Ventricular Electrical Dyssynchrony as a Predictor of Heart Failure

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Abstract

Heart failure (HF) is a growing global health concern, increasingly affecting younger populations. While several clinical criteria exist for HF diagnostic, a reliable electrocardiographic (ECG) marker for early HF prediction is still lacking.

In this study, we introduce ventricular electrical dyssynchrony (VED)—a measure of interventricular conduction delay derived from precordial ECG leads—as a potential predictor of HF. Leveraging data from the MIMIC-IV clinical and ECG database (19,974 subjects, including 2,180 who developed HF based on ICD9/10 coding), we assessed the association between VED and future HF events using multivariate Cox regression. VED was categorized into three groups: Low VED (–20 to 15 ms), High-Negative VED (<–20 ms), and High-Positive VED (>15 ms). Compared to the Low VED group, the High-Negative VED group showed a hazard ratio (HR) of 1.55 (95% CI: 1.21–1.97, p <0.001), and the High-Positive VED group had an HR of 1.94 (95% CI: 1.49-2.52, p <0.001), after adjusting for age, sex, and QRS duration.

These findings highlight VED as a promising ECG-based marker that could enhance early risk stratification for heart failure; however, further validation incorporating standard clinical HF markers is necessary to confirm its diagnostic utility.

1. Introduction

Heart failure (HF) has been described as an emerging epidemic, with the number of affected individuals continuing to rise. This trend is driven not only by an aging population but also by an increasing rate of obesity. While incidence has stabilized in some groups, HF is becoming more common in younger adults. At the same time, there is a growing proportion of patients with heart failure with preserved ejection fraction (HFpEF), a form that is often more difficult to detect and manage [1].

Several clinical and research criteria have been proposed for diagnosing HF, each with its own advantages and limitations. These include clinical signs and symptoms (which often lack sensitivity), echocardiographic measures (which can be subject to high variability), natriuretic peptide levels (NTproBNP) (which may be normal in many patients with HFpEF), or chest X-rays [1]. What remains lacking in this field is a reliable electrocardiographic (ECG) marker for identifying heart failure. Despite being a simple, noninvasive, and widely used diagnostic tool in cardiology, the ECG has not become standard in diagnosing HF. Ventricular electrical dyssynchrony (VED)—a quantitative measure of the delay between right and left ventricular activation—has been shown to predict heart failure and all-cause mortality in patients enrolled in the MADIT-CRT trial, and to identify individuals who may benefit from cardiac resynchronization therapy [2]. We hypothesize that ventricular conduction abnormalities may precede the clinical manifestation of heart failure. In this study, we introduce a VED metric, derived from precordial ECG leads (V1–V6) using a deep neural network, as an early predictor of heart failure, utilizing data from the MIMIC-IV clinical database.

2. Dataset

In this study, we utilized the MIMIC-IV Clinical Database [3, 4] and the MIMIC-IV-ECG database [5], along with the MIMIC-IV-ECG-Ext-ICD database, which links the clinical and ECG databases [6]. These databases contain data recorded between 2008 and 2022. MIMIC-IV is derived from two in-hospital database systems: a custom hospital-wide electronic health record (EHR) system and an intensive care unit (ICU) database. If a patient appears in the MIMIC-IV Clinical Database, all available ECG waveforms from that patient were retrieved and stored in the MIMIC-IV-ECG database. This dataset includes ECGs recorded between 2008 and 2022 from various hospital settings, including the emergency department, inpatient wards (including the ICU), and outpatient care centers at Beth Israel Deaconess Medical Center (BIDMC).

The databases are linked through study and subject IDs, enabling ECGs to be matched with corresponding hospital admissions. The MIMIC-IV databases also contain ICD-9/10 diagnostic codes assigned to each hospital stay, representing diagnoses determined by trained professionals based on a review of signed patient notes.

For this study, we focused on ECGs from patients who had never been diagnosed with heart failure (HF) and excluded all subjects with any prior HF-related admissions based on ICD-9/10 codes. In addition to diagnostic codes, we extracted demographic information, including patient age at the time of ECG recording and sex. All ECGs in the dataset are 10 seconds long, sampled at 500 Hz. Since a single subject could have multiple ECGs, and survival analysis assumes independent observations, we selected only the first ECG recorded for each subject.

The primary objective of this study was to predict HF-related hospital admission in individuals with no prior history of HF. We defined two subject groups: (1) those who remained HF-free throughout the study period and (2) those who were later diagnosed with HF, as identified by ICD codes. HF diagnoses were extracted based on ICD-10 codes beginning with "I50" (e.g., I500, I501) and ICD-9 codes beginning with "428". For survival analysis, we measured time-to-event for outcomes: for the no-HF group, we recorded the time from the ECG to the subject's last documented appearance in the database (any type of hospital admission), and for the future-HF group, we recorded the time from the ECG to their first HF-related hospital admission (mean follow-up time 4.6 ± 3.6 years). We excluded subjects who died during the study period before developing HF.

In total, the study included 19,964 subjects, each contributing a single ECG, 49% being male and having a mean age of 57.6 ± 16.6 years. Of these, 2,180 people developed HF by the end of the study. The study included a 12-year follow-up period.

Additionally, MIMIC-IV contains supplementary tables, such as `chartevents`, which records bedside monitor data. When available, we extracted body mass index (BMI), as obesity is significant HF-related comorbidity. The BMI subanalysis included 3,637 subjects, with 449 later diagnosed with HF.

3. Method

In this study, we initially trained a deep neural network to estimate VED from ultra-high-frequency ECG data, as the MIMIC-IV database does not support the standard UHF-ECG processing required for direct VED computation. We then applied the trained model to MIMIC-IV data and performed multivariate Cox regression to assess the association between VED and survival outcomes, focusing on heart failure prediction.

3.1. Computation of Ventricular Electrical Dyssynchrony

Ultra-high-frequency ECG (UHF-ECG) is a technique that enables more precise identification of the temporal-spatial distribution of ventricular electrical depolarization and the assessment of ventricular electrical dyssynchrony (VED) [7]. By comparing depolarization activation patterns across different ventricular segments (leads) and computing interlead depolarization delay, ventricular electrical dyssynchrony can be quaintified in milliseconds.

The process of computing ventricular electrical dyssynchrony begins with analyzing ECG signals at high sampling frequencies—5 kHz in the original method design—followed by the detection of QRS complexes, which are then categorized based on their morphology. This approach primarily focuses on the dominant QRS morphology, meaning that only QRS complexes from the major morphological group are utilized in further analysis. Next, the Fourier and Hilbert transforms are applied to compute 16 amplitude envelopes across the 150–1000 Hz frequency range. These amplitude envelopes are then averaged with an R-wave trigger and smoothed using a 0–40 Hz passband filter (UHFQRS). The VED parameter is defined by the maximum time differences in the positions of centers of gravity within these envelopes, specifically between leads V1 and V6 [2,7]. This computed VED serves as the ground truth for training a neural network on high-frequency ECG that has been downsampled to a standard diagnostic sampling rate (500 Hz).

3.2. Deep Learning Model

Although UHF-ECG provides valuable information about ventricular dyssynchrony, high frequency components are not available in standard clinical settings, where ECGs are typically recorded at 500 Hz. To bridge this gap, we developed DyssynchronyNet [8], a neural network designed to predict UHF-ECG-derived VED from conventional 500 Hz ECG recordings.

The model was trained on UHF-ECG recordings downsampled from 5 kHz to 500 Hz. The preprocessing steps included downsampling, signal differentiation, and z-score normalization. The input to the network consisted of six precordial leads (V1–V6), formatted as a $6 \times 5{,}000$ matrix representing a 10-second segment sampled at 500 Hz.

The data used to develop DyssynchronyNet was provided by VDI Technologies and included three distinct sources of private data. DyssynchronyNet was trained and validated using 3,857 recordings from one medical center and 2,507 recordings from a second medical center. The final model was evaluated on an independent test set consisting of 583 recordings from a third independent medical center. All recordings across these datasets were sampled at a frequency of 5 kHz. Since the original ECG recordings had an average duration of 2 minutes, during training, we randomly selected five 10-second segments per recording in each epoch to improve robustness.

DyssynchronyNet is a deep convolutional neural net-

work with stacked convolutional layers using batch normalization and ReLU activation. Max pooling enables hierarchical feature extraction, culminating in global max pooling and fully connected layers that produces VED. Dropout is used to improve generalization and reduce overfitting.

To validate the model's ability to predict VED before transitioning to the MIMIC-IV dataset, we evaluated its performance on the independent test set, obtaining a mean absolute error (MAE) of 13.71 ± 12.05 ms.

3.3. Application to MIMIC-IV and Survival Analysis

After training the model on ultra-high-frequency ECG data, we applied DyssynchronyNet to ECG recordings from the MIMIC-IV database to estimate VED values.

To evaluate the clinical significance of VED, we performed a multivariate Cox regression analysis to assess its impact on HF prediction.

The Cox proportional hazards regression model is given by: $h(t \mid X) = h_0(t) \exp(\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_p X_p)$

where $h(t \mid X)$ is the hazard function at time t, $h_0(t)$ is the baseline hazard, and $\beta_1, \beta_2, \ldots, \beta_p$ are the regression coefficients. The computed risk is represented by the linear predictor: $\eta = \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_p X_p$ which estimates the likelihood of an event occurring.

The input variables for Cox regression included VED, along with QRS duration (QRSd) to compare its predictive performance to VED. Additional covariates included age and sex (Male = 1, Female = 0). Age was standardized using z-score normalization, and both VED and QRSd were categorized. VED was divided into three groups: Low-VED (-20 to 15 ms), High-negative-VED (<-20 ms), and High-positive-VED (>15 ms). Histogram of VED for our subset of MIMIC-IV ECGs and its categorization could be observed in Figure 1. Similarly, QRSd was categorized as Low QRSd (0–100 ms), Medium QRSd (100–130 ms), and High QRSd (>130 ms).

Given that obesity is a recognized comorbidity and risk factor for heart failure (HF), we conducted an additional Cox regression sub-analysis on subjects with available BMI data. BMI was treated as a continuous variable and standardized using z-score.

4. Results

The results of the multivariate Cox regression are presented in Table 1. The corresponding Kaplan-Meier curve, stratified by VED categories, is shown in Figure 2. We also compared two Cox regression models: one using only covariates for heart failure prediction (Age, Sex, and QRSd) and another incorporating VED along with these covariates. The Akaike Information Criterion (AIC), which evaluates model fit while penalizing complexity, yielded values of 35,298 and 35,276, respectively, indicating an improvement in the model when VED was included.

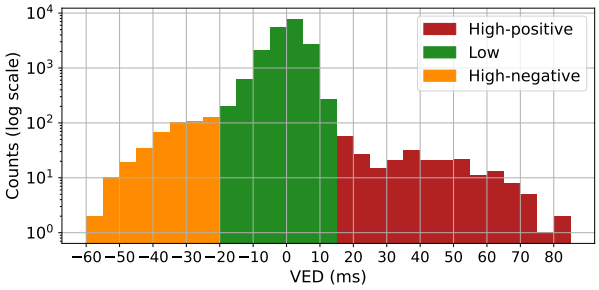

Figure 1. A distribution the predicted values of ventricular electrical dyssynchrony (VED) in the MIMIC-IV database. The colors indicate three VED categories: Low-VED (green), High-negative-VED (orange), and High-positive-VED (red).

Next, we conducted a subanalysis including BMI as a covariate for a subset of subjects, as shown in Table 2. Comparing the AIC values of the model using only covariates (Age, Sex, QRSd, and BMI) versus the one incorporating VED, we observed a decrease in AIC from 4,768 to 4,761, further suggesting an improvement in model performance.

Table 1. Results of Cox-regression.

Covariate	Hazard ratio	p-value
VED <-20 ms	1.55 (1.21 -1.97)	p<0.001
VED >15 ms	1.94 (1.49 - 2.52)	p<0.0001
QRSd (100-130] ms	1.38 (1.24 - 1.53)	p<0.0001
QRSd >130 ms	1.40 (1.15 - 1.70)	p<0.0001
Age	2.09 (1.98 - 2.21)	p<0.001
Sex	1.06 (0.97 - 1.16)	p = 0.21

Table 2. Results of Cox-regression including BMI.

Covariate	Hazard ratio	p-value
VED <-20 ms	1.89 (1.19 - 3.02)	p<0.01
VED >15 ms	2.33 (1.31 - 4.14)	p<0.01
QRSd Low-Medium	1.51 (1.2 - 1.91)	p<0.001
QRSd Low-High	1.24 (0.84 - 1.83)	p=0.23
Age	1.90 (1.66 - 2.18)	p<0.001
Sex	0.79 (0.64 - 0.97)	p = 0.03
BMI	1.20 (1.08 - 1.33)	p<0.001

5. Discussion and Conclusion

The results of the multivariate Cox regression analysis highlight the significant predictive value of VED as

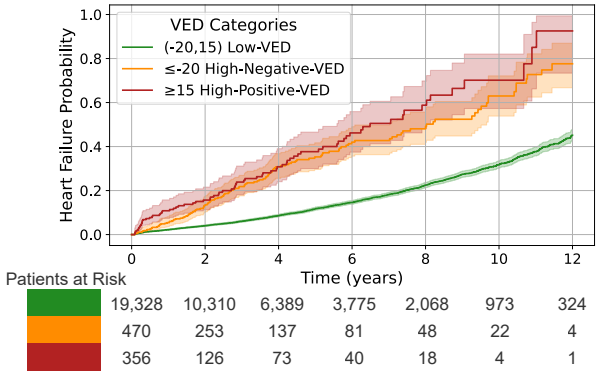

Figure 2. Cumulative incidence curve for heart failure prediction stratified by three categories of ventricular electrical dyssynchrony (VED). The curve colors represent the VED groups: Low VED (green), High-negative VED (orange), and High-positive VED (red).

a covariate for heart failure risk. In the main analysis, the hazard ratios for the VED categories — high negative (1.55, $p<0.001$) and high positive (1.94, $p<0.0001$) — indicate a strong association with heart failure outcomes. Additionally, the subanalysis including BMI showed hazard ratios of 1.89 ($p<0.01$) for high negative and 2.33 ($p<0.01$) for high positive VED, further reinforcing this link. These findings suggest that delays in ventricular depolarization may contribute significantly to the development of heart failure. Consequently, VED shows promise as a novel biomarker for heart failure, complementing traditional clinical covariates.

When comparing the inclusion of VED to other covariates, the results, particularly in terms of AIC, underscore the added value of incorporating VED into the model.

While our study shows that VED can serve as an effective predictor of heart failure risk, several limitations must be acknowledged. First, the analysis relies solely on ICD codes without the support of a longitudinal follow-up. Additionally, our dataset lacks important clinical indicators such as the NYHA classification, laboratory findings, and key diagnostic parameters like ejection fraction and NT-proBNP levels, which are commonly used to evaluate and confirm heart failure. Although NT-proBNP data were available for a subset of patients, the data were too sparse and did not yield statistically significant results; therefore, NT-proBNP was not included as a variable in our analysis.

Despite these limitations, the findings of this study provide a strong foundation for future research on ventricular electrical dyssynchrony as a precursor of heart failure, with the potential to improve clinical risk stratification.

Acknowledgments

The research was supported by the Czech Technological Agency grant number FW06010766 and the project RVO:68081731 by the Czech Academy of Sciences. We would like to thank VDI Technologies for generously supplying the data used in this study.

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