survival of several wild species depends to a large extent on their reproduction in captivity; however, reproduction in captivity requires a broad knowledge of the biology and clinical criteria of normality in these species.[58]

Capuchin monkeys have been extensively studied as an animal model for biomedical research due to the similarity of their anatomic and physiologic characteristics to those of humans.[65] Capuchins have provided important data to the scientific community since 1932, when these animals were used in experiments to improve the development of techniques for the diagnosis and treatment of diseases in humans.[47] These animals are useful experimental models in the study of Chagas disease, demonstrating numerous electrocardiographic abnormalities and myocardial fibrosis.[45] In addition, capuchin monkeys may be important natural reservoirs and vectors of *Trypanosoma cruzi*.[7] Furthermore, aged NHP have been recognized as a natural and important animal model for human aging due to the advantages afforded by the biologic similarities and genetic homology among primate species.[47]

Electrocardiography is an important diagnostic tool that is used for cardiac evaluation and has increasingly been used in veterinary science.[39] Electrocardiography is relatively inexpensive, noninvasive, and rapid.[17,49] However, this method is not yet fully established in wild animal medicine, although the literature includes some research that has been conducted in an attempt to standardize ECG in species such as ferrets (*Mustela putorius furo*),[5,14] psittacids,[61] turtles (*Podocnemis expansa,* Schweigger, 1812),[8] agoutis (*Dasyprocta prymnolopha*),[11] and macaques (*Macaca cyclopis*).[31]

Cardiovascular diseases have been reported in some NHP species. Owl monkeys (*Aotus* spp.) are highly susceptible to hypertrophic cardiomyopathy and can die suddenly after periods of stress or physical activity. Owl monkeys show electrocardiographic changes consistent with left ventricular hypertrophy associated with cardiac electrical-axis deviation.[42,60] Dilated cardiomyopathy occurs in squirrel monkeys (*Saimiri sciureus*), which consequently show contractility deficits, a decreased ejection fraction, and fractional shortening. Electrocardiographic findings in squirrel monkeys with dilated cardiomyopathy include increased QRS duration and ST segment depression.[55]

Analyses of the various complexes, intervals, and waveforms assist clinicians in the diagnosis of cardiac diseases and the differentiation of congenital and acquired heart diseases from normal physiologic conditions.[2,12] In addition, the use of electrocardiography in NHP is an important component in the conservation of endangered species and the provision of information related to their biology, thus facilitating the management of these species in captivity and the wild.[2,6,21,28]

Most wild NHP species require chemical restraint or even general anesthesia to undergo medical or research procedures;

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this requirement emphasizes the importance of defining the normal cardiovascular functional patterns in these species to enable facilitate their monitoring and the choice of the optimal drug(s) for this purpose.[15] Among the drugs of choice, ketamine has been widely used for the immobilization of wild animals because of broad safety margin, which allows its use even when an animal's exact weight is unknown and which makes its use in NHP practical.[21] In addition, ketamine has good intramuscular absorption, which facilitates its application by using darts.[30] However, ketamine should be used in combination with other drugs, such as α2 agonists, benzodiazepines, or neuroleptic anesthesia, such as azaperone, depending on the species involved.[24,57] For example, the combination of ketamine and midazolam promotes myorelaxation, thus reducing muscular hypertonicity and promoting tranquilization, hypnosis, and amnesia, in addition to exerting an anticonvulsive activity.[40,44] This anesthetic protocol is commonly used for procedures in small animals and has been demonstrated to be a good option for work with wild animals, including NHP.[11,25,41]

In light of the need for chemical restraint for handling wild animals and given the wide use of pharmacologic combinations in medical clinics for wild animals, the objective of this study was to characterize the electrocardiograms of tufted capuchins (*Cebus apella*, Linnaeus, 1758) restrained with ketamine and midazolam.

Materials and Methods

Animals. The study population comprised 16 healthy capuchin monkeys (*Cebus apella*; *n* = 16) from the Wild Animal Triage Center (Teresina, Piauí, Brazil). All animals were adults (mean age, 3 y) and weighed 1.0 to 2.9 kg. The animals were housed on small islands within an artificial lake and were divided into 2 groups (*n* = 8 males; *n* = 8 females), one on each island. The monkeys were fed a diet of fruit pulp, seeds, corn, and new shoots of local vegetation. Their health was confirmed through general physical examinations; cardiovascular studies, including echocardiography; and hematologic and serum biochemical assays that considered liver and renal function.[27,28,46]

The protocols used in this study were approved by the Committee on Ethics in Animal Experimentation (no. 0.47/2015) and were authorized by the Ministry of the Environment through the System of Authorization and Information of Biodiversity of the Brazilian Institute of the Environment and Renewable Natural Resources (no. 48113-1).

Inclusion and exclusion criteria. Subjects with an unremarkable clinical history and physical examination were included in the study. The cardiovascular and respiratory systems were evaluated though auscultation of the heart valves and lung fields. Hemodynamic investigation included capillary perfusion time and dehydration assessment. Systemic infectious processes were assessed by palpating the peripheral lymph nodes (submandibular, cervical, and popliteal) and abdomen and measuring body temperature. In addition, all of the animals underwent blood, biochemical, and electrolyte tests. Animals with evidence of systemic disease, cardiovascular abnormality (murmurs, arrhythmias), or valvular insufficiency on echocardiography and those that exhibited excessive stress during the examinations were excluded from the study.

Anesthetic protocol. The animals were food-fasted for 12 h, and water was withheld for 4 h. The monkeys initially were caught in traps and restrained physically by using leather gloves. For chemical restraint, a combination of 5% ketamine hydrochloride (15 mg/kg IM) and midazolam (0.5 mg/kg IM) was administered.[43] Once anesthesia had been achieved, the electrocardiographic procedures were initiated. The protocols required an average anesthetic time of 30 to 40 min in all monkeys, none of which required a second dose of any drug during the examinations.

Computerized electrocardiography. To perform the tests, the monkeys were placed in the right lateral decubitus position, with the limbs parallel, extended, and perpendicular to the long axis of the body, on a table with a rubber insulating surface to prevent interference. Electrocardiography was performed by using a computerized method with a digital veterinary electrocardiograph (Electrocardiogram Acquisition Module for Computer, EKG-PC, Windows 95 version, Brazilian Electronic Technology, São Paulo, São Paulo, Brazil), with 10 derivations that consisted of an electronic circuit connected externally to a laptop and software that was installed on the hard disk of the computer. After the examination, the results from each animal were analyzed and wave measurements were calculated. Heart rate was measured from the electrocardiographic tracing.

The electrodes were placed in standardized combinations on each animal as described previously[53] to acquire standard electrocardiographic derivations, which were obtained through the potential differences between the electrodes. The right and left thoracic electrodes were positioned above the olecranon on the caudal aspect, and the right and left pelvic electrodes were placed above the patellar ligaments on the cranial aspect of each limb. The recording speed was 25 mm/s, with a voltage calibration of 1 cm per millivolt (1 mV = 1 cm).

The evaluated parameters included the heart rate, duration (in ms) and amplitude (in mV) of the P wave, PR interval (ms), QRS complex (ms), amplitude of the R wave (mV), ST segment leveling, QT interval (ms), corrected QT interval (QTc),[4] and T-wave polarity. All parameters were analyzed in bipolar derivation II (DII) in addition to the cardiac electrical axis (in °) according to the previously proposed table of axes (DI/DIII).[53] The electrocardiographic measurements were analyzed as described previously.[53]

Statistical analysis. Prism 7 (GraphPad Software, La Jolla, CA) software was used to analyze the data, with nonparametric Wilcoxon–Mann–Whitney (Mann–Whitney *U*) tests used to evaluate differences in the variables between sexes. The Spearman rank correlation coefficient was used to assess dependence. For all tests, a *P* value of 0.05 was considered to indicate statistical significance.

Results

None of the electrocardiographic characteristics (Table 1), heart rate, weight, or age differed significantly between our female and male capuchin monkeys. The QRS duration of our capuchin monkeys exhibited no correlation with the age or weight of the animals (males, $r = 0.02$; females, $r = 0.06$). However age and QT interval were correlated, particularly in female monkeys (males, $r = 0.21$; females, $r = 0.70$). The variation between QTc and QT was 11.8% for males and 14.1% for females. However, neither interval differed significantly between males and females, nor did QT differ from QTc in either sex.

All monkeys demonstrated normal sinus rhythms (Figure 1). No arrhythmias of any type or any alterations suggestive of cardiac or extracardiac pathologies were observed.

None of the duration parameters differed between males and females (Table 1). No significant differences in the amplitudes (mV) of the P and R waves were present between male and female monkeys. The observed P waves were small, monophasic, and positive in the I, II, III, aVF, rV2, V2, V4, and V10 derivations but negative in the aVR and aVL derivations. The R wave was positive in the D1, D2, aVL, AVF, V2, V4, and V10 derivations

Table 1. Durations and amplitudes of the P, R, and T waves and the duration of the QRS complex, PR interval, and QT interval from male and female capuchin monkeys restrained with ketamine and midazolam

	P (ms)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)	P (mV)	R (mV)	T (mV)
Females	46.0 ± 6.9	81.3 ± 5.8	46.7 ± 4.1	157.0 ± 62.8	178.0 ± 20.8	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.1
Males	47.3 ± 10.6	94.4 ± 25.6	51.9 ± 4.3	201.9 ± 46.2	234.3 ± 23.5	0.2 ± 0.1	0.4 ± 0.2	0.1 ± 0.0

Data are given as mean ± 1 SD. The parameters were recorded in derivation DII at a velocity of 25 mm/s and in N-mode.
None of the parameters differed significantly between female and male monkeys.

but negative in the D3, aVR, and rV2 derivations. In all animals in the study, the T wave exhibited negative polarity only in the aVR derivation, and no significant differences occurred between sexes. Male capuchin monkeys exhibited depression of the ST segment, but this feature lacked clinical significance; in contrast, females presented an isoelectric ST segment.

Neither weight (male, 1.50 ± 0.44 kg; female, 1.95 ± 0.48 kg) nor age (male, 3.0 ± 1 y; female, 3.5 ± 1.4 y) differed significantly between sexes. Although numerically higher in females, mean heart rate was statistically equivalent between sexes (male, 158.3 ± 49.1 bpm; female, 198.00 ± 38.3 bpm). The cardiac electrical axis varied among individual animals but was consistently displaced to the left. Among the total of 16 monkeys, 12 (75%; 7 males and 5 females) presented with cardiac electrical axes between 30° and 60°, and the remaining 4 (25%; (2 males and 2 females) presented with cardiac electrical axes between 60° and 83°.

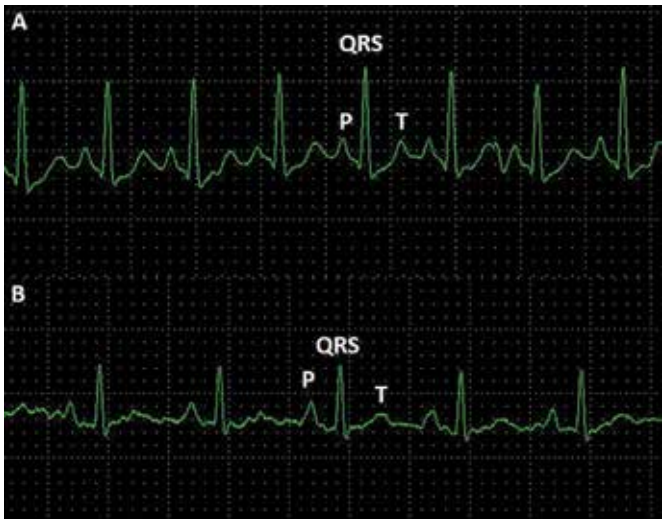

Figure 1. Normal digital electrocardiographic tracing recorded in DII lead, 25 mm/s and N-mode from a healthy adult capuchin monkey (*Cebus apella*, Linnaeus, 1758) restrained with ketamine and midazolam. (A) Sinus rhythm, P wave, QRS complex, and T wave (positive polarity) of a representative male monkey. (B) Sinus rhythm, P wave, QRS complex and T wave (positive polarity) of a representative female monkey.

Discussion

An important factor related to electrocardiography in exotic species is that not many standards of normality have been established, due to the diversity of available anesthetic protocols. In capuchin monkeys, electrocardiographic patterns have previously been established for animals anesthetized with ketamine;[21,29] ketamine and xylazine, tiletamine, and zolazepan;[48] and midazolam and propofol.[6,10] However, descriptive studies of electrocardiographic tracings from tufted capuchins sedated by using a ketamine–midazolam protocol have not been reported to date.

The capuchin monkeys in the current study did not present with any abnormal electrocardiographic patterns suggestive of the presence of cardiac or extracardiac pathologies that have been found in other NHP, including arrhythmias, extrasystolic complexes, branch blocks, and overloads.[33,54] Squirrel monkeys (*Saimiri sciureus*) with dilated cardiomyopathy present QRS prolongation and ST segment depression, especially in the DII and DIII leads.[55] Owl monkeys (*Aotus* spp.) are highly susceptible to hypertrophic cardiomyopathy and can die suddenly after periods of stress or physical activity.[42,60]

The heart rates of our male and female monkeys that were chemically restrained by using ketamine–midazolam (198 bpm and 158 bpm, respectively) were higher than those in other animals of the same species that underwent different anesthetic protocols, such as ketamine and xylazine (123.0 ± 19.8 bpm).[48] However, the heart rates in our monkeys that underwent the ketamine–midazolam protocol are lower than those for protocols involving midazolam–propofol (198.4 ± 22.9 bpm),[6] ketamine (230 ± 27 bpm),[28] and tiletamine–zolazepam (212 ± 23.7 bpm).[48] Therefore, chemical restraint with ketamine–midazolam did not elicit strong effects on heart rate because the values were within the normal range for the species (165 to 225 bpm).[10] In fact, the combination of ketamine–xylazine causes central vasomotor depression, increases in vagal tone and baroreceptor activity, and subsequent bradycardia, thus making combinations such as midazolam-propofol and ketamine-midazolam safer anesthetic protocols.[19,50] Moreover, the ketamine–midazolam combination facilitates safe anesthesia with minimal changes in respiratory mechanics, blood gases, and acid–base balance and thus provides some cardiovascular stability.[9]

The cardiac electrical axis is a highly variable parameter in several species of NHP,[6,22,33,54] even in the case of healthy animals and with standardized positioning during tests. These results may be related to the rotation capacity of the heart around its own longitudinal and transverse axes.[23]

The mean values for the duration of the P wave and the QRS complex in our capuchin monkeys were higher than those in others anesthetized with ketamine–xylazine,[21,27-29,47] midazolam–propofol,[6] or tiletamine–zolazepan.[48] Ketamine might produce an eventual negative inotropism, which might unexpectedly reduce myocardial contractility and QRS enlargement. However, ketamine–xylazine anesthesia balance the cardiodepressant effect of xylazine and exacerbates the positive inotropic effect of ketamine, causing increased blood pressure and heart rate and decreased QRS duration.[32,38] In addition, studies in humans have shown that drugs such as succinylcholine derivatives and propofol can influence cardiac function by promoting bradycardia, various arrhythmias, or prolongation of the QRS complex.[19,50,56,59]

The PR interval in the tufted capuchin monkeys we evaluated was similar to those elsewhere in this same species despite the use of different anesthetic protocols.[4,48] The normal health status, young age, and similar morphology within the species and genera support the small variations found in this range.[53] However, this variation was greater than that observed in black-tufted marmosets (*Callithrix penicillata*) and smaller than that observed in *Macaca fascicularis*.[52] Such changes may reflect the differences in body weight and heart rate between species.[20]

Although the male capuchin monkeys in our study showed discrete depression of the ST segment, this effect was not clinically

significant, given the results of the prestudy examinations we performed to select the study population. Small deviations of the J point and ST segment of 0.1 mV maximum in the peripheral leads or 0.2 mV maximum in the precordial leads can occur in humans that lack cardiopathies.[35] Similarly, dogs can exhibit discrete ST segment depressions of less than 0.2 mV or elevations of less than 0.15 mV that are considered normal.[25,53] Furthermore, in *Macaca mulatta*, a depression or elevation of 0.5 mV is considered normal.[1,34]

The mean of the QT interval for our capuchin monkeys was higher than the means recorded for black-tufted marmosets[20] and rhesus monkeys[41] and lower than those of cynomolgus monkeys,[3] Japanese monkeys,[31] and red-faced monkeys (*Macaca arctoides*).[33] This value was higher than that of tufted capuchins anesthetized with ketamine only[22] and lower than that when xylazine was added to the anesthetic protocol. This characteristic is due to the severe bradycardia induced by xylazine, which tends to prolong the QT interval in relation to other protocols.[48,64] The QT interval increases with age due to age-associated myocardial thickening, another well-documented and normal phenomenon in humans.[13,26,62]

Variation in the QT interval is clinically important in the determination of cardiac electrical instability in humans, and it is a key factor considered in toxicity studies and drug use.[63] Correction of the QT interval was first proposed to distinguish the direct effects on the QT interval from the indirect effects promoted by the heart rate.[4] For the male and females monkeys we studied, we corrected the QT interval (QTc) according to the Bazett formula[4] and noted that QT differed from QTc by 11.79% in males and 14.1% in females. The variation between QT and QTc is lower in humans (4.35% for males and 6.38% for females),[26,37] whereas in cynomolgus macaques, the variation was approximately 3% in both sexes.[18] Despite this variation, research has demonstrated the need to standardize QT interstitial interval correction, especially for the response to maximal concentration of drugs after administration and to consider species-specific factors that promote residual effects of heart rate on QTc.[13,62]

The morphology of the QRS complex in the capuchin monkeys was similar to that in other NHP and in humans. However, the duration of this complex was shorter than that found in humans[9] and longer than the values found in tufted capuchins restrained with ketamine.[21,28,29] However, capuchin monkeys restrained with benzodiazepines maintain similar values those we obtained, thus corroborating our findings.[6,48]

The differences in electrocardiographic parameters between NHP in the current study and others may have been due to individual factors but were mainly related to differences between the anesthetic protocols used, which have different effects on the cardiovascular system that are inherently related to inotropic and chronotropic factors.[15,28,38] The anesthetic protocol we used here favored reliability of the parameters because no cardiorespiratory depression occurred due to the use of ketamine. However, when used alone, ketamine may trigger an increase in blood pressure, a reduction in cardiac output, and an increase in myocardial oxygen consumption.[51] The use of midazolam as a means of reducing the undesirable effects of ketamine, thus contributing to the maintenance of cardiovascular stability, was of paramount importance.

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