Frequency and complexity of arrhythmias in rhesus macaques with and without hypertrophic cardiomyopathy

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Background

• Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease in humans with a prevalence rate of 1 in 500. The diagnosis of HCM requires documented left ventricular hypertrophy, a pathologic abnormality that results in diastolic dysfunction.

• Between 1992 and 2014 LVH was found in 1.3% of post mortem exams of rhesus macaques at the California National Primate Research Center (CNPRC). Nearly 50% of these deaths (N=74) were recorded as sudden death events. Following up on this finding, antemortem echocardiographic diagnosis of LVH and diastolic dysfunction was identified in 12% of the population that confirmed cases of sudden death and LVH. When extensive pedigree analysis was performed a significant founder effect was identified. All of these findings suggest a naturally occurring model of HCM exists in the rhesus macaque colony at the CNPRC.

• In human HCM the risk of sudden death has been shown to increases proportionally with increasing measures of LVH and the severity of LVH is related to the presence of increasingly complex ventricular arrhythmias. Ventricular arrhythmias represent an important contributor to the risk of sudden death in the process. Although some ventricular premature complexes (VPCs) are considered a normal finding during 24-hour ECG recordings in humans and animals, more severe or sinister ventricular arrhythmias are a plausible explanation for sudden cardiac death with HCM.

• Supraventricular arrhythmias such as atrial premature complexes and atrial fibrillation are commonly diagnosed in humans with HCM and are associated with more severe cardiac disease, increased mortality and higher risk of thromboembolic events.

• Heart rate variability is a quantifiable expression of autonomic balance and is often reduced in disease states. Reduced HRV is associated with more severe cardiac disease and sudden cardiac death.

• In this study we aim to quantify and compare the incidence of ventricular arrhythmias and supraventricular arrhythmias in rhesus macaques with and without echocardiographically diagnosed occult HCM. Heart rate variability will also be analyzed between control and HCM groups. 24-hour ambulatory (Holter) electrocardiography is employed to accomplish these aims.

Methods

Control animals (n=10)  ▪ No history of functional heart disease identifiable on sedated echocardiogram  ▪ No known systemic illness

HCM animals (n=10)  ▪ LVH and diastolic dysfunction identified on sedated echocardiogram (Figure 1A-E)  ▪ No known systemic illness

ECG Parameters Control HCM P-Value
Heart rate (bpm) 140 ± 26.05 153 ± 24.01 0.25
P wave duration (msec) 42 ± 0.33 36 ± 10.75 0.15
P wave amplitude (mV) 0.13 ± 0.02 0.17 ± 0.08 0.17
PR interval (msec) 88 ± 14.3 90 ± 18.7 0.45
QT interval (msec) 218 ± 26.16 212 ± 16.87 0.55
QRS complex duration (msec) 46 ± 5.56 57.5 ± 4.22 0.0002
R wave amplitude (mV) 0.96 (75.1-160) 0.92 (73.1-130) 0.81
Mean Electrical Axis (degrees) 08 (0-90) 08 (0-120) 0.74

Table 1: Shown here are the standard ECG parameters tested for statistical significance between the control group and the HCM group. Normally was tested using a D’Agostino & Pearson normality test. Normally distributed data are displayed as Mean ± SD and were tested for significance by an unpaired t-test. Nonparametric data are displayed as median (inter-quartile range), and were tested for significant differences by a Mann-Whitney test. Software used: Piren 7.0 for Mac OS X. GraphPad Software, Inc. La Jolla CA USA.

Control (n=10) HCM (n=10) P-Value
Total Ventricular arrhythmias 22 (17.5 - 54.25) 5 (1.75 - 33.25) 0.21
Total Supraventricular arrhythmias 0.5 (0-0.26) 1 (0-0.5) 0.90
Overall arrhythmia complexity 1 (0-3) 1 (0-2) >0.99
Mean heart rate (bpm) 152.3 ± 16.10 146.8 ± 27.77 0.16

Table 2: Shown here are the ventricular arrhythmias, supraventricular arrhythmias, overall arrhythmia complexity and mean heart rate, which were tested for statistical significance between the control group and the HCM group. Normality was tested using a D’Agostino & Pearson normality test. Normally distributed data are displayed as Mean ± SD and were tested for significance by an unpaired t-test. Nonparametric data are displayed as median (inter-quartile range), and were tested for significant differences by a Mann-Whitney test. Software used: Piren 7.0 for Mac OS X. GraphPad Software Inc. La Jolla CA USA.

Hypothesis:

Rhesus macaques with subclinical HCM have more frequent and more complex cardiac arrhythmias than age and sex-matched controls.

Results

• 6-lead ECG tracing measurements were completed and data compared between groups. QRS complex duration was significantly longer in HCM compared to control animals. This parameter suggests slower conduction time through the ventricle may be explained by the increased LV mass in HCM subjects.

• Seventeen complete echocardiograms were analyzed due to time constraints. Within this data the tracings are high quality and readily interpreted.

• It was found that there was very little difference between the frequency and complexity of both ventricular and supraventricular arrhythmias between the two groups. Both of the subject groups also proved to have a limited amount of cardiac arrhythmias, with no statistically significant difference between controls and HCM subjects.

Discussion

• The data provided within this study refute our hypothesis and demonstrate no statistical difference between subclinical HCM and control rhesus macaques.

• One limitation of this study is the small sample size. As we continue identifying affected animals within the CNPRC colony, continued evaluation of arrhythmias is warranted.

• The natural history of this disease is still unknown within rhesus macaques and long-term follow-up of these animals is ongoing to investigate the value of ECG monitoring antemortem.

• The presence of a relatively small number of ventricular and supraventricular arrhythmias in all of the subjects in this study would suggest that some arrhythmogenesis is normal in rhesus macaques.

• We continue to evaluate the data generated and are in the process of recording heart rate variability parameters. We are hopeful that differences in heart rate variability may be more useful in the evaluation of rhesus macaques with subclinical HCM.

• Overall Holter monitoring was safe and feasible in the rhesus macaque. To our knowledge this study establishes the first Holter monitoring protocol and validates software commonly utilized for arrhythmia and HRV analysis in this species.

References


Acknowledgements

• This research was supported in part by California’s Medical Research Center at the University of California Davis, the National Institutes of Health grants R01HL108559 and P01HL103755, and the California National Primate Research Center.