Safety Pharmacology Society

Arrhythmia Analysis in Telemetered Non-Human Primates

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WEBINAR

Outline

- Questions about arrhythmias in non-human primates:
  - What is background incidence in telemetry colony?
  - How long does animal have to be monitored to establish “baseline”?
  - Types of arrhythmias?
- Analysis approach
- Results
- Best practice recommendations

Looking for a needle in a haystack

- Cardiac arrhythmia = electrical abnormality or perturbation of the myocardium
- Normal animals → sporadic events
- Paucity of literature evaluating continuous data in normal, healthy monkeys
  - published data involves snapshots with physically/chemically-restrained animals

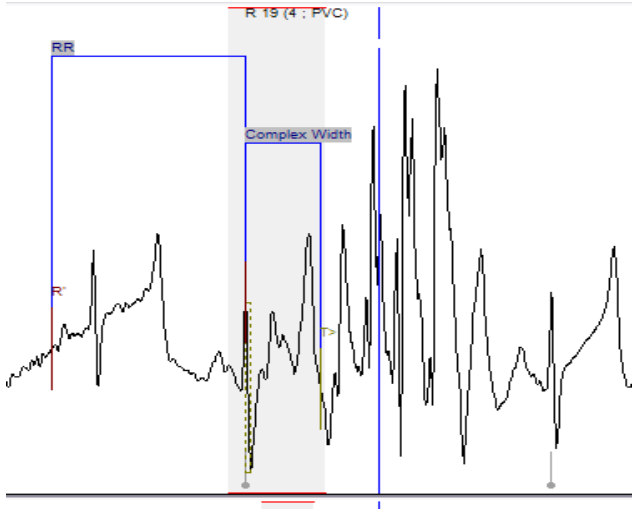
- Cardiovascular safety pharmacology considerations
  - drug effects
  - instrumentation artifacts
  - colony maintenance

Challenges

- Data volume
  - HR 100 bpm → 144K in 24 hrs (1” apart → 12K feet (3600 m) of recording!!!)

- Can software replace human eye?
  - efficiently processes routine data
  - identifies “gaps”

- How to differentiate from “crap”?
  - arrhythmias are low frequency events
    - real vs. muscle/activity noise
    - morphology depends on source (epicard, intracard, SC, surface)



Methods

- Cynomolgus monkeys (non-human primate, NHP) from Amgen's telemetry colony
  - 3.1 – 6.5 kg, 3.4 – 6.3 years old
  - implanted with DSI TL11M2-D70-PCT (L II, SC)
  - pressure catheter in abdominal aorta
- Data recorded continuously for 22 – 26 hrs, 11 days total (over 6 month period)
- Analyzed with EMKA ecgAuto
  - identified both atrial and ventricular arrhythmias

Software approach

- Automated
  - Primary analysis
    - HR/RR analysis (<50, >270 bpm)
    - ECG waveform (normal pattern recognition)
  - Secondary analysis (if needed)
    - Shape-based analysis (mainly used to find PVC's)

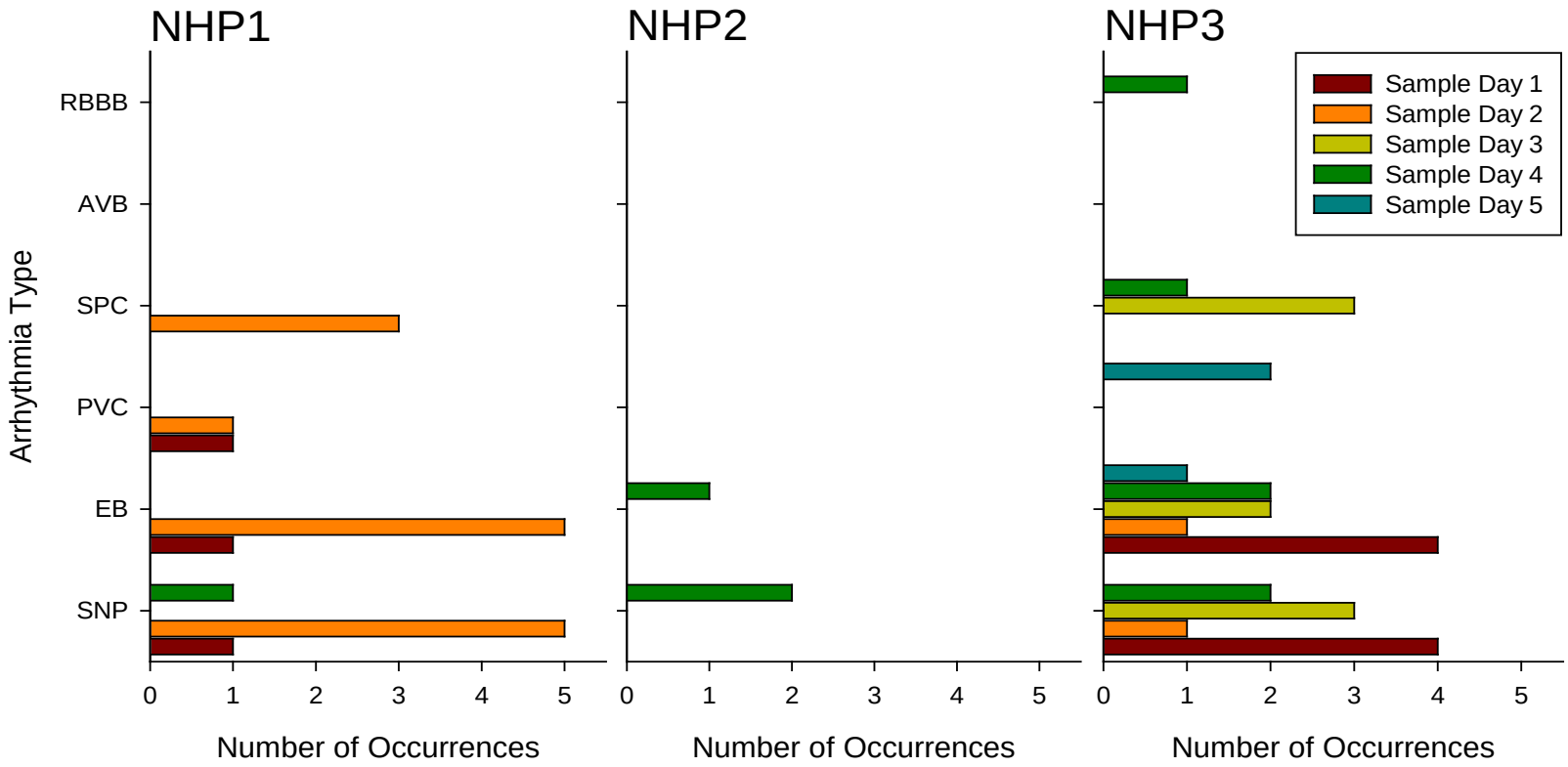
- Manual overreading
  - separate real data from noise
  - identification of arrhythmia type

Resource commitment

- Current study
  - up to 18 NHP's
  - HR @ 120 bpm
    - → ~187K/24 hrs
    - → ~24.3 million total beats

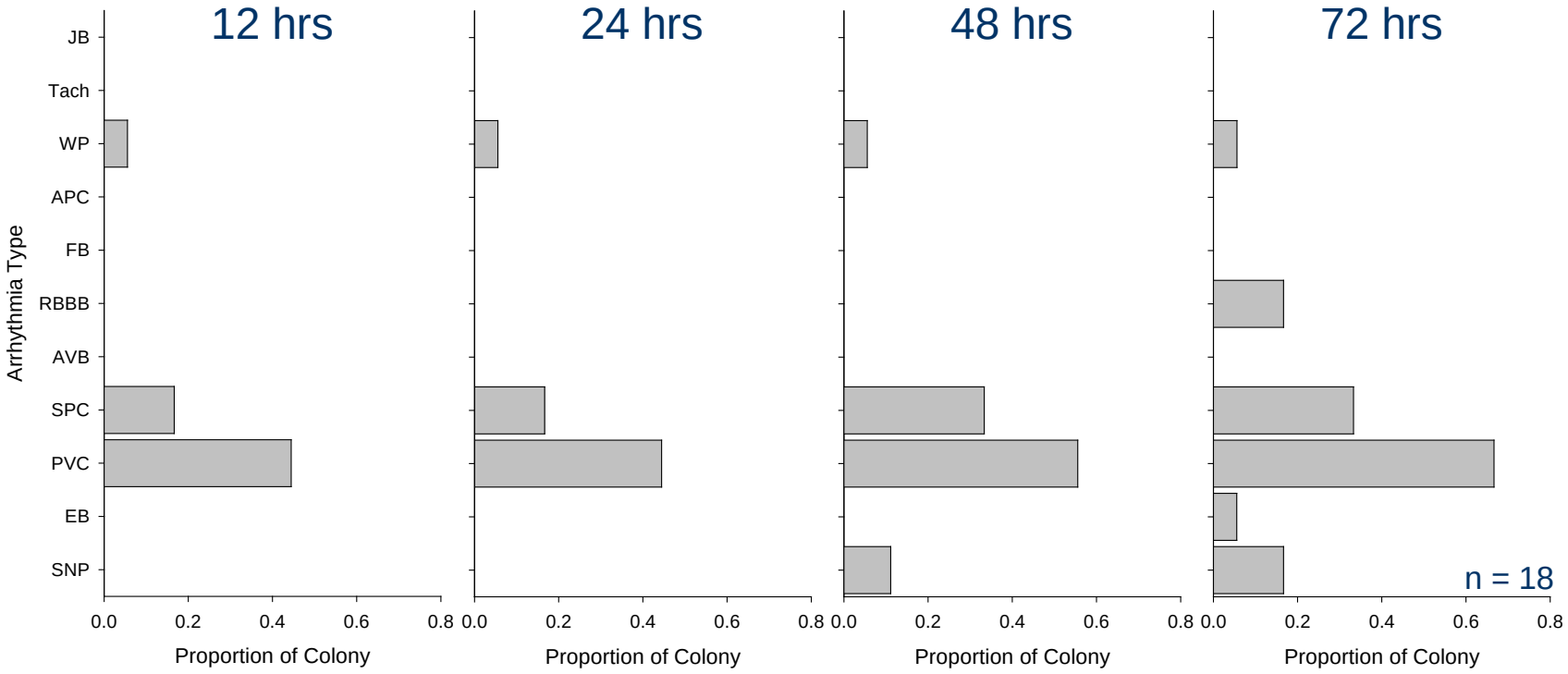
Total processing time ~ 100 HOURS

Are all NHP's created equal?



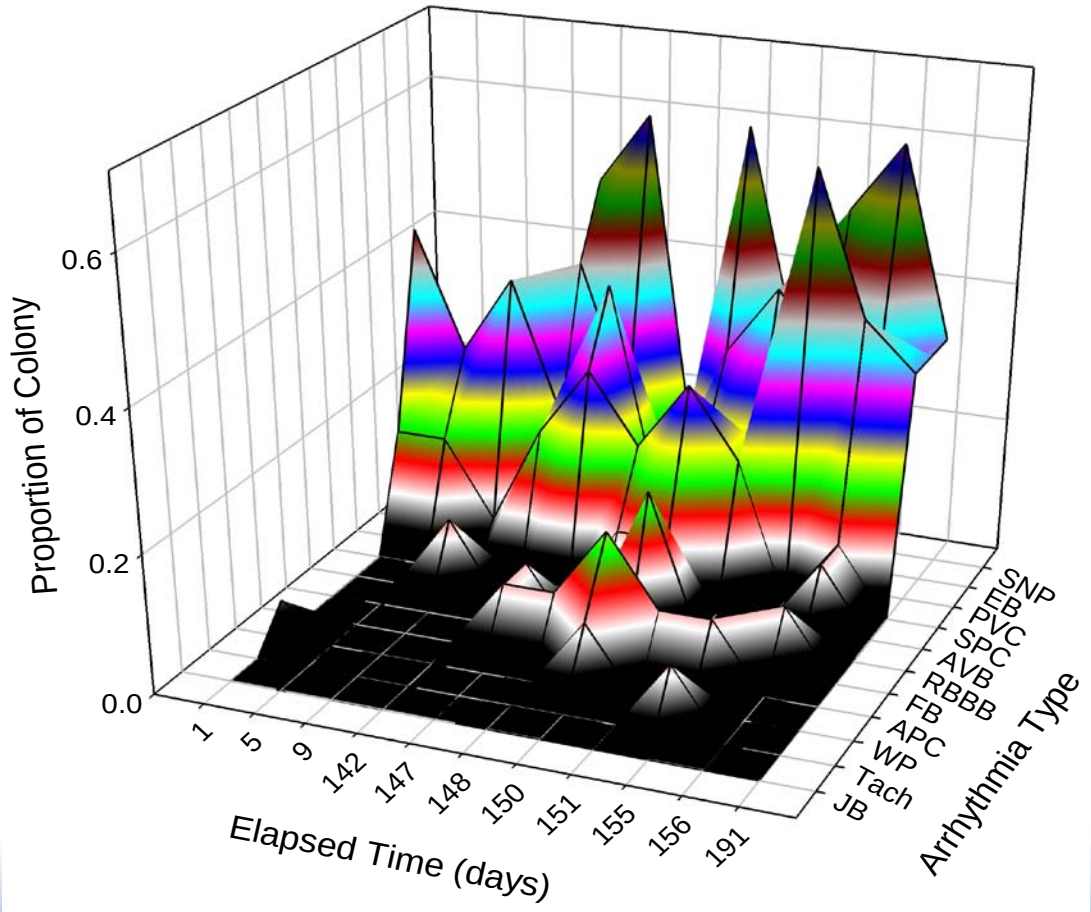
Arrhythmia incidence varies within each individual and across animals.

Is duration of sampling important?



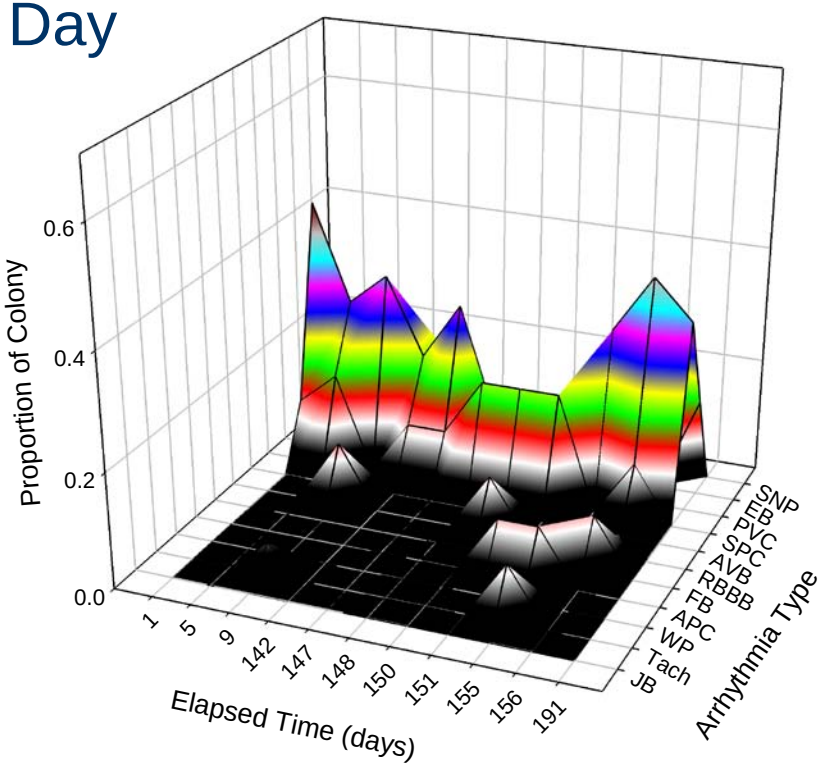
Difficult to detect low frequency events in short sampling periods.

Arrhythmia incidence over 6 months

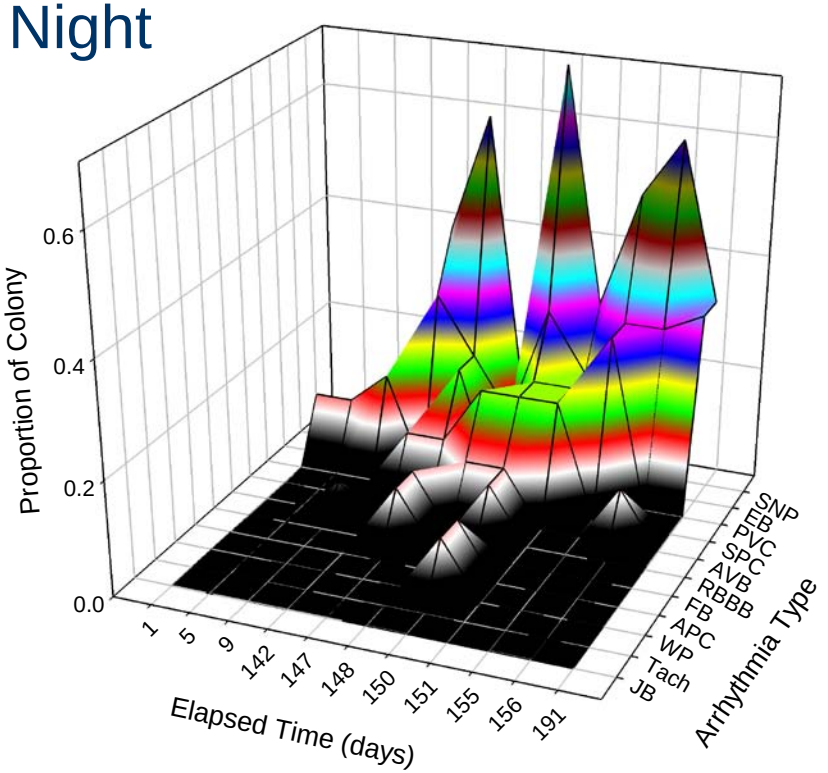


Circadian influences

Day



Night

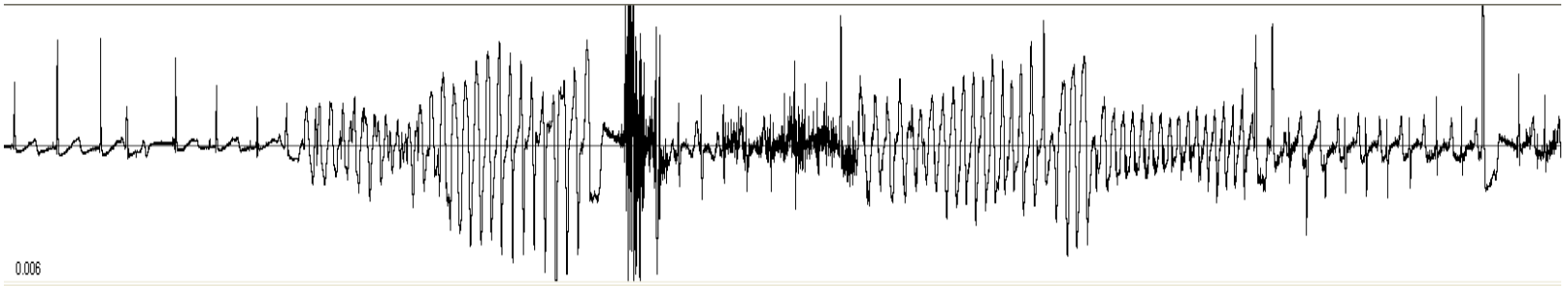


Abnormalities observed depends on the time of day…

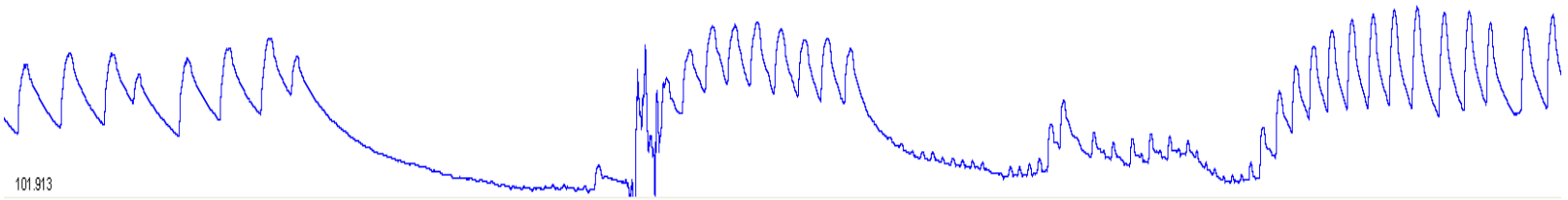
Real arrhythmia

- Torsades de Pointes (dofetilide, 0.1 mg/kg, po)

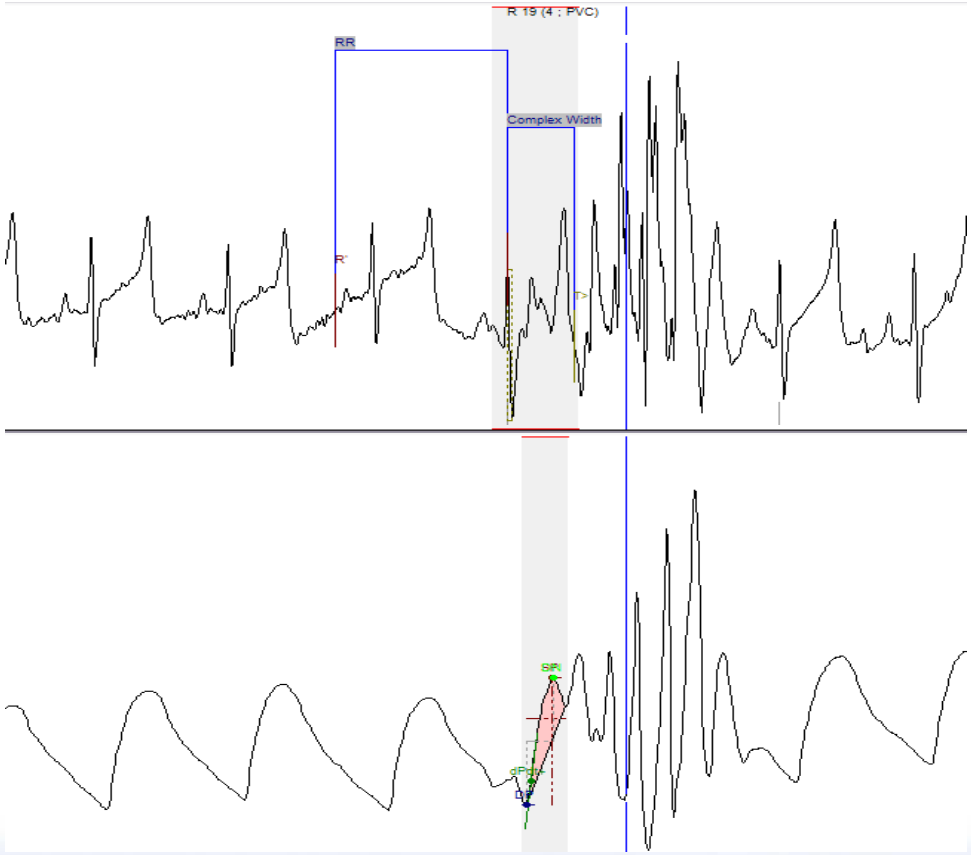
ECG



BP



Real arrhythmia?



Pressure wave helps identify abnormality

Best practices (part 1)

- Normal animals in Amgen's colony exhibit a variety of different arrhythmias, in the absence of treatment
  - quantification of incidence in telemetry colony is consistent with best practices (Leishman et al., in preparation)

- Computerized analysis software is needed to interrogate large data volume

- Continuous data, over multiple days, is critical to detect low frequency events and improve understanding about individual variation

Best practices (part 2)

- Multiple channels can be advantageous
  - cross-channel comparison to blood pressure waveforms (or physical activity)

- Manual overreading by trained eye is needed to define arrhythmia type, and distinguish from ECG noise

- Is an animal normal?
  - 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)

Acknowledgements

- Amgen
  - Hugo Vargas
  - Kathy Derakhchan
  - Mike Engwall

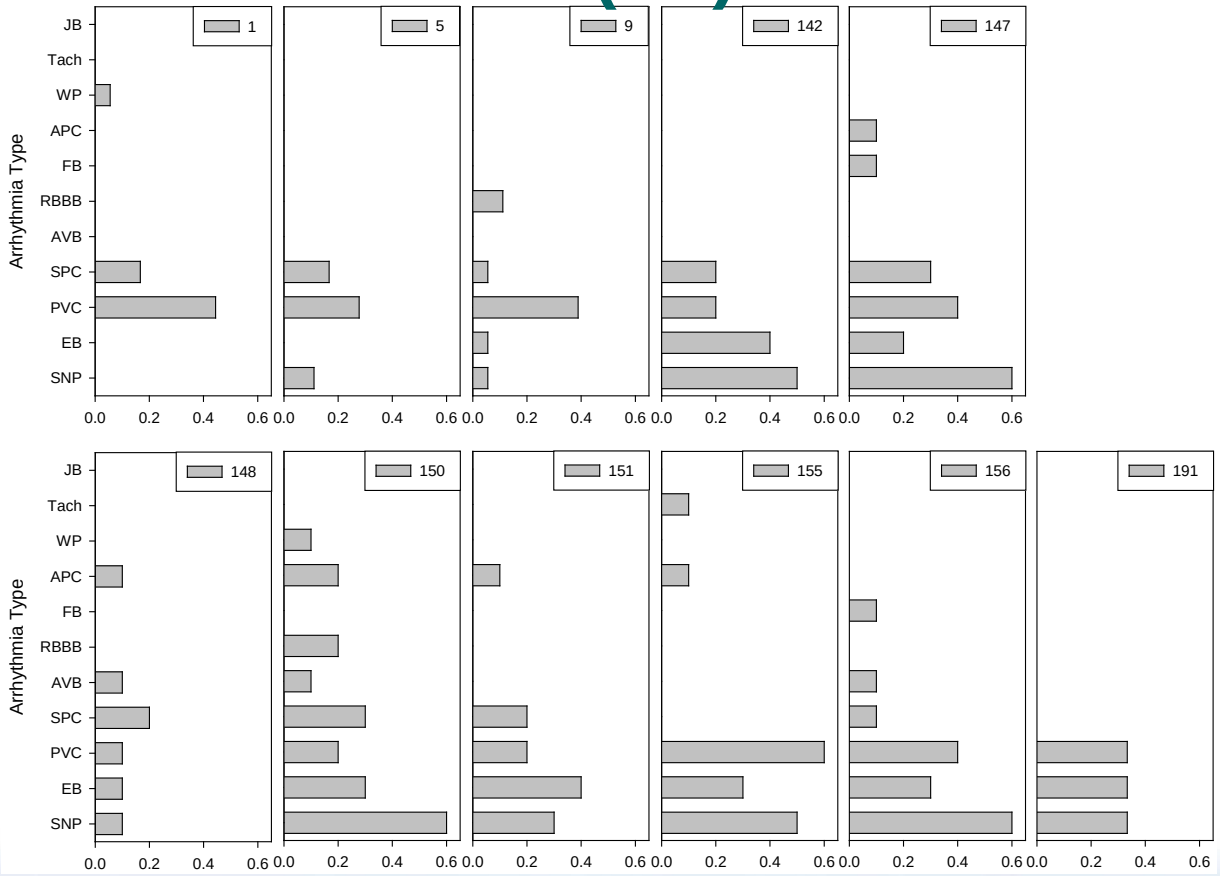
- EMKA
  - Emily Nolan

Backup Slides

References

- 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.
- 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.
- Leishman DJ et al. Best practice in key nonclinical cardiovascular assessments in drug development: recommendations from the Safety Pharmacology Society. (in preparation).

Arrhythmia incidence (2D)



Abbreviations

APC: atrial premature contraction
AVB: atrioventricular block
EB: escaped beat
FB: fusion beat
JB: junctional beat
PVC: premature ventricular contraction
RBBB: right bundle branch block
SNP: sinus node pause
SPC: supraventricular premature contraction
Tach: tachycardia
WP: wandering pacemaker