

## Approach to Create a Brand-New Technique Based on Heart Rate Variability-HRV for Anticipating Drug-Induced Seizures

Sudhindra M\*

Department of Biomedical Sciences, College of Health Sciences, Midwestern University, Glendale, Unites States

### Introduction

Although drug-induced convulsion may be a serious side event, no useful biomarkers have been found for it. We prefer to suggest an alternative approach that is backed by pulse variability (Heart Rate Variability-HRV) and a machine learning algorithm for forecasting drug-induced convulsions in monkeys [1]. Since involuntary neuronal activity is changed during convulsions and these modifications have an impact on HRV, convulsions can be anticipated by monitoring HRV. Convulsion warnings are sent out after abnormal changes in HRV are discovered in the intended technique, which uses a convulsion prediction model to monitor aberrant changes in various HRV parameters [2,3]. The multivariate statistical process control (MSPC), a well-known anomaly detection approach in machine learning, is the foundation upon which the convulsion prediction model is built.

In this investigation, several doses of the convulsant drugs pentylenetetrazol (PTZ) and picrotoxin (PTX), which are GABA receptor antagonists, were given to four cynomolgus monkeys. As a negative control, pilocarpine (PILO) at modest dosages was also given. 12 HRV parameters were measured over the course of 3 hours as medication delivery was tracked using the prediction model's mean. At medium and high dosages of PTZ and PTX (corresponding to 1/3 or 1/4 of the convulsion dose), the frequency and length of convulsion warnings from HRV increased. On the other hand, PILO did not result in an increase in the frequency of convulsion alerts. All medicines caused vomiting, but convulsion alarms weren't connected to the vomiting. The use of convulsion alarms as a biomarker for convulsions brought on by GABA receptor antagonists is therefore possible [4-8].

Our goal was to create a brand-new technique based on HRV for anticipating drug-induced seizures. Since electrocardiograms for HRV analysis can be collected without limitation in animals, and HRV has been used to monitor autonomic functioning in both people and animals, we first tried to predict convulsions in monkeys in this work. Through tests with cynomolgus monkeys, the effect of alcohol was assessed using HRV. Kerem attempted to use HRV to predict rats' generalised epileptic episodes. A rat middle cerebral artery occlusion model was used to create an HRV-based ischemic stroke diagnosis approach. Through research with Kv1, the cardiorespiratory characteristics, particularly HRV, may be employed as biomarkers for sudden unexpected death in epilepsy. We gathered HRV data from cynomolgus monkeys given picrotoxin (PTX) and pentylenetetrazol (PTZ), two well-known convulsants and GABA receptor antagonists. In addition, pilocarpine (PILO) was given to animals in small dosages as a preventative measure. We applied the planned biomarker to the collected HRV information for predicting drug-induced convulsions to evaluate its validity. The Institutional Animal Care and Use Committee (IACUC), published by the National Institutes of Health, gave its clearance for this study to be carried out. The number of animals used was based on the standard test protocol for safety pharmacology studies on the evaluation of the cardiovascular system in non-rodents, and four male cynomolgus monkeys were used because they are one of the most frequently used animals for ECG measurements in a safety

pharmacology study, which is crucial for drug development [9,10].

Only two of the monkeys in this research experienced convulsions when given PTX; nonetheless, a biomarker must be able to detect convulsion risk below the convulsion-inducing dosage. Therefore, even though not all of the animals experienced convulsions, this experiment and information analysis achieved the goal of the study. When PTZ and PTX are administered in medium and high dosages, we frequently correctly send convulsion alerts. The fact that the medium dosages were 1/3 and 1/4 of the convulsion doses suggests that we may be able to anticipate convulsion liability without inducing a convulsion that would violate our prediction model. A convulsion was also anticipated by the intended approach when 0.5 mg/kg of PTX was administered. This finding suggests that the convulsion alarm generated using the intended approach may be utilised as a biomarker for drug-induced convulsions, and that the frequency and length of convulsion alarms may be used to predict the likelihood of convulsions in the near future. The occurrence of ECG artefacts brought on by measurement errors or cardiac arrhythmias also triggers a convulsion alert. Although we visually examined the recorded ECG signals around the time of convulsion alarms, there were no artefacts or cardiac arrhythmia, indicating that the convulsion alarms wouldn't be troubled by either throughout this investigation [11-13].

At 0 mg/kg-PILO administration in M2, there were several convulsion alarms that weren't connected to the drug's administration. Convulsion alarm instances were not accompanied by ECG artefacts or cardiac arrhythmia. Thus, these alerts were erroneous positive results. There is a chance that M2 was asleep during this assessment because variations in sleep quality have a significant impact on HRV and should cause false positives. Although we were unable to tell if the animal slept, video analysis and activity tracking showed that it did not move when the sirens went off [14]. Since such data won't contain sleep information throughout this investigation, we used the three-hour data with administration between the start of administration to train the convulsion prediction models. On the other hand, throughout this experiment, we tended to gather measurement data over a 24-hour period, and we attempted to train convulsion prediction models using this data. Following the administration of PTX, M represents the total number of convulsion alarms generated by models M1-M4.

**\*Corresponding author:** Sudhindra M, Department of Biomedical Sciences, College of Health Sciences, Midwestern University, Glendale, Unites States, E-mail: sudhindra98@gmail.com

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## Conclusion

This study demonstrates that the number of convulsion alarms greatly increased with 0 mg/kg of PTX, whose alarm numbers are zero. As a result, the models developed using the 24-h HRV data did not perform as intended. Due to eating and sleeping, the 24-h data showed significant variations in the ANS's activity; however, HRV data showing these changes was not useful for training the model. As a result, since ANS activities are stable under resting circumstances, the convulsion prediction model must be developed using HRV data. This shows that carefully choosing the modelling data is necessary, which is a typical issue in machine learning.

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## Conflict of Interest

None to declare

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