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Article

Electrocardiogram reference intervals for clinically normal wild-born chimpanzees (*Pan troglodytes*)

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OBJECTIVE

To generate reference intervals for ECG variables in clinically normal chimpanzees (*Pan troglodytes*).

ANIMALS

100 clinically normal (51 young [< 10 years old] and 49 adult [≥ 10 years old]) wild-born chimpanzees.

PROCEDURES

Electrocardiograms collected between 2009 and 2013 at the Tchimpounga Chimpanzee Rehabilitation Centre were assessed to determine heart rate, PR interval, QRS duration, QT interval, QRS axis, P axis, and T axis. Electrocardiographic characteristics for left ventricular hypertrophy (LVH) and morphology of the ST segment, T wave, and QRS complex were identified. Reference intervals for young and old animals were calculated as mean ± 1.96•SD for normally distributed data and as 5th to 95th percentiles for data not normally distributed. Differences between age groups were assessed by use of unpaired Student *t* tests.

RESULTS

Reference intervals were generated for young and adult wild-born chimpanzees. Most animals had sinus rhythm with small or normal P wave morphology; 24 of 51 (47%) young chimpanzees and 30 of 49 (61%) adult chimpanzees had evidence of LVH as determined on the basis of criteria for humans.

CONCLUSIONS AND CLINICAL RELEVANCE

Cardiac disease has been implicated as the major cause of death in captive chimpanzees. Species-specific ECG reference intervals for chimpanzees may aid in the diagnosis and treatment of animals with, or at risk of developing, heart disease. Chimpanzees with ECG characteristics outside of these intervals should be considered for follow-up assessment and regular cardiac monitoring. (*Am J Vet Res* 2015;76:688–693)

Similar to the situation for humans in the Western world, heart disease has been identified as a leading cause of death in captive chimpanzees (*Pan troglodytes*).[1] However, in contrast to the situation in humans, the cause of cardiac death in chimpanzees is not related to atherosclerotic disease. Rather, it has been proposed that chimpanzees develop idiopathic myocardial fibrosis, which may predispose to a fatal cardiac arrhythmia.[2,3] For humans and other animals, ECG is routinely used to assess cardiac health and help differentiate between physiologic adaptation and underlying cardiac disease and even noncardiac pathological changes. The duration, amplitude, and morphology of the various ECG intervals and waveforms (eg, P, PR, QRS, and QT) can help clinicians in the diagnosis of cardiac conditions and differentiation of congenital and acquired heart disease from normal cardiac function in healthy subjects. However, reference intervals are required for ECGs to be diagnostically useful. Currently, ECG reference intervals do not exist for chimpanzees, and data that are available have been derived from populations of animals housed in scientific research facilities[4] or from small case series.[5] Accordingly, an ECG cannot currently be used in effective monitoring or assessment of cardiac health in this endangered species. The purpose of the study reported here was to generate ECG reference intervals on the basis of results for a relatively large population of wild-born chimpanzees.

ABBREVIATIONS

LVH	Left ventricular hypertrophy
QTc	QT interval corrected for heart rate

Materials and Methods

Animals

Between 2009 and 2013, as part of routine preventative health examinations at the Tchimpounga Chimpanzee Rehabilitation Centre, Tchimpounga Animal Sanctuary, Republic of the Congo, ECGs were collected from 102 chimpanzees. Animals were of 2 sub-

species: central chimpanzees (*Pan troglodytes troglodytes*) and eastern chimpanzees (*Pan troglodytes schweinfurthii*). All animals were wild-born orphaned chimpanzees confiscated by wildlife authorities and cared for in a semi-free-ranging enclosure. All animals had access to forests and native vegetation during the day and, depending on age, were provided with locally sourced supplemental food up to 3 times/d. Water was available ad libitum. At the time of assessment, all animals were free of clinical signs of disease and presumed healthy on the basis of clinical observations and medical history. Protocols for the study were approved by the Pan African Sanctuary Alliance Advisory Council and adhered to all legal requirements of the Republic of the Congo.

Procedures

At the time of arrival at the sanctuary and every 2 to 3 years thereafter, each animal underwent a complete health assessment, including physical examination, fecal and urinary analysis, dental examination (and dental floating, if necessary), a CBC, hematologic biochemical analysis, abdominal ultrasonography, thoracic and abdominal radiography, tuberculosis testing, body temperature measurement, bacteriologic culture of respiratory secretions, and ECG. In addition, vaccinations were administered (if required).

Food was withheld from all animals overnight preceding the examination procedures, but water was available ad libitum. Immediately before the examination procedures, body weight was estimated. Chimpanzees were anesthetized by administration of a combination of ketamine hydrochloride[a] (5 mg/kg) and medetomidine[b] (50 μg/kg). Anesthetic agents were administrated IM by manual injection or by dart injection with a blowpipe.[c] After completion of all procedures, anesthesia was reversed with atipamezole[d] (0.25 mg/kg).

After animals were anesthetized and unresponsive to external stimuli, they were placed in dorsal recumbency and a 12-lead ECG[e] was collected. Electrocardiograms were obtained with a paper speed of 25 mm/s and gain of 10 mm/mV. On the basis of anatomic similarities between humans and chimpanzees, electrodes were placed in accordance with standard human locations.[6] Briefly, limb electrodes (right thoracic limb, left thoracic limb, right pelvic limb, and left pelvic limb) were attached to the respective carpus and tarsus. Precordial electrodes were placed as follows: V1 and V2 were positioned in the fourth intercostal space on the left and right sternal borders, respectively; V3 was placed between V2 and V4; V4, V5, and V6 were positioned on the midclavicular, ventral-axillar, and ventral-midaxillar lines, respectively, with V4 positioned in the fifth intercostal space and V5 and V6 horizontally aligned with V4. Skin was prepared with ethanol, and electrodes were attached with alligator clips or suction cups. To improve conductivity, a water-based gel was applied to the electrodes. Again, on the basis of similar anatomy between humans and chimpanzees, standard (I, II, and III) and augmented (aVL, aVF, and aVR) limb leads as well as precordial (V1, V2, V3, V4, V5, and V6) chest leads were recorded as described for humans.[6] All ECGs were monitored, but not recorded, for approximately 30 to 60 seconds; a tracing of the ECG was then printed. After ECGs were collected, they were electronically scanned for storage and subsequent batch analysis. Age, sex, and general health status of each chimpanzee were noted during each assessment; when known, subspecies was recorded.

Electrocardiogram analysis

For all ECGs, heart rate, PR interval, QRS duration, QT interval, QRS axis, P axis, and T axis were automatically measured and manually verified. Cardiac rhythm was characterized as sinus, sinus with atrial or premature ventricular complexes, or low atrial rhythm (defined as P wave inversion in the pelvic limb leads [II, III and aVF], which indicated that the foci for the initiation of atrial depolarization was positioned low in the atria). The initial QT interval was corrected for heart rate on the basis of 4 correction formulas (Hodges et al,[f] Bazett,[7] Fridericia,[8] or the Framingham Heart Study[9]). Because of the relatively small amplitude of the P waves, Q waves (if present), ST segment, and T waves and the fact that we were unable to transfer ECGs to dedicated-analysis software, a broad classification approach to these components was used. Voltage and morphology of P waves were assessed for leads II and V1 and were defined as small (amplitude < 0.5 mV), P mitrale (duration ≥ 120 milliseconds or biphasic notched waveform), or P pulmonale (peaked waveform with amplitude ≥ 2.5 mV). It was noted if Q waves were present for any lead and exceeded 0.04 seconds in duration or if amplitude of the Q wave exceeded 25% of the height of the R wave; similarly, T wave inversion (amplitude ≥ 0.2 mV) or flattening (amplitude < 0.2 mV) was also recorded for leads other than V1, aVR, and III. For the ST segment, depression (amplitude ≥ 0.1 mV) or elevation (amplitude ≥ 0.1 mV for limb leads and ≥ 0.2 mV for chest leads) was recorded. The Sokolow-Lyon voltage criteria (sum of amplitude of the S wave for lead V1 and the R wave for lead V5 or V6) was calculated.[10] In addition, presence of a slurred upstroke of the QRS complex and J waves (positive deflection at the J point) were identified.

Data analysis

Because of the potential influence of age on ECG results, chimpanzees were allocated into 2 groups, young (< 10 years old) and adult (≥ 10 years old). The threshold age of 10 years was based on previously reported maturation rates in chimpanzees.[11] For each group, data were tested for normality by means of the Kolmogorov-Smirnov test. For normally distributed data, reference intervals were calculated as mean ± 1.96•SD. For data that were not normally distributed, reference intervals were calculated as the 5th and 95th

percentiles. Differences between age groups were assessed by use of independent *t* tests. Values of $P < 0.05$ were considered significant.

Results

After completion of the routine examination procedures, 2 animals were identified as febrile because of respiratory tract (n = 1) or parasitic (1) infection; these animals were removed prior to data analysis, resulting in a final sample size of 100 animals. Most animals were of the central chimpanzee subspecies (*P troglodytes troglodytes*), with a few more females than males **(Table 1)**. Of the 100 animals, 51 were young (median, 7 years old) and 49 were adult (median, 14 years old). Heart rate, PR interval, QRS duration, QT interval, QTc, and Sokolow-Lyon criteria data were all normally distributed, whereas data for the P axis, QRS axis, and T axis were not normally distributed. Mean values and reference intervals for heart rate, PR interval, QRS duration, QT interval, QTc, P axis, QRS axis, T axis, and Sokolow-Lyon criteria for young and adult chimpanzees were calculated **(Table 2)**.

Heart rate was significantly less in adult chimpanzees than in young chimpanzees, whereas PR interval, QRS duration, and QTc were all significantly greater in adult chimpanzees than in young chimpanzees. Most chimpanzees had sinus rhythm with small or normal P wave morphology, as defined on the basis of the criteria **(Table 3)**. One young male chimpanzee had a single premature ventricular complex during the ECG recording period. Limited T wave inversion or flattening was evident in 23 of 51 (45%) and 34 of 49 (69%) young and adult chimpanzees, respectively. A small but meaningful proportion of animals had ST segment elevation in the pelvic limb leads (II, III, and aVF) and chest leads, with a slightly higher prevalence in young animals, but ST segment depression was not evident. In addition, Q waves were evident in 16 of 100 (16%) animals; however, the Q waves were always < 25% of the height of the succeeding R wave **(Figure 1)**. A Sokolow-Lyon criteria > 3.5 mV was evident in 24 of 51 (47%) young animals and 30 of 49 (61%) adult animals. Slurred upstroke of the QRS complex was observed in 33 of 51 (65%) young animals and 24 of 49 (49%) adult animals. One adult male had slurred upstroke of the QRS complex coupled with a PR interval (84 milliseconds) less than the reference interval defined for this group of adult chimpanzees. Furthermore, J waves were also present in most of the chimpanzees.

Discussion

Heart disease has been identified as a leading cause of death in captive chimpanzee populations,[1] with

Table 1—Demographic characteristics of 100 clinically normal wild-born chimpanzees (*Pan troglodytes*) examined at the Tchimpounga Chimpanzee Rehabilitation Centre between 2009 and 2013.

Variable	Total (n = 100)	Female (n = 54)	Male (n = 46)	Young (n = 51)	Adult (n = 49)
Age (y)					
Mean ± SD	11 ± 6	12 ± 6	10 ± 5	9 ± 1	16 ± 5
Median	10	10	10	7	14
Subspecies					
Pan troglodytes troglodytes	75	39	36	42	33
Pan troglodytes schweinfurthii	10	5	5	4	6
Unknown	15	10	5	5	10

Young (< 10 years old) chimpanzees comprised 27 females and 24 males and adult (≥ 10 years old) chimpanzees comprised 27 females and 22 males.

Table 2—Mean ± SD and reference intervals calculated for ECG characteristics of 100 clinically normal wild-born chimpanzees.

Variable	Young (n = 51)	Adult (n = 49)
Heart rate (beats/min)	71 ± 9* (53 to 89)	63 ± 9 (46 to 80)
PR interval (ms)	150 ± 23* (105 to 195)	173 ± 35 (104 to 242)
QRS duration (ms)	70 ± 9* (53 to 87)	81 ± 11 (59 to 103)
QT interval (ms)	358 ± 30* (299 to 417)	386 ± 30 (327 to 445)
QTc Fridericia	378 ± 24* (331 to 425)	392 ± 22 (349 to 435)
QTc Hodges	379 ± 22* (336 to 422)	393 ± 23 (348 to 438)
QTc Bazett	389 ± 25 (340 to 438)	396 ± 22 (353 to 439)
QTc Framingham	381 ± 22* (338 to 424)	393 ± 22 (350 to 436)
P axis (°)	49 ± 40 (6 to 90)†	47 ± 28 (−18 to 75)†
QRS axis (°)	49 ± 26 (5 to 72)†	51 ± 23 (−7 to 78)†
T axis (°)	55 ± 44 (13 to 141)†	53 ± 21 (10 to 90)†
Sokolow-Lyon criteria for LVH (mV)	3.3 ± 1.0* (1.4 to 5.3)	3.8 ± 1.0 (1.7 to 5.8)

*Value differs significantly ($P < 0.05$) from the value for adult chimpanzees. †Reference interval calculated as 5th to 95th percentiles because data were not normally distributed.

Table 3—Number (%) of various ECG characteristics for 100 clinically normal wild-born chimpanzees.

Variable	Young (n = 51)	Adult (n = 49)
Rhythm		
Sinus	45 (88)	44 (89)
Sinus and ventricular premature complex	1 (2)	0 (0)
Low atrial	5 (10)	5 (10)
P wave morphology		
Normal (duration < 120 ms; amplitude, 0.5–2.5 mV)	26 (51)	26 (53)
Small (amplitude < 0.5 mV)	21 (41)	14 (29)
P mitrale (duration ≥ 120 ms)	4 (8)	7 (14)
P pulmonale (amplitude ≥ 2.5 mV).	0 (0)	1 (2)
P mitrale and P pulmonale (duration ≥ 120 ms and amplitude ≥ 2.5 mV)	0 (0)	1 (2)
Q waves (< 25% of the height of the R wave)	8 (16)	8 (16)
T wave inversion		
Amplitude ≥ 2 mm	0 (0)	1 (2)
Amplitude < 2 mm	23 (45)	29 (59)
ST segment		
Depression ≥ 1 mm	0 (0)	0 (0)
Elevation ≥ 1 mm (pelvic limb leads [II, III and aVF])	8 (16)	3 (6)
Elevation ≥ 2 mm (chest leads)	9 (18)	5 (10)
Slurred upstroke of QRS complex	33 (65)	24 (49)
J waves	47 (92)	36 (94)
Sokolow-Lyon criteria for LVH (> 3.5 mV)	24 (47)	30 (61)

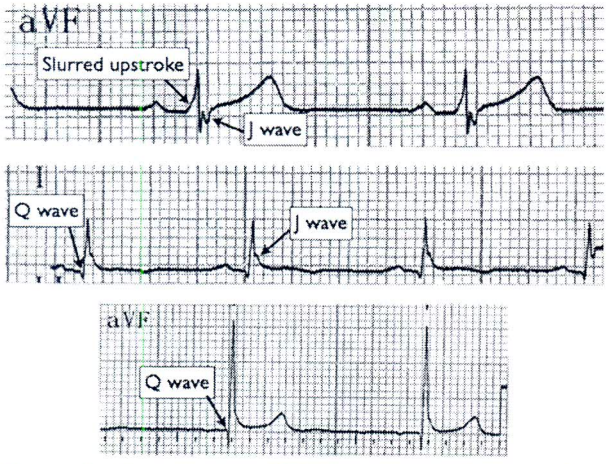

Figure 1—Representative ECG traces obtained from a clinically normal chimpanzee (*Pan troglodytes*) for leads aVF (top and bottom) and I (middle). Notice the slurred upstroke of the QRS complex and the J and Q waves. Paper speed = 25 mm/s; 10 mm = 1 mV.

some authors reporting evidence of idiopathic fibrosis.[2] However, a definitive diagnosis, or cause for the fibrotic infiltrate, has not been established. It is possible that a number of pathological processes (eg, structural, metabolic, or ion-channelopathy disease) are responsible for the deaths that have been attributed to heart disease, and it is likely that ECG may be useful in discriminating among these diseases. The data reported in the present study represented the first report of reference intervals for ECG variables in healthy wild-born chimpanzees. Animals with ECG characteristics outside of these reference intervals should be considered for further evaluation or longitudinal monitoring for the presence or development of underlying cardiac disease.

Investigators of previous studies[12–14] conducted to examine cardiac disease in great apes have used human reference intervals, and specialists in human cardiology are often involved in the assessment and management of cardiac health in captive great apes. However, it appeared from analysis of data for the present study that the use of human reference intervals was inappropriate, and findings in chimpanzees should not be interpreted on the basis of results for humans. For example, on the basis of human criteria, 30 (61%) adult and 24 (47%) young chimpanzees assessed would have been classified as having LVH. In addition, a small but meaningful proportion of chimpanzees had ST segment and T wave morphology that could be suggestive of pathological lesions if analyzed on the basis of human criteria. Given that the animals of the present study were healthy, these results indicated the inappropriateness of applying human ECG criteria to ECG data of chimpanzees.

Given that LVH is inherent to a number of cardiac pathological processes, the ability to identify LVH on the basis of results for ECG would be useful in the identification and management of heart disease in captive chimpanzees. However, ECG criteria for LVH need to be related to phenotypic expression of ventricular mass, and until reference intervals for ventricular structures are established and related to QRS voltage, chimpanzee-specific ECG criteria for LVH cannot be generated. Further studies that combine ECG results with cardiac imaging are required. In addition to determining diagnostic ECG criteria for ventricular hypertrophy, the anatomic structure or prevailing physiology responsible for the large QRS voltages in chimpanzees is also worthy of further investigation.

In the chimpanzee cohort of the present study, the PR interval, QRS duration, QT interval, and LVH criteria were all significantly greater for the adult group. Given that cardiac mass increases with age, these findings were not surprising. A prominent feature of the

chimpanzee ECGs was the high proportion with a slurred QRS upstroke. A slurred upstroke of the QRS complex combined with a short PR interval could indicate rapid conduction through the atrioventricular ring, possibly related to the presence of an accessory conduction pathway. However, in all chimpanzees except one, the slurred QRS complex was not accompanied by a short PR interval (as defined by the proposed reference interval). Accordingly, it is unlikely that the slurred QRS upstroke observed in more than half of the chimpanzees represented an accessory pathway; rather, it likely reflected physiologic depolarization through the atrioventricular ring in chimpanzees.

Another prominent ECG feature observed was the presence of J waves in most animals. Both hypothermia[15] and hypercalcemia[16] can cause J waves in humans, but considering that temperature and humoral calcium concentration were within reference limits for these chimpanzees, it is likely that J waves were also a normal characteristic of the chimpanzee ECG. However, we cannot rule out the potential influence of the anesthetic regimen on ECG morphology. Studies to compare various anesthetic regimens are warranted.

In 1 study,[4] investigators found arrhythmia in 34 of 265 captive animals; in contrast for the study reported here, we found only a single premature ventricular complex in 1 chimpanzee. Investigators of another study[17] also found a greater incidence of arrhythmia in a large laboratory population of chimpanzees. The discrepancy between the present study and those other studies may be related to the limited time period for ECG recording in the present study. However, it should be mentioned that a second or third tracing was often recorded and reviewed for arrhythmia. Therefore, it is possible that the greater incidence of arrhythmia in those previous studies[4,17] was related to increasing age or disease state. The animals in those previous studies were from a large research facility that contained a number of animals with known infection and with a substantially higher mean age than the animals in the present study. It is also possible that the difference in anesthetic regimen may account for some of the differences; however, the sedation protocol for those reports has not been associated with marked arrhythmia in other primate species.[18,19] Therefore, it is possible that the greater prevalence of arrhythmia in previous studies was related to increasing age of chimpanzees; whether a greater prevalence of arrhythmia is related to the onset of idiopathic fibrosis previously described[2,3] is not clear. Longitudinal studies will be required to provide better understanding of this relationship.

Electrocardiography should not be considered in isolation; rather, it should form part of the overall clinical and cardiac evaluation. Until it is possible to consider ECG alongside the full cardiac phenotype or to longitudinally monitor changes during life, it is difficult to discern the clinical or physiologic importance of the specific chimpanzee ECG characteristics. As such, longitudinal studies are required before the full clinical value of ECG can be realized for chimpanzees.

Even though 100 wild-born chimpanzees represent a large population in exotic veterinary medicine, it is still a relatively small cohort; accordingly, we were unable to calculate sex-specific reference intervals. The cohort of chimpanzees in the present study was relatively young, so the reference intervals generated may be relevant only for animals of a comparable age. We recognize that for some of the ECG variables (eg, P wave, Q wave, ST segment, and T wave), objective interval measurements were not reported. An older ECG system was used to collect these data; thus, it was not possible to directly export ECGs to an analysis software package that could have provided accurate measurements. Manually measuring these small wave forms would likely have introduced considerable error to the data; accordingly, a broad classification process was used. Future studies that involve the use of ECG equipment with advanced measurement tools will provide more precise characterization of these ECG variables.

For logistic reasons, it was not possible to collect ECG data from nonanesthetized chimpanzees, and we acknowledge that the anesthetic agents used may have influenced our findings. However, other than bradycardia, there is limited evidence from other mammalian species to suggest that medetomidine or ketamine markedly impacts ECG variables.[20] Although all of the chimpanzees assessed in the present study were apparently healthy, it is possible that some had underlying cardiac disease and LVH; therefore, some of the results may have been influenced by undiagnosed disease. In future studies, investigators should collect ECG data concurrently with echocardiographic measures of cardiac structure to rule out the potential confounding influence of undiagnosed cardiac disease and also to establish chimpanzee-specific criteria for ventricular hypertrophy.

In the present study, ECG reference intervals for a population of wild-born chimpanzees were reported. It is recommended that these reference intervals be used in future investigations of heart disease in chimpanzees. Further longitudinal studies are required that combine both ECG and imaging techniques to establish chimpanzee-specific criteria for ventricular hypertrophy and to examine whether the slurred upstroke of the QRS complex and the J waves reflected pathological lesions or were variants of the ECG of clinically normal chimpanzees.

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Footnotes

a. Kyron Laboratories, Benrose, Johannesburg, Republic of South Africa.

b. Dormitor, Pfizer Animal Health, Kent, England.
c. Telinject USA Inc, Agua Dulce, Calif.
d. Antisedan, Pfizer Australia, Melrose Park, NSW, Australia.
e. ECG Cardiofax-9620, Nihon Kohden, Tokyo, Japan.
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