



Comprehensive Arrhythmia Analysis in Telemetered Non-Human Primates



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Introduction

The occurrence of drug-induced arrhythmia in safety pharmacology or toxicology studies is a primary safety concern, but the risk assessment requires an accurate knowledge of background arrhythmia frequency in the test species.

The purpose of this study was to determine the normal frequency of arrhythmias in a colony of telemetered cynomolgus monkeys, since there is a data gap in background arrhythmias in this species. To conduct this analysis, continuous ECG data (24 hr) were recorded from 18 telemetered monkeys on 3 separate days, over an 8 day period. For each animal, an arrhythmia waveform library was manually created, then applied to the waveform file using EMKA ecgAuto, a pattern recognition-based software application. On day 1, 8/18 monkeys showed at least 1 premature ventricular contraction (PVC; range: 1-12), with 2/18 showing 1 incidence of supraventricular premature complexes (SPC). On day 4, a similar pattern emerged: 5/18 monkeys showed at least 1 PVC (range: 1-12) and 3/18 had 1 incidence of SPC. On day 8, 7/18 NHP displayed at least 1 PVC and 1/18 had a SPC. Other arrhythmias were noted sporadically: right bundle branch block, wandering pacemaker, SA node pause. The pattern of arrhythmia was relatively consistent in each NHP.

These findings suggest that a single 24 hr assessment period may be insufficient to determine arrhythmia background. A best practice recommendation is to determine the background arrhythmia rate in each telemetry animal to aid interpretation of potential proarrhythmic properties of new test articles.

Materials and Methods

Animals:

18 male cynomolgus monkeys (*Macaca fascicularis*, 3.1 – 6.5 kg) were obtained from a stock colony of surgically implanted animals. These animals were 3.4 to 6.3 years of age at the initiation of the study. Animals were provided with water, *ad libitum*, and food was available one to two times daily. All animals were housed in climate-controlled conditions with 12 hour light/dark cycles.

Telemetry Hardware:

All animals were implanted previously with TL11M2-D70-PCT (subcutaneous, Data Sciences International (DSI, St. Paul, MN)) with ECG leads in an approximate Lead II configuration and the pressure catheter placed in an artery and advanced into the abdominal aorta.

Data Acquisition and File Conversion:

Data was collected continuously using DSI OpenART telemetry equipment (Ponemah Physiology Platform, version 4.7). Data was recorded for approximately 26 hours per day for 3 days over an 8 day period (days 1, 4 and 8). Arterial pressure was digitized at a sampling rate of 250 Hz and the ECG signal at a rate of 500 Hz. All Ponemah raw data were converted with EMKA ecg-auto (version 2.5.1.30; Paris, France) into *.d01 files for analysis purposes.

Fig. 1. Analysis approach
Arrhythmia Detection Strategies

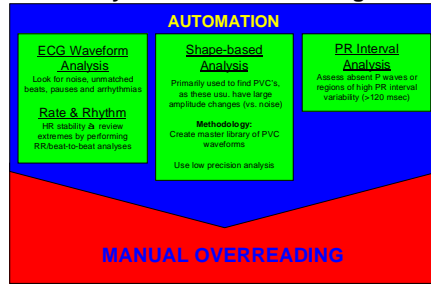


Table 2. Arrhythmia Waveforms and Results

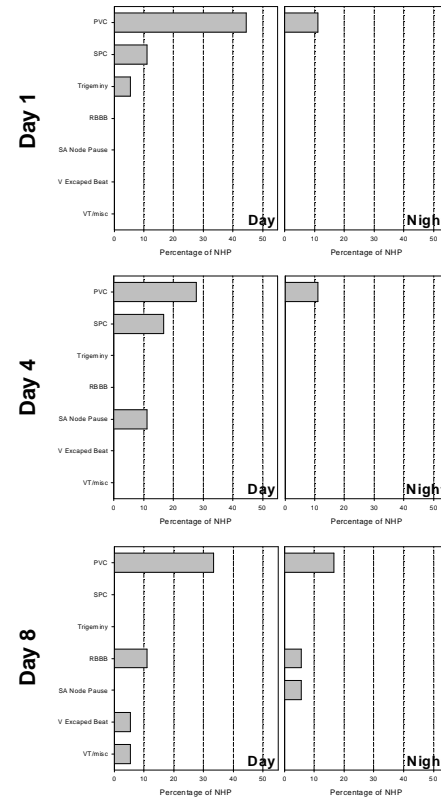
Arrhythmia Type	Day 1	Day 4	Day 8
Premature Ventricular Contraction (PVC)	8 animals (1-12)	5 animals (1-12)	7 animals (1-12)
Supraventricular Premature Complex (SPC)	2 animals (1-2)	2 animals (1-2)	1 animal (1-2)
Right Bundle Branch Block (RBBB)	1 animal (1)	1 animal (1)	1 animal (1)
SA Node Pause			2 animals (1-2)
Wandering Pacemaker			1 animal (1)
SA Node Block			2 animals (1-2)
Wandering Pacemaker			2 animals (1-2)
SA Node Pause			1 animal (1)
Wandering Pacemaker			1 animal (1)
SA Node Pause			1 animal (1)
Wandering Pacemaker			1 animal (1)

Table 1. Summary Stats

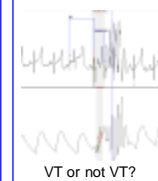
Number of NHP on study	18
Approx. no. beats per NHP	187200 (~ 120 bpm)
Approx. total beats analyzed	3.37 million
Processing Time	38 hrs
Baseline ECG Parameters:	
PR (mean ± SD)	73 ± 6 msec
QRS (mean ± SD)	42 ± 6 msec
QT (mean ± SD)	248 ± 25 msec
HR (mean ± SD)	125 ± 19 bpm
Mean arterial pressure	96 ± 9 mmHg

Note: Baseline ECG data are consistent with published literature (Ando et al., 2005)

Fig 2. Results



Considerations



1. Automated software detection is only the first step à some degree of manual overreading is needed to define arrhythmia type, and distinguish from ECG noise.
2. A single ECG lead can be problematic for arrhythmia interpretation, so cross-channel comparison to blood pressure waveforms can be helpful à multi-lead ECG beneficial.

Summary

1. Accurate arrhythmia detection using automated software should use a multi-tiered approach.
2. Evaluation of continuous data can enable a more comprehensive determination of background arrhythmias (compared to intermittent sampling) to capture low frequency arrhythmias.
3. A comprehensive ECG waveform assessment of a telemetry colony during pre-study can help define the normal arrhythmia background, which may be important to assess drug-induced arrhythmia (Ando et al., 2005; Haushalter et al., 2008).

Automated ECG analysis software can be leveraged to streamline detection, however manual overreading is still a critical aspect of arrhythmia assessment.

Quantification of arrhythmia incidence in telemetry colony is consistent with best practice recommendations.
(Leishman et al., in preparation)

References

1. Ando K et al. QT PRODACT: In vivo QT assay with a conscious monkey for assessment of the potential for drug-induced QT interval prolongation. *J Pharmacol Sci* 99: 487 – 500, 2005.
2. Haushalter TM et al. The cardiovascular and pharmacokinetic profile of dofetilide in conscious telemetered beagle dogs and cynomolgus monkeys. *Brit J Pharmacology* 154: 1457 – 1464, 2008.
3. Leishman DJ et al. Best practice in key nonclinical cardiovascular assessments in drug development: recommendations from the Safety Pharmacology Society. (in preparation).
4. ICH. The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. 2005.
<http://www.ich.org/LOB/media/MEDIA2192.pdf>