Information-Theoretic Characterization of Short-Term Heart Rate Variability in Ischemic and Non-Ischemic Heart Failure Patients During Exercise

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Abstract

Heart failure with reduced ejection fraction (HFrEF) remains a major cause of morbidity and mortality worldwide. The underlying etiology, ischemic (IHF) or non-ischemic (NIHF), influences disease course, autonomic control and therapy response. This study investigates whether nonlinear information-theoretic heart rate variability (HRV) metrics can reveal etiology-specific differences in cardiac autonomic dynamics under exercise stress overlooked by traditional methods.

Fifty-two transplant-listed HFrEF patients underwent electrocardiogram recordings at rest and during graded exercise. RR interval time series were derived and HRV features computed across three phases: rest, early, and late exercise. Metrics included conventional time- and frequency-domain indices and entropy-based measures of complexity, Conditional Entropy (CE) and Self-Entropy (SE). Traditional HRV indices showed expected exercise-related trends but no group differences. In contrast, information-theoretic metrics revealed distinct autonomic signatures: NIHF patients displayed higher CE and lower SE during late exercise, indicating greater HRV complexity and reduced predictability. In conclusion, information-theoretic HRV analysis revealed differences missed by conventional methods, possibly enhancing risk assessment and understanding of autonomic dysfunction in HFrEF.

1. Introduction

Heart failure with reduced ejection fraction (HFrEF) remains a major public health concern, affecting millions worldwide and contributing significantly to morbidity, mortality and healthcare burden [1]. This condition can arise from a broad spectrum of underlying causes.

Among HFrEF patients, etiology plays a critical role in disease progression and clinical outcomes. Ischemic heart failure (IHF), resulting from coronary artery disease, differs markedly from non-ischemic heart failure (NIHF), which encompasses a range of causes including idiopathic, valvular, genetic and inflammatory cardiomyopathies. These etiological differences are known to influence structural remodeling, autonomic regulation and exercise tolerance, which are key prognostic factors in advanced heart failure [2].

Heart rate variability (HRV) has been established as a non-invasive tool for assessing autonomic nervous system activity and cardiovascular health [3]. Traditional time- and frequency-domain HRV measures have shown value in stratifying heart failure risk and evaluating therapy response [4]. However, these conventional approaches may overlook complex dynamics in heart rate regulation, especially under stress conditions such as exercise.

In recent years, nonlinear and information-theoretic methods have been employed for their ability to capture subtle and complex patterns in physiological signals, which may provide insight into underlying pathophysiological mechanisms [5, 6]. Entropy-based measures provide a framework to quantify the unpredictability and complexity of RR interval dynamics beyond linear variability metrics [7].

Despite increasing interest in nonlinear HRV analysis, the potential of these metrics to differentiate between heart failure etiologies during exercise remains largely unexplored. Investigating these distinctions could yield valuable insights into etiology-specific autonomic regulation patterns and support more accurate risk stratification, particularly in transplant-listed populations. Furthermore, advancements in HRV analysis using ultra-short-term (UST) electrocardiogram (ECG) recordings, typically defined as segments shorter than five minutes, offer promising opportunities for efficient real-time assessment of cardiac dynamics. This approach has been shown to reliably capture physiological changes [8, 9], potentially enhancing both clinical decision-making and continuous monitoring in everyday settings.

The present study aims to characterize and compare the nonlinear information-theoretic features of HRV in IHF and NIHF HFrEF patients during resting and exercise conditions. By applying entropy-based metrics and examining their evolution across distinct exercise phases, we seek to identify etiology-specific autonomic modulation patterns that may remain undetected through conventional HRV analysis. The description of these differences could have important clinical implications, particularly in high-risk transplant-listed individuals. Such insights may contribute to precision monitoring, guide personalized rehabilitation strategies and enhance prognostic modeling in advanced heart failure management.

2. Materials and Methods

2.1. Patients

For this study, 52 patients (39 males, 13 females; age: 53.17 ± 9.46 years; Body Mass Index: 27.52 ± 4.42 kg/m^2) with advanced heart failure with reduced ejection fraction (HFrEF), all listed for heart transplantation, were enrolled. All participants were undergoing beta-blocker therapy at the time of evaluation.

The cohort was stratified by etiology into two groups: 33 patients with ischemic HFrEF (IHF) and 19 patients with non-ischemic HFrEF (NIHF). Demographic and clinical variables, including age, gender, body mass index (BMI), New York Heart Association (NYHA) functional class and concurrent pharmacological therapies such as ACE inhibitors and ARNI, were assessed to ensure that potential confounding factors did not bias the results.

2.2. Acquisition Protocol

Electrocardiogram data were acquired using a PC-ECG 1200 (Wireless 12-Lead ECG, NORAV Medical, Germany) system, configured in a standard 12-lead setup with a sampling frequency of 500 Hz. Recordings were performed continuously across two phases: a resting baseline and a graded exercise protocol. During the resting phase, participants remained seated and ECG signals were recorded for 3 minutes to capture baseline cardiac activity. Afterwards, participants underwent a 10-minute exercise test on a calibrated cycloergometer following a ramp-like protocol, where workload was progressively increased to induce a continuous rise in cardiovascular effort. The ramp profile was individually tailored based on each subject's age, physical condition and clinical status at the time of testing, with the goal of enabling participants to complete the entire duration of the exercise protocol.

2.3. HRV Analysis

HRV parameters were derived from segments of 150 consecutive heartbeats extracted from the resting-state ECG recordings. For the exercise condition, the first and last 300 heartbeats were selected to represent the early and late phases of the working period, respectively. Accordingly, three distinct phases were analyzed and compared: Rest, Early exercise and Late exercise. R-peak detection was performed using the Pan-Tompkins algorithm, and all results were visually inspected to ensure accuracy. Manual corrections were applied in cases of misidentified R-peaks or in the presence of ectopic beats. Recordings exhibiting excessive noise or poor signal quality were excluded from further analysis to ensure the reliability of HRV computations.

The RR interval time series, defined as the time differences between successive R-peaks, were computed for each segment. Time-domain HRV metrics included the mean (MeanRR) and standard deviation (SDRR) of RR intervals, serving as basic statistical descriptors of cardiac timing variability. These time series were then normalized by subtracting the mean, followed by the application of an autoregressive high-pass filter to remove slow baseline trends. Frequency-domain analysis was conducted to evaluate the oscillatory components of HRV within the low-frequency (LF, 0.04–0.15 Hz) and high-frequency (HF, 0.15–0.4 Hz) bands. Power spectral density (PSD) of the RR interval series was estimated using the non-parametric Blackman-Tukey method, applying a Hamming window and a bandwidth of 0.04 Hz. Afterwards, the LF to HF ratio (LF/HF) was computed as an indicator of sympathovagal balance [3].

In addition, information-theoretic measures were employed to explore the complexity of cardiac dynamics. Specifically, Conditional Entropy (CE) and Self-Entropy (SE) were calculated to quantify the variability of RR intervals [10], using a k-nearest neighbor estimator with embedding dimension m = 2 and k = 10 neighbors [11].

Etiology HFrEF	IHF (19)	NIHF (33)
Age [years]	56.4 ± 8.25	51.3 ± 9.7
Sex [M/F]	15 / 4	22 / 9
BMI [kg/m^2]	26.9 ± 3.7	27.8 ± 4.8
NYHA Class [0-4]	2.6 ± 0.6	2.6 ± 0.6
ACE [%]	31.6	39.4
ARNI [%]	52.6	51.5

Table 1. Demographic and clinical characteristics of patients with Ischemic Heart Failure and Non-Ischemic Heart Failure. No statistically significant differences were observed between groups.

Group comparisons were performed using a two-sided non-parametric Wilcoxon rank-sum test, with statistical significance set at $p < 0.05$.

3. Results

First, in order to ensure group comparability and minimize potential confounding bias, statistical analyses were performed to assess differences in baseline demographic and clinical characteristics. No statistically significant differences were observed between the groups. Table I summarizes the distribution of these parameters.

Figure 1 illustrates the group-wise comparison of time- and frequency-domain HRV parameters across the three stages: Rest, Early exercise and Late exercise. No statistically significant differences were observed between the IHF and NIHF groups at any stage. As expected, a progressive decrease in mean RR interval was evident with increasing exercise intensity. Additionally, a narrowing of the SDRR distribution was noted during the Late exercise phase, reflecting reduced overall variability under higher cardiovascular demand. However, no consistent trends or significant group differences were detected in the analyzed parameters. Similarly, when considering the LF/HF ratio, no differences between groups were observed.

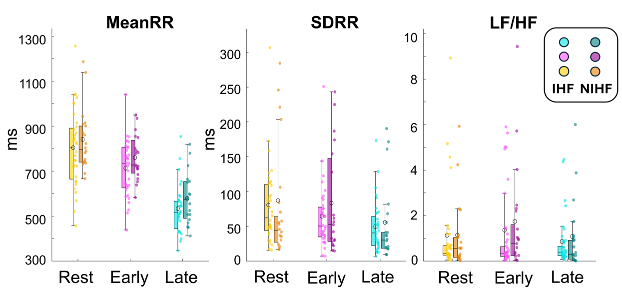

Figure 1. Time- and frequency-domain HRV parameters computed for IHF and NIHF patients at Rest, Early and Late exercise phases. No statistically significant differences were observed.

Figure 2 presents the distribution of information-theoretic metrics across the three exercise stages, Rest, Early exercise and Late exercise, for both IHF and NIHF patient groups. In contrast to conventional HRV measures, this domain reveals a clearer trend. As exercise intensity increases, differences between the two groups become more pronounced, with statistically significant differences emerging during the Late exercise phase, corresponding to peak cardiovascular demand.

Notably, CE values were significantly higher in NIHF patients compared to IHF patients during the last exercise stage, with this divergence already beginning to emerge during the Early exercise phase. Conversely, SE showed an opposite pattern, with lower values in NIHF patients relative to IHF, also reaching statistical significance in the Late exercise phase.

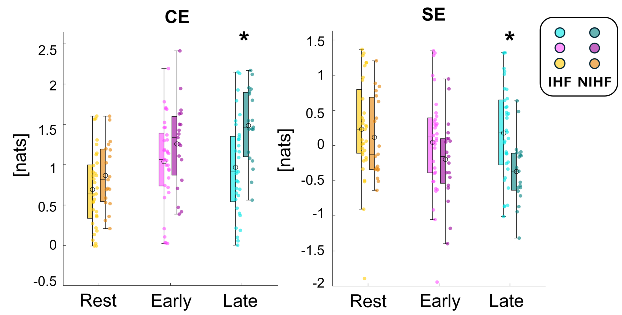

Figure 2. Information-theoretic-domain HRV parameters computed for IHF and NIHF patients at Rest, Early and Late exercise phases. Statistically significant differences ($p < 0.05$) are reported as $*$.

4. Discussion

Our results underscore the value of model-free HRV analysis in revealing etiology-specific differences in cardiac autonomic regulation during exercise from UST-ECG recordings. Conventional time- and frequency-domain metrics, although sensitive to general changes in heart rate dynamics with increasing workload, failed to distinguish between IHF and NIHF HFrEF populations. In contrast, information-theoretic entropy measures of dynamical complexity, i.e. CE and SE, uncovered divergent autonomic patterns that became prominent under cardiovascular stress.

During the late phase of exercise, NIHF patients demonstrated significantly higher CE values, indicative of increased complexity in RR interval time series. Moreover, SE values were lower in NIHF patients, pointing to decreased regularity in their heart rate dynamics. This may suggest a more adaptable or less constrained autonomic response to exertion. In fact, these contrasting patterns, higher CE and lower SE, suggest a more flexible yet less stereotyped autonomic output in NIHF, potentially linked to preserved or compensatory neural control mechanisms. Conversely, IHF patients exhibited lower CE and higher SE during peak effort, reflecting reduced complexity and greater internal predictability when compared to NIHF subjects, a pattern consistent with impaired autonomic adaptability.

Although sympathetic activation in chronic heart failure has traditionally been considered independent of underlying etiology [12], our findings are in line with previous evidence linking ischemic etiology to diminished HRV complexity and blunted sympathetic responsiveness under load [13]. In fact, these distinctions were only statistically significant under exercise conditions, emphasizing the importance of analyzing HRV across varying levels of exercise intensity to capture subtle physiological adaptations.

Notably, ischemic patients appear more vulnerable to potentially fatal ventricular arrhythmias, often triggered by the post-infarction scar tissue [14]. As a result, these patients are more frequently candidates for prophylactic implantation of an implantable cardioverter-defibrillator (ICD). This observation supports the idea that autonomic dysfunction, as captured by entropy-derived HRV metrics, might have prognostic value in identifying individuals at greater risk of malignant ventricular arrhythmias. Such influence from the autonomic system could could contribute to the predictionin of life-threatening ventricular arrhythmias, which are relatively common in patients with HFrEF.

5. Conclusion

This preliminary study demonstrates that the implementation of nonlinear information-theoretic metrics in a clinical setting can enhance the characterization of cardiac dynamics in HFrEF patients. These advanced measures offer a promising approach for uncovering autonomic regulation patterns that may not be detected through traditional HRV analysis.

However, the study has several limitations. First, despite the well established reduction in HRV among heart failure patients compared to healthy individuals, the absence of a control group limits the contextualization of our findings. Including a cohort of healthy subjects would strengthen the characterization of disease-specific alterations in cardiac autonomic function. Second, the sample size remains relatively small and a larger cohort would enhance statistical power and generalizability. Furthermore, future works should focus on investigating whether entropy measures can serve as predictive markers for ventricular arrhythmias or for appropriate implantable cardioverter-defibrillator activation in this population.

Finally, the integration of additional physiological parameters, such as metabolic and respiratory data obtained during cardiopulmonary exercise testing, could provide a more comprehensive view of cardiovascular regulation and its relationship to autonomic dysfunction.

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