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A Gut Feeling from the Heart: An ECG Biomarker for Detection of Emesis

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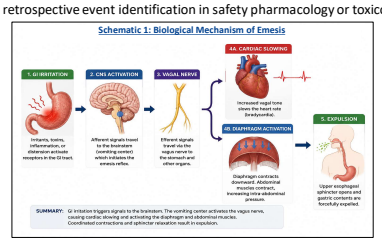
Introduction

Recent ICHE14 S7B Q&A updates have increased the importance of accurately assessing preclinical concentration-QT (cQTc) relationships. However, emetic episodes can significantly alter drug exposure and confound interpretation, while precise detection often requires labor intensive video review. Although emesis is traditionally associated with gastrointestinal (GI) and central nervous system activation, the event is accompanied by a distinct physiological signature involving cardiovascular and respiratory responses. Previous studies identified concurrent EMG and heart rate changes during vomiting (Milano, et.al., 1995; Kearney, et.al., 2016), but the ECG signature itself has not been fully explored. Here, we evaluate a characteristic ECG biomarker of emesis that may enable automated retrospective event identification in safety pharmacology or toxicology studies.

Schematic 1: Biological Mechanism of Emesis



Materials and Methods

MATERIALS

Subjects Exhibiting Emesis

- 8 Beagle dogs (12-24 months)
- 14 Cynomolgus NHPs (2-5 years)
- 6 Göttingen minipigs (3-8 months)
- 2 healthy human volunteer researchers (old enough to know better)*

Routes of Administration

- IV and/or Oral dosing
- Emesis was induced in human volunteers via saltwater gargling or water loading*

Data Collection and Analysis

- Data were collected using implanted telemetry (dogs, NHPs) or external jacketed telemetry (minipigs, humans)
- ECG data were analyzed using ecgAUTO software (emkaTECHNOLOGIES) employing pattern recognition algorithms
  - ECG endpoints included heart rate changes, heart rate variability, baseline amplitude shifts from the isoelectric line, and signal noise associated with emetic events (electromyography EMG)

METHODS

- Concurrent video and telemetry data from dogs and NHPs were used for algorithm development
- Following algorithm refinement, minipigs and human volunteers were evaluated to assess cross-species applicability

Results

A characteristic ECG biomarker of emesis was identified across all evaluated species, consisting of:

- A transient increase in heart rate (tachycardia) occurring immediately prior to the emetic event.
- A period of vagally mediated bradycardia associated with productive retching, with species-dependent differences in magnitude.
- Distinct EMG artifact and rolling isoelectric baseline shifts (due to respiratory variation) during retching episodes.
- A brief period of post-emetic tachycardia before return toward baseline heart rate

The generalized pattern was observed in beagle dogs, cynomolgus NHPs, Göttingen minipigs, and human volunteers despite differences in telemetry methodology and route of administration.

Although the overall pattern was consistent, species-specific differences were observed. Dogs exhibited the greatest degree of vagal influence, whereas nonhuman primates and human subjects demonstrated comparatively attenuated bradycardic responses. These findings may reflect differences in autonomic regulation, emetic mechanisms, or the method by which emesis was induced.

The biomarker was observed across species, administration routes, and telemetry systems, demonstrating broad applicability for automated emesis detection. Detection performance was influenced by signal quality, and additional studies are warranted to further evaluate algorithm performance and sources of interspecies variability.

Discussion and Conclusion

Discussion: A reproducible ECG signature of emesis was observed across species, supporting the feasibility of automated emesis detection using routinely collected ECG data. Although a common physiologic pattern was identified, algorithm parameters required species-specific refinement to optimize detection performance.

Differences in vagal influence were observed between species, with dogs demonstrating a more pronounced bradycardic response than nonhuman primates and human subjects. The reduced bradycardia observed in human volunteers may be potentially be related to the self-induced nature of the emetic event and differences in autonomic or central nervous system regulation.

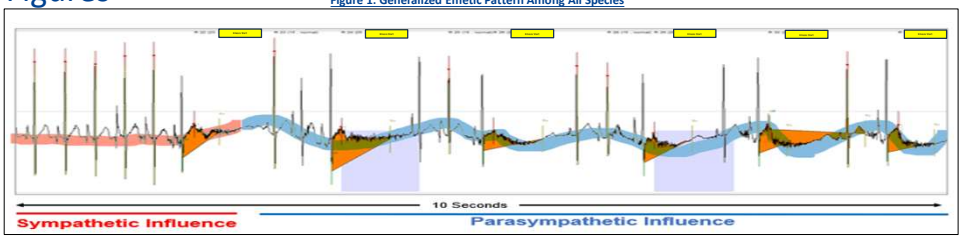
Algorithm performance was dependent upon signal quality, and elevated basal heart rates increased the likelihood of false positive detections. Additional studies with larger datasets are needed to further assess algorithm sensitivity and specificity and to determine whether factors such as age contribute to variability in the ECG emetic signature.

Emetic algorithm was found to be superior to in room observations for identification of emetic events, with a significant advantage of much greater temporal resolution.

Conclusion: Automated identification of emetic events from standard telemetry recordings may reduce reliance on labor-intensive video review and improve interpretation of safety pharmacology endpoints when emesis may alter drug exposure.

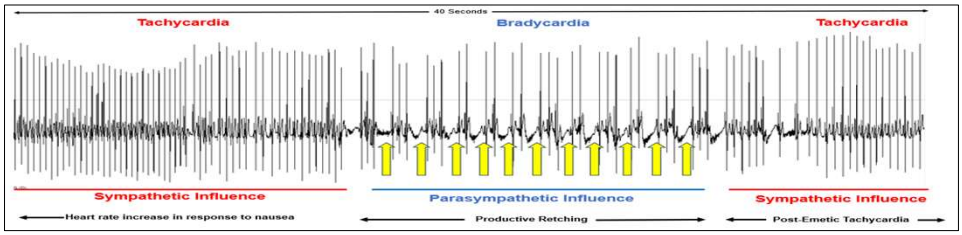
Figures

Figure 1: Generalized Emetic Pattern Among All Species



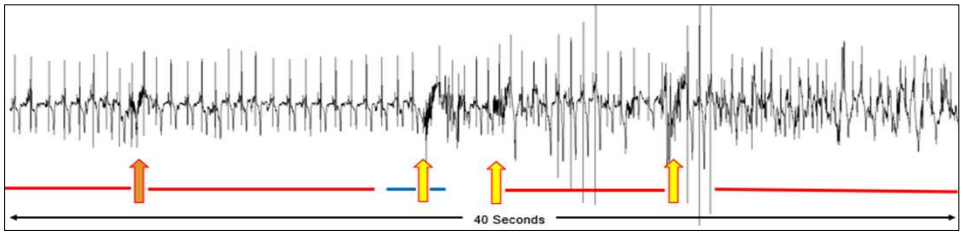
ECG tracing demonstrates the generalized characteristic of emetic signature, with transient tachycardia immediately preceding marked vagally mediated bradycardia during active emesis. A rolling isoelectric line (resulting from respiratory variation) and EMG artifact are present during retching, illustrating the temporal relationship between emesis and autonomic modulation of heart rate observed across species. Automated analysis algorithm depicts onset of emetic episode (yellow highlight).

Figure 2: Beagle Dog Emetic Signature (Implanted Telemetry)



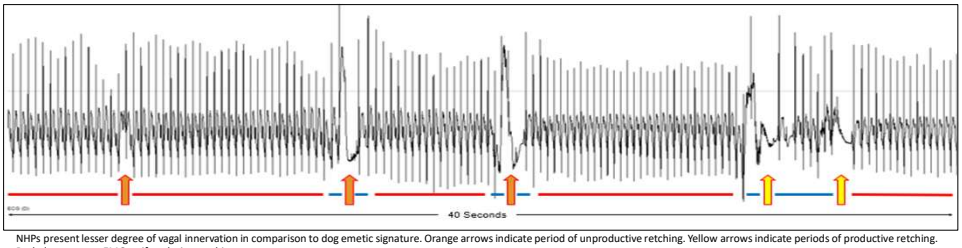
Heart rate increases within 2 minutes of emetic episode. Following sympathetic response to nausea, an abrupt pause in heart rate is noted, resulting from vagal innervation. Episodic EMG artifact noted in the ECG signal during retching (vagal influence and EMG artifact highlighted with yellow arrows). Following emetic episode(s), sympathetic influence continues for a brief period before heart rate returns to baseline.

Figure 3: Minipig Emetic Signature (Jacketed Telemetry)



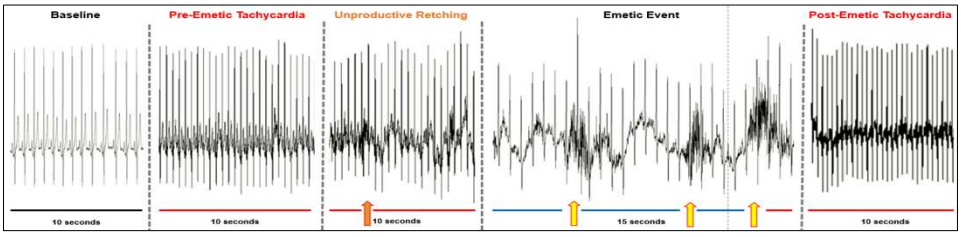
Tachycardia precedes the emetic event with abrupt (although brief in duration) vagal influence following first productive retching event (yellow arrow). Distinct EMG artifact surrounding retching events with rolling of isoelectric baseline.

Figure 4: Cynomolgus NHP Emetic Signature (Implanted Telemetry)



NHPs present lesser degree of vagal innervation in comparison to dog emetic signature. Orange arrows indicate period of unproductive retching. Yellow arrows indicate periods of productive retching. Both demonstrate EMG artifact during retching.

Figure 5: Human Emetic Signature (Jacketed Telemetry; non-clinical data)



Human emetic signature mimics the dog, with pre- and post-emetic tachycardia and EMG artifact during retching. However, similar to primate (but to greater extent), less vagal innervation is observed during unproductive (orange arrows) and productive retching (yellow arrows). Rolling isoelectric line with EMG artifact presents a common signature among species.*

Acknowledgements and References

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* Human data were generated for entertainment purposes and to understand translational correlation between humans and preclinical animal models.