

## RESEARCH ARTICLE

# Machine Learning Model Using Heart Rate Variability for the Prediction of Vasovagal Syncope

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**ABSTRACT** Vasovagal syncope is a reversible condition that can cause serious events, such as cerebral hemorrhage. Predicting its occurrence is challenging; thus, this study aimed to develop machine learning models that use heart rate variability to predict the occurrence of vasovagal syncope episodes. We investigated 80 patients experiencing syncope who underwent Holter monitoring during the head-up tilt test. Twenty-six machine learning models were examined for the prediction of vasovagal syncope using heart rate variability parameters. We randomly split the subjects into training and testing sets at a 7:3 ratio (training set: 46 positive and 9 negative subjects; testing set: 21 positive and 4 negative subjects). The XGB classifier achieved the highest performance compared with that of the other algorithms (accuracy, 0.72; area under the curve, 0.801; sensitivity, 0.857; specificity, 0.621). When examining the time taken to predict syncope occurrence using the developed prediction model, it was found that the model could forecast an episode approximately 3 min (equivalent to 193.2 beats) prior to the onset of symptoms. The machine learning model, which utilized heart rate variability parameters, was proficient in preemptively predicting vasovagal syncope incidents. In practical applications, this approach may help prevent unexpected events by leveraging the heart rate variability to predict vasovagal syncope.

**INDEX TERMS** Head-up tilt test, heart rate variability, machine learning, prediction algorithm, vasovagal syncope.

## I. INTRODUCTION

Vasovagal syncope (VVS) is a subtype of neurally mediated reflex syncope characterized by an abrupt decline in blood pressure and a concomitant decrease in heart rate, leading to episodes of loss of consciousness [1], [2]. VVS is a common condition which can significantly diminish patients' quality of life and potentially lead to post-traumatic stress disorder [3]. Additionally, individuals in high-risk professions and older patients without prodromal symptoms are at an increased risk of falls and injuries due to syncope. This

underscores the critical need for a better understanding of this condition and the development of effective management strategies [4]. Although the pathophysiology of VVS is not yet clearly understood, research has confirmed that VVS is characterized by a disturbance of the autonomic nervous system. This includes an initial increase in sympathetic activity, followed by an increase in vagally mediated parasympathetic activity, and subsequent withdrawal of sympathetic activity [5], [6].

Heart rate variability (HRV) reflects the autonomic tone. Autonomic tones influences blood pressure, gas exchange, heart, gut, and vascular tones [7]. HRV is an emergent property of interdependent regulatory systems that operate at

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different timescales, allowing adaptation to environmental and psychological stressors. However, whether HRV can predict the occurrence of VVS remains controversial. The results vary depending on the time and protocol, but seem to correlate [8]. Machine learning (ML) uses computer algorithms to identify patterns in large datasets with multiple variables, capturing high-dimensional and nonlinear relationships among clinical features. There have been previous studies predicting the occurrence of VVS. However, these studies used variables related to both blood pressure and HRV. When using only HRV variables, the predictive power was not high [9], [10]. Therefore, we aimed to develop ML models to predict VVS using only HRV parameters. We also investigated how quickly our developed model could predict the occurrence of syncope episodes in advance.

## II. METHODS

### A. STUDY POPULATION

We retrospectively investigated 80 patients who underwent Holter testing during the head-up tilt (HUT) test. All individuals had a medical history suggestive of neurally mediated syncope. All participants underwent medical evaluations according to the European Society of Cardiology guidelines [2]. Medications capable of interacting with the autonomic nervous system, such as beta-blockers, were discontinued for a minimum of five half-lives prior to the HUT test. This study was approved by the Institutional Review Board of the Chung-Ang University Hospital and complied with the principles of the Declaration of Helsinki.

### B. HEAD-UP TILT TEST

The HUT test was conducted according to the Italian protocol in a quiet room with no distractions [11], [12]. The tilt table used in the test was electrically driven and equipped with footplate support.

Prior to the initiation of the tilt phase, each patient underwent a baseline rest period lasting 20 minutes in the supine position. During this time, continuous monitoring of the patients' blood pressure and electrocardiogram (ECG) was performed to establish a baseline hemodynamic status. This rest period was critical to ensure that the patient's cardiovascular system had reached a stable resting state, reducing the influence of external factors on the subsequent tilt phase.

After the resting period, the tilt phase was initiated. The table was smoothly elevated to a 60° angle, a standard angle for tilt testing designed to stimulate orthostatic stress while minimizing patient discomfort. The patient was kept in this upright position for 20 minutes. During this phase, close monitoring of the patient's heart rate, blood pressure, and symptoms was carried out to observe for any signs of presyncope or syncope. This phase is intended to provoke a vasovagal response by challenging the autonomic nervous system's ability to regulate blood pressure and heart rate in response to gravity.

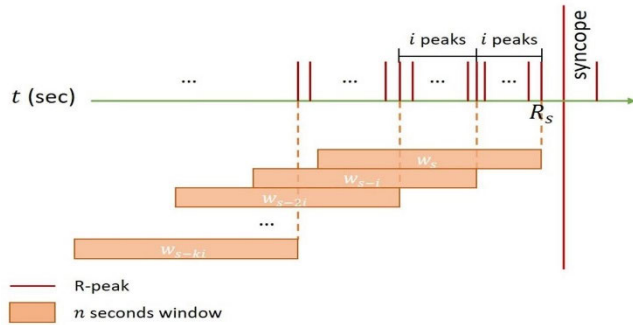
If no syncope or significant symptoms were observed during the initial 20-minute tilt period, a pharmacological provocation phase was initiated. At this point, 300  $\mu\text{g}$  of nitroglycerin spray was administered sublingually to induce venous pooling and reduce venous return, further stressing the cardiovascular system and enhancing the likelihood of provoking a vasovagal response. The patient remained tilted at the 60-degree angle for an additional 20 minutes after nitroglycerin administration, or until syncope occurred. If the patient experienced syncope during the tilt or provocation phase, the test was immediately terminated, and the patient was rapidly returned to the supine position to restore normal blood flow and consciousness. If no syncope occurred by the end of the provocation phase, the test was considered complete, and the patient was returned to the supine position slowly to avoid abrupt hemodynamic changes.

The hemodynamic response to the HUT test was classified according to the VASIS classification system [13], which categorizes vasovagal responses based on the patient's blood pressure and heart rate changes during the test. This classification helps to identify the specific type of reflex-mediated syncope, whether it involves hypotension, bradycardia, or a mixed response.

Based on the HUT test results, the patients were divided into two groups. Group 1 included those who experienced definite syncope episodes during the HUT test; and Group 2 included those who had a negative response to the HUT test.

### C. HEART RATE VARIABILITY DATA PROCESSING AND PARAMETERS

HRV parameters were obtained via Holter monitoring during the HUT test. To extract the HRV parameters, only intervals between the R-peaks were required, making it sufficient to use only the one channel that provided the most accurate R-peak times. In this study, Lead I was selected from the three available channels (Lead I, Lead II, Lead III) for R-peak detection. Quantitative HRV analysis was performed according to the guidelines of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [14]. The procedures for preprocessing the Holter data and analyzing the HRV parameters included noise removal, R-peak detection, HRV parameter extraction, and HRV analysis. For the robust detection of R-peaks in ECG data, bandpass filtering is commonly performed to reduce redundant noise, such as baseline wander problems, electrical noise, and patient tremors [15]. Bandpass filtering of the 5-20 Hz frequency bandwidth was performed for this study. To extract R-peaks from ECG signals, we used a python library called "heartpy" [16], [17]. Using a moving average of 0.75 seconds, we first extracted a set of ranges surpassing the accumulated moving average. We then identified the time with the maximum ECG signal value within each range as a candidate for the R-peak. To enhance the accuracy of the R-peaks extraction, we adjusted the moving average by

Figure 1.  $n$  Seconds windows containing R-peaks**FIGURE 1.**  $n$  Seconds windows containing R-peaks.

multiplying it with a constant value. The constant value was selected from a predefined set to minimize the global standard deviation of the differences between adjacent RR interval lengths. The constant set was defined as [0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, 1.00, 1.10, 1.20, 1.50, 2.00, 3.00]. A Python library, “hrvanalysis,” was utilized to extract various HRV parameters, including time and frequency domain [14], [18], [19], [20]. Time-domain HRV parameters were used to quantify the amount of variability in measurements of the interbeat interval, which is the time between successive heartbeats. Frequency-domain HRV parameters were calculated using Fast Fourier Transform (FFT) and autoregressive modeling and were used to estimate the distribution of absolute or relative power in four frequency bands [7], [14]. HRV parameters were derived from multiple R-peaks by dividing the time into windows containing several R-peaks, from which the HRV parameters from each window were extracted. A window size of 180 s was used in this study. The extracted time and frequency domain HRV parameters are listed in Supplementary Table 1.

#### D. DATA SPLIT, WINDOW SELECTION, AND AUGMENTATION

Eighty patients (Group 1: 67 patients; Group 2: 13 patients) were selected for analysis. We randomly split the subjects into training and testing sets at a 7:3 ratio. The training set included 46 positive and 9 negative subjects, and the testing set included 21 positive and four negative subjects. In this study, positive windows of  $n$ s were selected from Group 1 based on the latest ending time within the tilt state that did not exceed the syncope time. To ensure a reliable and robust separation with of the syncope sign from the HUT test state windows of Group 1, negative windows of  $n$ s were selected from the tilt state of Group 2. Furthermore, negative windows from both Groups 1 and 2 were randomly sampled outside the time range of the HUT test and added as negative windows.

To address the problem of imbalanced data in the training dataset, a data augmentation technique was proposed to augment the positive data. The aim of this technique is to capture the precursor signs of syncope in the preceding window. The windows were periodically sampled based on the R-peak times. The selection of hyperparameters was crucial for

**TABLE 1.** Baseline characteristics of the datasets.

|             | Training set    |                   |                  |         | Test set          |                  |         |
|-------------|-----------------|-------------------|------------------|---------|-------------------|------------------|---------|
|             | Total<br>(n=80) | Group 1<br>(n=46) | Group 2<br>(n=9) | p-value | Group 1<br>(n=21) | Group 2<br>(n=4) | p-value |
| Age, years  | 52.5 ± 18.5     | 56.2 ± 17.4       | 51.1 ± 17.1      | NS      | 44.5 ± 19.6       | 55.3 ± 21.6      | NS      |
| Male (%)    | 41.3            | 39.1              | 33.3             | NS      | 47.6              | 50.0             | NS      |
| HR (bpm)    | 69.1 ± 13.4     | 68.4 ± 13.3       | 69.0 ± 9.3       | NS      | 68.4 ± 14.4       | 80.8 ± 16.8      | NS      |
| SBP (mm·Hg) | 122.3 ± 16.7    | 121.7 ± 17.8      | 130.8 ± 20.6     | NS      | 120.1 ± 12.2      | 122.3 ± 14.8     | NS      |
| DBP (mm·Hg) | 71.6 ± 12.6     | 69.9 ± 13.1       | 81.4 ± 10.4      | 0.012   | 70.4 ± 10.9       | 75.5 ± 13.4      | NS      |

HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure.

appropriate window sampling. As shown in Fig. 1, the syncope window  $w_s$  ends with the last R-peak,  $R_s$ , right before syncope. We denoted the  $i$ -th R-peak as  $R_{s-i}$ , representing the  $i$ -th R-peak counted in reverse order starting from  $R_s$ , while  $w_{s-i}$  ended with  $R_{s-i}$ . To augment the last window of the tilt-testing time, we sampled  $k$  windows periodically with a step of  $i$  R-peak times. If  $k$  windows were augmented, we selected the windows from  $w_{s-i}$  to  $w_{s-ki}$  for syncope subjects from Group 1. The hyperparameter search identified the optimal values as follows:  $n = 180$ ,  $i = 10$ , and  $k = 34$ , with the following search spaces: (60, 120, 180, 300) for  $n$ , [1, 40] for  $i$ , and [0, 40] for  $k$  in the validation data. The final training set comprised 460 and 179 positive and negative windows, respectively, selected from 46 positive and 9 negative subjects.

#### E. MACHINE LEARNING ALGORITHMS AND FEATURE IMPORTANCE

Twenty-six ML algorithms were selected for VVS episode prediction. The hyperparameters were tuned using a grid search of the separated validation set. We estimated the SHapley Additive exPlanations (SHAP) of each variable in the ML model to improve the interpretability of the feature importance values. The SHAP value represents the change in the log-odds when a variable is hidden from the model.

#### F. STATISTICAL ANALYSIS

Continuous variables were expressed as mean ± standard deviation (SD), or median [interquartile range], and were compared using the Student’s t-test or Wilcoxon rank-sum test. Categorical variables were expressed as proportions and compared using the  $\chi^2$  test. ML-based models developed from the training population were compared using the area under the receiver operating characteristic curve (AUC) of the validation population. Statistical significance was set at  $p < 0.05$  for all analyses.

**TABLE 2. Metrics for the 26 machine learning algorithms to classify vasovagal syncope.**

| Model                           | Balanced | Accuracy | ROC AUC | F1 Score | Time Taken |
|---------------------------------|----------|----------|---------|----------|------------|
| XBG Classifier                  | 0.72     | 0.73     | 0.73    | 0.72     | 0.13       |
| Extra Trees Classifier          | 0.64     | 0.66     | 0.66    | 0.64     | 0.17       |
| LGBM Classifier                 | 0.66     | 0.65     | 0.65    | 0.66     | 0.07       |
| Linear Discriminant Analysis    | 0.60     | 0.65     | 0.65    | 0.57     | 0.03       |
| Extra Tree Classifier           | 0.62     | 0.64     | 0.64    | 0.62     | 0.01       |
| Linear SVC                      | 0.58     | 0.63     | 0.63    | 0.54     | 0.03       |
| Random Forest Classifier        | 0.60     | 0.62     | 0.62    | 0.60     | 0.22       |
| Ada Boost Classifier            | 0.60     | 0.61     | 0.61    | 0.60     | 0.14       |
| Ridge Classifier CV             | 0.54     | 0.60     | 0.60    | 0.47     | 0.02       |
| Ridge Classifier                | 0.54     | 0.60     | 0.60    | 0.47     | 0.02       |
| Logistic Regression             | 0.54     | 0.60     | 0.60    | 0.49     | 0.04       |
| Bagging Classifier              | 0.58     | 0.59     | 0.59    | 0.58     | 0.05       |
| Label Propagation               | 0.54     | 0.58     | 0.58    | 0.51     | 0.03       |
| Label Spreading                 | 0.54     | 0.58     | 0.58    | 0.51     | 0.02       |
| Bernoulli NB                    | 0.58     | 0.57     | 0.57    | 0.58     | 0.02       |
| Calibrated Classifier CV        | 0.50     | 0.57     | 0.57    | 0.40     | 0.09       |
| Passive Aggressive Classifier   | 0.56     | 0.56     | 0.56    | 0.56     | 0.02       |
| Perceptron                      | 0.58     | 0.55     | 0.55    | 0.56     | 0.01       |
| Decision Tree Classifier        | 0.54     | 0.54     | 0.54    | 0.54     | 0.02       |
| Nearest Centroid                | 0.58     | 0.54     | 0.54    | 0.55     | 0.02       |
| SGD Classifier                  | 0.46     | 0.53     | 0.53    | 0.36     | 0.01       |
| Gaussian NB                     | 0.56     | 0.51     | 0.51    | 0.51     | 0.02       |
| Quadratic Discriminant Analysis | 0.58     | 0.50     | 0.50    | 0.43     | 0.02       |
| SVC                             | 0.42     | 0.50     | 0.50    | 0.25     | 0.03       |
| Dummy Classifier                | 0.42     | 0.50     | 0.50    | 0.25     | 0.02       |
| KNeighbors Classifier           | 0.42     | 0.47     | 0.47    | 0.35     | 0.11       |

ROC AUC, area under the receiver operating characteristic curve

### III. RESULTS

#### A. PATIENT CHARACTERISTICS

Table 1 presents the baseline characteristics of the datasets. The average age of all participants was  $52.5 \pm 18.5$  years,

and 41.3% were male. There were no significant differences in age or sex between the positive (Group 1) and negative (Group 2) responders to the HUT test in either the training or test sets. The Holter monitoring time was 23.36 hours

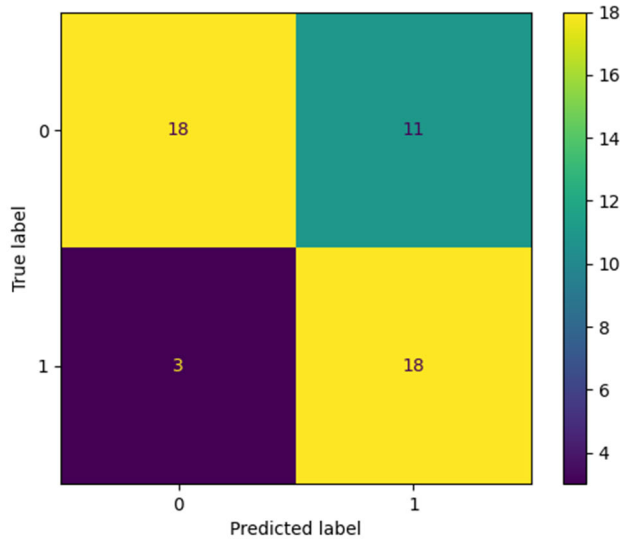


FIGURE 2. Confusion metrics for XGB classification.

TABLE 3. Metrics of XGB classification.

| Measure                   | Value  | Derivations                 |
|---------------------------|--------|-----------------------------|
| Sensitivity               | 0.8571 | $\frac{TP}{TP + FN}$        |
| Specificity               | 0.6207 | $\frac{TN}{FP + TN}$        |
| Precision                 | 0.6207 | $\frac{TP}{TP + FP}$        |
| Negative Predictive Value | 0.8571 | $\frac{TN}{TN + FN}$        |
| Accuracy                  | 0.7200 | $\frac{TP + TN}{P + N}$     |
| F1 Score                  | 0.7200 | $\frac{2TP}{2TP + FP + FN}$ |

TP, True Positive; FN, False Negative; FP, False Positive; TN, True Negative; P, Positive; N, Negative

for Group 1 and 23.44 hours for Group 2. The mean heart rate during Holter monitoring was 72 beats/min for Group 1 and 76 beats/min for Group 2. The resting hemodynamic parameters before starting HUT were similar between the two groups, excluding diastolic blood pressure in the training set where the values were  $69.9 \pm 13.1$  and  $81.4 \pm 10.4$  in Groups 1 and 2, respectively ( $p = 0.012$ ).

## B. MODEL SELECTION AND HYPERPARAMETERS

Twenty-six ML models were trained and tested on the same sets to select the best model. Among these models, the XGB classifier achieved the highest score for the data, as detailed in Table 2. The hyperparameters of the XGB classifier were tuned using a grid search for the following combinations and initial values based on AUROC performances via a 5-fold validation test: Colsample\_bytree, representing the subsample

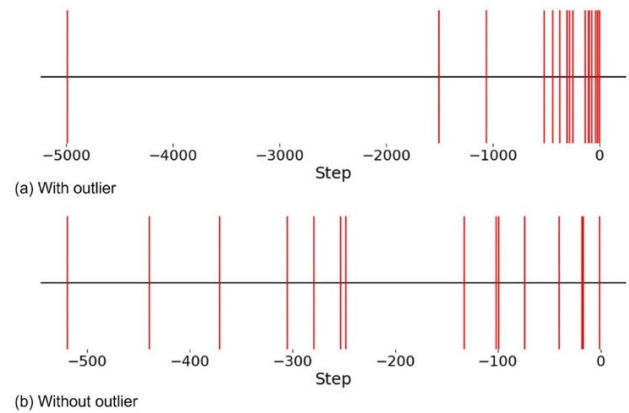


FIGURE 3. Distribution of  $I$  for the test set includes outliers that exceed 1,000, and (b) does not include outliers.

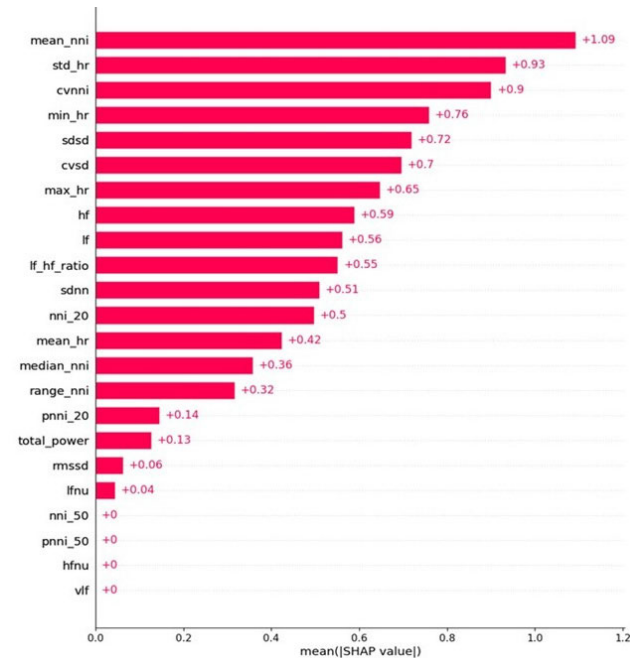
ratio of columns when constructing each tree, set to 0.95; learning\_rate, determining the step-size shrinkage used in the update which prevented overfitting, set to 0.999; max\_depth, specifying the maximum depth of a tree (higher values lead to increased model complexity and potential to overfit), set to 9; and min\_child\_weight, denoting the minimum sum of the instance weights needed in a child (by increasing its value, the model becomes more conservative), was set to 3. Other XGB parameters were excluded from this optimization process due to their minimal impact on the results.

## C. MODEL CLASSIFICATION

Model evaluation was conducted on a test set consisting of 21 positive and 4 negative subjects using optimized datasets and model parameters. Positive windows were selected from Group 1 without any augmentation, while negative windows were selected from the tilt state of the HUT test in Group 2, and windows without the HUT test in Groups 1 and 2. The test set comprised 21 positive and 29 negative windows. The results presented in Fig. 2 and Table 3 show that the model achieved an accuracy of 0.7200, AUC of 0.8013, sensitivity of 0.8571, and specificity of 0.6207.

## D. SYNCOPED TIME PREDICTION

To investigate the feasibility of predicting syncope episode occurrence in advance, the trained model was evaluated using windows from the test set, starting with  $w_s$  and stepping back one R-peak at a time until it reached window  $w_{s-l}$ , where the first negative window was detected. Fig. 3(a) shows the distribution of  $I$  for the test set, where 0 represents the syncope episode time (0 steps). On average, the model made positive predictions approximately 8 min before the onset of syncope, corresponding to 497.95 R-peak steps. Six of the 21 subjects were excluded as outliers, either because they did not receive positive predictions, or because their  $I$  value exceeded 1,000. For the remaining 15 subjects, the model made positive predictions approximately 3 min (193.2 steps on average) before syncope occurrence, as shown in Fig. 3(b).



**FIGURE 4.** SHAPley Additive exPlanations (SHAP) values for XGB classification A. Higher scores have a greater impact on classification.

#### E. FEATURE IMPORTANCE

In our study, SHAP importance values were employed to determine the most important HRV features for identifying syncope windows in the trained model. These values indicated the extent to which each feature contributed to the syncope prediction of the model. We generated a bar plot that displayed the SHAP values of the 23 HRV features in descending order, as shown in Fig. 4. The y-axis represents the features, and the x-axis represents their respective SHAP values. The average of all intervals between normal beats excluding ectopy or noise intervals (mean NN), standard deviation of heart rate (Std HR), coefficient of variation equal to the ratio of the standard deviation of differences between adjacent RR-intervals divided by mean NN (CVNNi), minimum heart rate (Min HR), and standard deviation of differences between adjacent RR-intervals (SDSD) were important features of our study.

#### IV. DISCUSSION

In the present study, we developed an ML-based VVS prediction model utilizing only HRV and attempted to predict syncope timing. Among the 26 ML algorithms evaluated, the XGB classifier exhibited the highest accuracy and predictive capability. The performance of the ML model in predicting VVS using HRV demonstrated an accuracy of 0.72, AUC of 0.8013, sensitivity of 0.8571, and specificity of 0.6207. The feasibility of predicting syncope onset was investigated by evaluating a trained model using windows from the test set. The model predicted positive 193.2 steps (approximately 3 min) before syncope occurrence, on average, which is significant as it is enough time to prevent secondary injuries

from syncope. Another strength of this study is that it only used HRV to predict VVS.

VVS, a common form of neurally mediated reflex syncope, is marked by an abrupt decrease in blood pressure and heart rate; often leading to syncope [1], [2]. VVS is characterized by a disturbance of the autonomic nervous system, including an initial increase in sympathetic activity, followed by an increase in vagally mediated parasympathetic activity, and withdrawal of sympathetic activity [5], [6]. Previous studies have identified dysfunctional baroreflex regulation, abnormal pressure receptor sensitivity, central nervous system processing abnormalities, and failed pressure regulatory mechanisms in patients with VVS [21]. The detection of these changes before symptom onset presents an opportunity to develop predictive systems for VVS.

A previous study showed that an algorithm based on the spectral analysis of heart rate and systolic blood pressure (SBP) variability had a 95% sensitivity and 93% specificity for predicting VVS in 1,150 patients who underwent the HUT test [9]. The average prediction time was  $128 \pm 216$  s, with a median of 59 s. They simultaneously analyzed the heart rate (RR interval), SBP, HRV, and blood pressure variability. In this study, the predictive accuracy was found to be highest when SBP was given 2.5 times more weight than RR, HRV, and blood pressure variability. The predictive accuracy of VVS using HRV alone was significantly lower than when including SBP, emphasizing the importance of blood pressure in VVS episode prediction. In a separate study, the findings suggested that performing short-term HRV analysis at the beginning and end of the first 20 min of the HUT test could help predict which patients would experience syncope after the administration of nitroglycerin per the Italian protocol, even before drug administration [10]. Recently, wearable devices have gained popularity for providing alarms in various situations, with the use of HRV becoming increasingly common. However, measuring blood pressure via a wearable device in real-life situations is challenging.

With the recent incorporation of HRV measurement functions into wearable devices, HRV analysis has become more accessible. Implementing the developed algorithm in wearable devices may help prevent fatal events, such as head trauma due to syncope, by offering early warnings of an VVS episode.

HRV analysis is a well-established approach to assess dynamic changes in the autonomic modulation of cardiovascular function, and has been combined with the HUT test to understand syncope development mechanisms and predict HUT test outcomes. In previous studies, the reported correlation with syncope varied greatly depending on the type of HRV parameters used, such as the time or frequency domains. Efremov et al. [10] revealed that a notable reduction in HF power can be observed during the initial 20 min of the HUT test, predicting a positive response to nitroglycerin and indicating the development of syncope. In this study, feature importance was confirmed by estimating the SHAP value of each HRV parameter. We found that time-domain parameters

(such as mean NN, Std HR, and CVNNi) contributed more than frequency-domain parameters (such as HF and LF).

The present study had some limitations; first, this was a retrospective analysis conducted at a single center with a small number of patients, making it susceptible to data selection and measurement bias. Additionally, there may be other factors influencing VVS, which could lead to the possibility of overestimation. Second, the ML-based models developed in this study were not externally validated. Although the model was divided into training and validation sets to avoid overfitting, complete avoidance was not guaranteed. Therefore, future studies should conduct performance tests using separate test data that were not part of the current model development process. Third, addressing the small sample size and imbalance of positive/negative groups is crucial. Thus, future studies should use larger and separate test data sets for performance evaluation, ensuring robustness in model assessment.

## V. CONCLUSION

The ML model utilizing only HRV demonstrated high accuracy in predicting VVS. Additionally, this model was able to predict syncope 193.2 beats (approximately 3 minutes) before its occurrence. The implementation of this approach in real-world practice could help prevent unforeseen accidents by improving the prediction of VVS using HRV.

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(Hyeon Bin Lee and Gangin Park are co-first authors.)

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