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Electrocardiographic Studies in Formosan Macaques (*Macaca cyclopis*)

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Sao-Ling Liang, Shih-Chien Chin, and Lih-Seng Yeh (2005) Electrocardiographic studies of Formosan macaques (*Macaca cyclopis*). *Zoological Studies* **44**(4):462-467. The Formosan macaque (*Macaca cyclopis*) is a threatened species, endemic to Taiwan. Data on the cardiovascular physiology of other nonhuman primates have been reported including electrocardiography, echocardiography, and radiography, but little is known of this aspect of Formosan macaques. In total, 38 clinically normal Formosan macaques (20 females and 18 males) undergoing routine annual health examinations were given electrocardiographic examinations at Taipei City Zoo. The mean weight of the animals was 10 ± 4.3 (range, 4-22.6) kg. The mean age of the animals was 6.9 ± 4.1 (range, 2-16) years old. Baseline parameters (heart rate, P wave, PR interval, QRS complex, QT interval and ST segment) of the electrocardiography (ECG) of Formosan macaques were established in this study. Values of the ECG parameters were a mean heart rate of 126 ± 20 beats/min, a mean P wave duration of 42 ± 7.8 ms, a mean PR interval of 97 ± 12 ms, a mean QRS complex duration of 43 ± 6.7 ms, and a mean QT of 296 ± 41.4 ms. Like other nonhuman primates, the Formosan macaque exhibited a sinus rhythm. Significant differences in ECG parameters were not found between males and females, between juveniles (< 7 years old) and adults (≥ 7 years old), or between animals with lighter body weights (≤ 10 kg) and heavier body weights (> 10 kg). http://zoolstud.sinica.edu.tw/Journals/44.4/462.pdf

Key words: Electrocardiography, Formosan macaque, *Macaca cyclopis*, Primate.

The Formosan macaque (*Macaca cyclopis*) is a threatened species which is endemic to Taiwan (Hsu and Agormoorthy 1997). It evolved from rhesus macaque (*M. mulatta*) ancestors when they became isolated on the island of Taiwan (Hoelzer and Melnick 1996). Studies of the anatomy, behavior, ecology, and infectious diseases of *Macaca cyclopis* are abundant, but the available literature on its cardiovascular physiology is limited (Wu 1986, Wu and Lin 1992, Hsu and Agormoorthy 1997). Recently, aging of nonhuman primates was recognized as a natural and important animal model through which to study the aging of humans, owing to the advantages of biological similarities and genetic homology (Roth et al 2004). Along with the biological changes that parallel aging in humans, nonhuman primates, such as rhesus macaques, also develop and die from similar chronic diseases. The major cause of death in 1 group of rhesus macaques was cardiac related and included such pathologies as endocarditis, aortic valve calcification, interstitial fibrosis, cardiac hypertrophy, myocardial infarction, acute cardiac arrest, and congestive heart failure (Bodkin et al. 2003). In Taiwan, Formosan macaques as an endemic nonhuman primate may be a good animal model, like rhesus macaques in other countries, for studying the aging process. To study cardiac-related or other diseases in aging Formosan macaques, basic data on the cardiovascular physiology including electrocardiography, radiography, and echocardiography urgently need to be established. In this study, we attempted to establish baseline data on typical ECG complexes

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and intervals in Formosan macaques.

MATERIALS AND METHODS

Animals

This study utilized 38 clinically normal Formosan macaques (20 females and 18 males) undergoing routine annual health examinations at Taipei City Zoo. The mean weight of the animals was 10 ± 4.3 (range, 4-22.6) kg, and the mean age of the animals was 6.9 ± 4.1 (range, 2-16) years.

Immobilization procedures

Animals were fasted overnight but had access to drinking water, in accordance with their usual daily routine. Each animal was restrained by the administration of 10 mg/kg ketamine (Imalgene, Merial, Lyon, France) given intramuscularly using a projectile syringe. With the animal in dorsal recumbency, the larynx was visualized with a laryngoscope. Lidocaine spray (10%, Xylocaine, Astra, Sodertalje, Sweden) was used to desensitize the larynx, and the trachea was intubated with a cuffed endotracheal tube (4.5 mm, Hi-Contour, Mallinckrodt, Mansfield, Ireland). Anesthesia was maintained with isoflurane (IsoFlo, Abbott, Queenborough, Kent, England) in oxygen and nitrous oxide, and the concentration of isoflurane delivered was adjusted to maintain an adequate plane of anesthesia. Routine blood samples for hematology and blood biochemistry were taken, and electrocardiograms and echocardiograms were recorded. Results of the hematological and biochemical analyses were unremarkable. Rubber gloves were worn when handling the animals to minimize the risk of zoonotic infections.

Electrocardiography

Each animal was placed in dorsal recumbency with its arms unrestrained beside itself. The hair was clipped from the carpal and tarsal areas, and alligator electrodes were placed on these areas. In each animal, 6-lead ECGs (leads I, II, III, aVR, aVL, and aVF) were recorded using an electrocardiograph (Cardisuny 502A, Fukuta M.E., Tokyo, Japan) at paper speeds of 25 mm/s, and at sensitivities of 1 and 2 cm/mV. Tracings were analyzed for heart rate (HR), mean electrical axis (MEA), P-wave amplitude and duration, PR interval, R-wave amplitude, QRS duration, QT interval, ST segment, and T-wave amplitude.

Statistical analysis

All data were analyzed by Student's *t*-test for independent samples. To assess correlations between the PR interval and 1/HR, and the QT interval and 1/HR, linear regressions of PR = f(1/HR) and QT = f(1/HR) were computed. The criterion for significance was set at $p \leq 0.05$. The SAS system package (8th ed. SAS Institute 2001) was used to perform the analyses.

RESULTS

Table 1 summarizes the ECG parameters from all 38 macaques. A typical ECG tracing of a Formosan macaque is presented in figure. 1. The average heart rate was 126 ± 20 (range, 84-171) beats/min. All animals had a normal sinus rhythm. ECG parameters of the 2 genders, as well as various body weight and age categories are presented in tables 2-4. Significant differences in ECG parameters were not found between males and females, between juveniles (< 7 years old) and

Table 1. Electrocardiogram parameters obtained from the analysis of Formosan macaques

Parameter	Value	Range
Rhythm	Sinus	All 38
Rate (beats min)	126 ± 20 (38)[a]	83-171
P wave duration (ms)	42 ± 7.8 (38)	30-60
PR interval (ms)	97 ± 12 (38)	80-120
QRS duration (ms)	43 ± 6.7 (38)	30-60
QT interval (ms)	296 ± 41.4 (38)	150-360

[a]Mean ± SD (number of monkeys).

adults (≥ 7 years old), or between animals with lighter body weights (≤ 10 kg) and heavier body weights (> 10 kg).

P waves: The duration of the P waves showed a mean of 42 ± 7.8 ms. The mean amplitude in lead II was 0.07 ± 0.02 mV. Tall peaked P waves were recorded in 13% (5/38) of the animals. The P wave was normally positioned in leads I, II, III, and AVF, but was inverted in the AVR. Its normal contour was gently rounded. The P wave duration did not vary with the heart rate.

PR and QT intervals: The PR interval was 97 ± 12 ms and varied with the heart rate as shown in table 5. The mean QT interval was 296 ± 41.4 ms and, like the PR interval, decreased with increasing heart rates. Linear regressions between the PR interval and 1/HR, and the QT interval and 1/HR showed significant linear relationships (p <

Table 2. Values of ECG parameters in male and female Formosan macaques

Sex	No. of animals	Heart rate (beats/min)	P wave duration (ms)	PR interval (ms)	QRS duration (ms)	QT interval (ms)
Female	20	122 ± 18[a]	42 ± 7.7	97 ± 12.3	43 ± 5.7	309 ± 36.8
Male	18	130 ± 22	42 ± 8.1	97 ± 11.9	44 ± 7.8	283 ± 43.1

[a]Mean ± SD.

Table 3. Values of ECG parameters in Formosan macaques stratified by body weight

Body weight	No. of animals	Heart rate (beats/min)	P wave duration (ms)	PR interval (ms)	QRS duration (ms)	QT interval (ms)
≤ 10 kg[a]	20	123 ± 18[b]	44 ± 6.8	97 ± 10.8	43 ± 4.7	303 ± 37.6
> 10 kg	18	128 ± 22	40 ± 8.4	96 ± 13.3	44 ± 8.5	288 ± 45.0

[a]Body weight was categorized into ≤ 10 kg and > 10 kg with regard to the mean value of body weight (10 kg) in this study. [b]Mean ± SD.

Table 4. Values of ECG parameters in different-aged Formosan macaques

Age	No. of animals	Heart rate (beats/min)	P wave duration (ms)	PR interval (ms)	QRS duration (ms)	QT interval (ms)
< 7 years old[a]	18	125 ± 18[b]	43 ± 6.7	98 ± 9.4	44 ± 7.0	301 ± 36.6
≥ 7 years old	20	126 ± 22	42 ± 8.8	96 ± 14.0	43 ± 6.4	292 ± 45.8

[a]Age was categorized into < 7 years old and ≥ 7 years old with regard to the maturation age (7 years old) of rhesus monkeys (Smucny et al. 2001). [b]Mean ± SD.

Table 5. Relationship of PR and QT intervals with an increase in the heart rate

Heart rate (beats/min)	No. of animals	PR interval (ms)	QT interval (ms)
≤ 120	17	101 ± 11.4[a]	319 ± 47.9
121-150	17	96 ± 10.6	282 ± 21.9
151-180	4	83 ± 9.6	260 ± 24.5

[a]Mean ± SD.

0.05). The percentage of variability in R^2 between the QT interval and 1/HR was 0.76 (Fig. 2), and between the PR interval and 1/HR was 0.10.

QRS complex: The mean duration of the QRS complex measured in lead II was 43 ± 6.7 ms. Lead I normally had a low amplitude (< 0.5 mV). Small Q (10.5%, 4/38) and S waves (26.3%, 10/38) were seen, but no Q or S wave was larger than 0.3 mV. The QRS complex was normally positive in leads I, II, III, and AVF; but was negative in lead AVR.

ST segment: The ST segment was mostly isoelectric. The J point was greater than 0.025 mV from the baseline. The highest J point was 0.1 mV.

T waves: The shape of the T waves was rounded and slightly asymmetrical. In most cases, the T waves were upright, but in a few cases (7.8%, 3/38), they were inverted. The height of the T waves never exceeded 0.3 mV in lead II.

Vector analysis: The mean QRS axis in the frontal plane was 75° ± 12.8° for 38 animals, with a range of 37° to 101°.

DISCUSSION

Ketamine-HCl is a widely used anesthetic in veterinary medicine. Its short-acting properties make it particularly desirable in the routine handling of nonhuman primates (Castro et al. 1981). But, recently, multiple intramuscular injections of ketamine for extended procedures were noted to produce increased cortisol levels in male rhesus macaques, while a single injection of ketamine did not (Bentson et al. 2003). Due to the extended time (30-40 min) required for the procedures of blood sampling, radiography, electrocardiography, and echocardiography in this study, the animals were not immobilized with a single dose of ketamine, but a combination with another agent was required. Isoflurane, a volatile anesthetic agent, was combined with ketamine in this study. During the period of anesthesia, oxygen saturation (S_PO_2) always exceeded 95%. No cardiac arrhythmias were observed. The recovery was smooth and uneventful. The experience of the extended anesthesia with ketamine/isoflurane in Formosan macaques was like that of ketamine/medetomidine/isoflurane in chimpanzees (*Pan troglodytes*) (Adams et al. 2003).

Electrocardiographic studies have been reported for a variety of species of nonhuman primates (Malinow 1966, Malinow and DeLannoy 1967, Malhotra et al. 1975, Bellinger et al. 1980, Atkins and Dickie 1986). However, there previous-

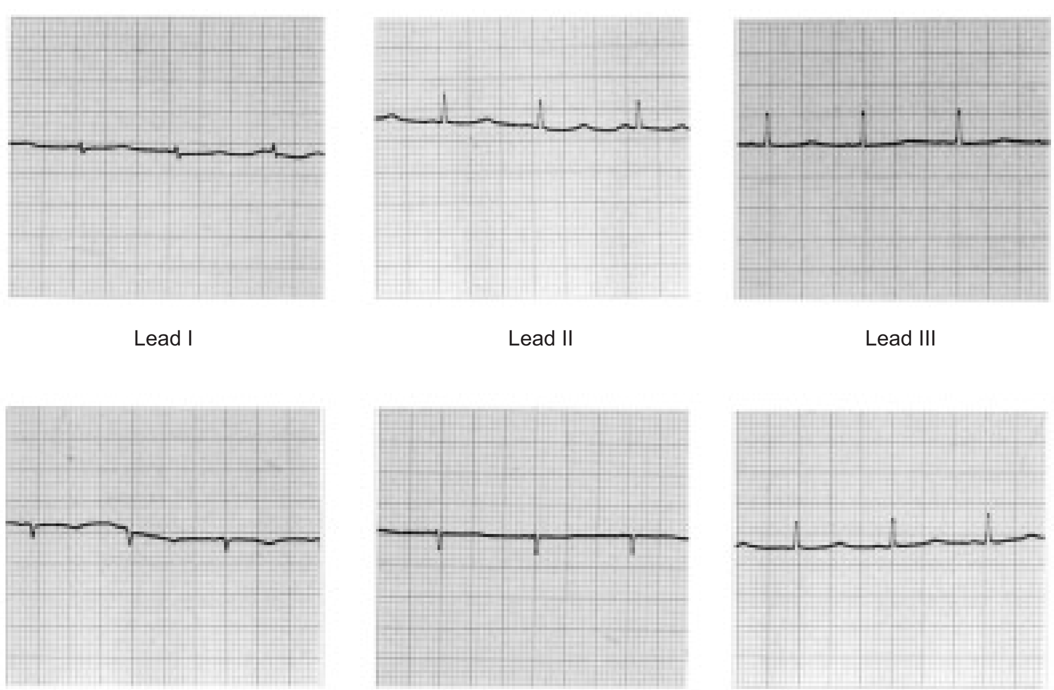

Fig. 1. Typical Formosan macaques electrocardiogram tracing (1.0 mV/cm; 25 mm/sec).

ly were no electrocardiographic studies of Formosan macaques. The heart rate of Formosan macaques (126 beats/min) was slower than those reported for rhesus macaques immobilized with restraints, without anesthesia (257 beats/min) (Malinow 1966), cynomolgus macaques with ketamine (182 beats/min) (Atkins and Dickie 1986), and Japanese macaques with restraints, without anesthesia (214 beats/min) (Malinow and DeLannoy 1967). This may have been related to the relatively larger size of the Formosan macaques (10 kg) used in this study, compared with other reports for rhesus macaques (4.9 kg) (Malinow 1966), cynomolgus macaques (3.2 kg) (Atkins and Dickie 1986), and Japanese macaques (6.8 kg) (Malinow and DeLannoy 1967). The heart rate of Formosan macaques was the same as that reported for stumptail macaques immobilized with phencycline hydrochloride intramuscularly and sodium pentobarbital intravenously (124 beats/min) (Malhotra et al. 1975), and this may be attributed to the similar body weight of stumptail macaques (9.8 kg). Another reason may have been the effect of the anesthesia (Bellinger et al. 1980), but more studies to evaluate the effects of different anesthetic agents in various nonhuman primates are needed.

Tall peaked P waves are not uncommon in nonhuman primates and have been reported in 30%-40% of rhesus monkeys (Malinow 1966), in 37% of *Macaca fuscata* (Malinow and DeLannoy 1967), and commonly in cynomolgus macaques (Toback et al. 1978). The PR interval of other primates varies from 70 ms in rhesus (Malinow 1966), to 80 ms in cynomolgus (Atkins and Dickie 1986), stumptail (Malhotra et al. 1975), and Japanese macaques (Malinow and DeLannoy 1967). The QT interval for other primates varies from 140 ms in rhesus (Malinow 1966), to 200 ms in cynomolgus (Atkins and Dickie 1986) and Japanese macaques (Malinow and DeLannoy 1967), and 270 ms in stumptail macaques (Malhotra et al. 1975). The PR and QT intervals vary with the heart rate (Malinow 1966, Malinow and DeLannoy 1967, Bellinger et al. 1980) as shown by the linear regression models of our study: PR = f(1/HR) and QT = f(1/HR). According to the values of R^2 in the linear regression, changes in 1/HR can highly explain changes in the QT interval, but poorly explain changes in the PR interval.

The QRS frontal axis is similar to that found in tall thin humans and that reported in most other Old World species (Malinow 1966, Malinow and DeLannoy 1967, Atkins and Dickie 1986). The axis was between 50° and 100° most of the time

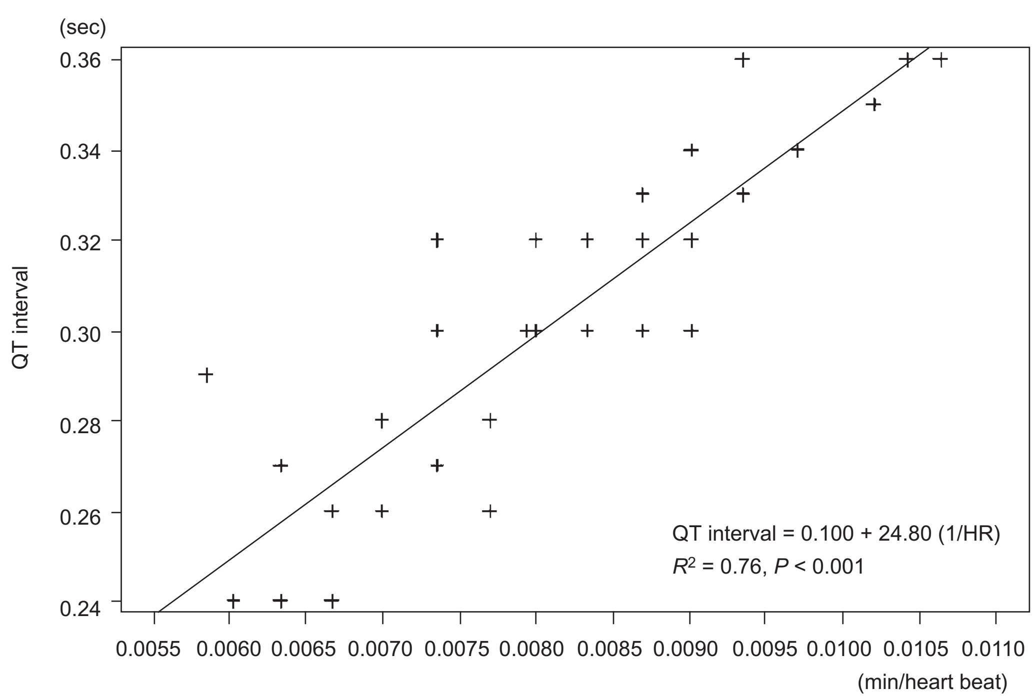

Fig. 2. Scatter plot and regression line of QT interval vs. 1/HR in Formosan macaques. The regression equation, R^2 calue and associated significance level of simple linear regression are displayed with scatter plot results.

in rhesus and fuscata macaques, with a mean for rhesus macaques of 61°. The mean axis for cynomolgus macaques was 69°.

Diffuse, flat T waves, inverted T waves, and slight ST segment elevations that were seen are probably normal variants for this species, yet a nonspecific repolarization abnormality cannot be ruled out (Bellinger et al. 1980). Unlike other non-human primates, Formosan macaques in this study did not present abnormal ECGs as a premature ventricular complex (Malinow 1966, Malhotra et al. 1975, Toback et al. 1978).

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