HRV-Derived Autonomic Responses to Noradrenaline Differentiate ICU Mortality Outcomes

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Abstract

Critically ill patients in the Intensive Care Unit (ICU) often require noradrenaline (NE) to maintain hemodynamic stability in states of vasodilatory hypotension and circulatory failure. This study investigates whether autonomic response phenotypes, quantified via heart rate variability (HRV), are associated with ICU mortality. We extracted RR intervals from ECG signals recorded by ICU monitors of patients receiving NE therapy and combined them with clinical data from the MIMIC-III database. HRV was analysed across four temporal stages relative to infusion: pre-infusion (-70 to -10 min), early infusion (+10 to +70 min), late infusion (-70 to -10 min before cessation), and post-infusion (+10 to +70 min). We stratified patients into two groups: (1) those who died in the ICU after the post-infusion stage, and (2) those discharged after this stage. We included 243 patients (24% mortality) in the analysis. Significant differences in HRV features between groups were observed at all stages except pre-infusion. The largest divergences occurred during late and post-infusion periods. Survivors exhibited a significantly higher level of HRV features related to complexity, particularly in detrended fluctuation analysis metrics such as DFA α_2 ($p < 0.01$ for late and post-infusion stages) and scale-dependent DFA exponents across a wide range of scales (16–100 for late infusion, and 20-50 for post-infusion). These findings suggest that late-stage and recovery-phase autonomic dynamics reflect physiological resilience and the capacity to restore coordinated control following hemodynamic stress. HRV-derived response phenotypes to NE may provide clinically relevant prognostic markers and support more personalised management strategies in critically ill patients.

1. Introduction

Intensive care units (ICUs) generate continuous streams of physiological data to support the management of critically ill patients. Despite this wealth of information, bedside monitoring remains largely focused on instantaneous values and predefined thresholds. The dynamic physiological response to therapeutic interventions is rarely exploited, although it may provide insights about the patient's capacity to adapt to acute stress.

Circulatory shock is a common life-threatening condition in the ICU, characterised by inadequate tissue perfusion and frequently accompanied by hypotension, with a risk of progressive organ dysfunction and death. Management commonly involves fluid resuscitation and vasopressor support, with norepinephrine (NE) as the first-line vasopressor in most forms of shock [1]. Treatment with exogenous NE mimics endogenous norepinephrine and rapidly increases dangerously low arterial blood pressure. It binds to alpha and beta receptors, triggering a sympathetic response that causes smooth muscle contraction and increases heart rate and contractile force. NE administration therefore represents not only a therapeutic intervention but also a controlled physiological perturbation during which cardiovascular adaptability can be investigated.

Heart rate variability (HRV) provides a non-invasive measure of beat-to-beat cardiovascular regulation and autonomic modulation. Beyond conventional HRV measures, detrended fluctuation analysis (DFA) characterises the temporal organisation of RR interval dynamics across different time scales. Its scale-dependent extension (sDFA) enables continuous examination of these properties across scales and has shown potential in cardiovascular risk assessment [2]. However, critical care HRV has largely been evaluated as a marker of the patient's current physiological state rather than as a dynamic response to treatment. Whether changes in multiscale HRV dynamics during vasopressor administration reflect cardiovascular adaptability and relate to clinical outcome remains largely unexplored. In this study, we investigated HRV trajectories before, during, and after NE therapy in ICU patients. We hypothesised that the cardiovascular response to NE differs between survivors and non-survivors and that scale-dependent HRV dynamics can reveal these differences beyond conventional HRV measures.

2. Methods

2.1. MIMIC-III Database

The study population was retrospectively collected from the Medical Information Mart for Intensive Care (MIMIC-III) databases available from the PhysioNet platform [3]: MIMIC-III Clinical Database (version 1.4; N=46,520 patients and 61,532 ICU stays) [4] and MIMIC-III Waveform Database Matched Subset (version 1.0; 10,282 ICU patients) [5] by combining the ECG from the bedside monitors and the tabular data, including patient demographics, administered NE timestamps, and the clinical outcome (death or discharge). Inclusion criteria were successful matching of the ECG signal with NE administration timestamps; exclusion criteria were atrial fibrillation and a working pacemaker during NE therapy, death during therapy, and low signal quality.

2.2. Norepinephrine Therapy Stages

We identified the first NE infusion episode during each ICU stay from medication records. Four 60-min analysis stages were selected relative to infusion initiation and cessation: Baseline (-70 to -10 min before initiation), Early NE infusion (+10 to +70 min after initiation), Late NE infusion (-70 to -10 min before cessation), and Post NE (+10 to +70 min after cessation). We introduced 10-min buffers around infusion initiation and cessation to account for uncertainty in documented administration times. We included only patients with available ECG waveform data covering all four stages.

2.3. Data processing and segmentation

Beat-to-beat RR intervals were extracted from ECG signals sampled at 125 Hz. ECGs were band-pass filtered (8th-order Butterworth, 4–40 Hz), and signal quality was assessed using the average-QRS method implemented in NeuroKit2; samples with quality scores < 0.5 were excluded from R-peak detection. We then identified R peaks using the NeuroKit2 implementation of the Rodrigues et al. algorithm [6].

Each 60-min analysis period was divided into six 10-min segments. Segments containing fewer than 100 RR intervals were excluded. RR intervals were further filtered using a local 31-beat rolling median (η): intervals outside $0.75\eta \leq RR_i \leq 1.5\eta$ or associated with successive changes > 200 ms were removed (this procedure were previously used in our previous work [7]). Segments with $> 20\%$ of RR intervals removed were discarded. We calculated heart rate variability (HRV) parameters separately for the remaining 10-min segments, and their median values were used to represent each 60-min period.

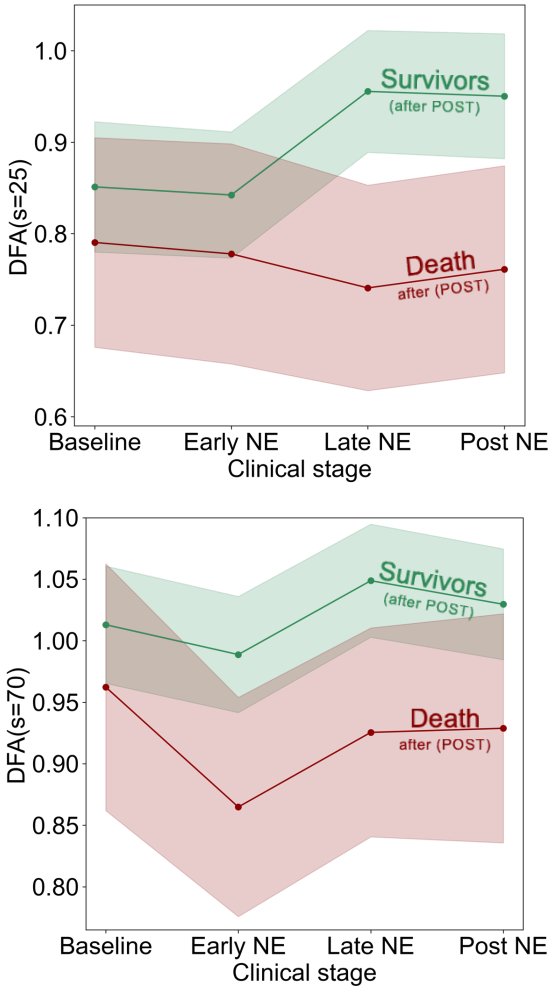

Figure 1. Averaged values of the DFA exponents for the study stages at two example scales (s=25 and s=70)

2.4. HRV analysis

HRV analysis included conventional time- and frequency-domain measures together with non-linear detrended fluctuation analysis (DFA). Time-domain measures comprised mean RR, SDRR, RMSSD, and pRR50, while frequency-domain measures included LF (0.04–0.15 Hz), HF (0.15–0.40 Hz), and the LF/HF ratio.

We used DFA to characterise the scale-dependent correlation properties of RR interval dynamics [8]. Conventional short- and long-term scaling exponents (α_1 and α_2) were estimated over scales of 4–16 and 16–64 beats, respectively. In addition, scale-dependent DFA (sDFA) was applied to estimate local scaling exponents continuously across individual temporal scales, avoiding restriction to predefined scaling ranges.

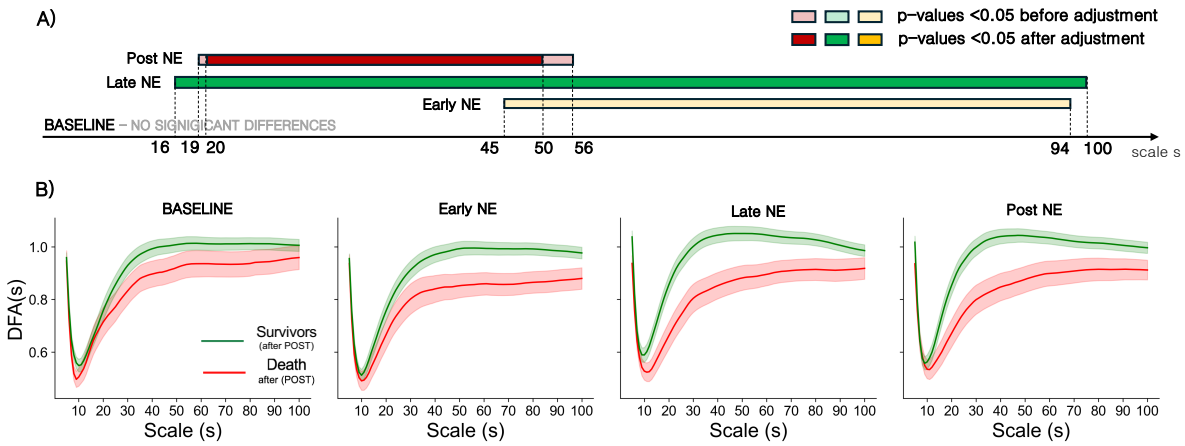

Figure 2. A) The diagram showing the scales for which the difference between mortality groups was significant for each study stage. B) The averaged DFA exponent values for each scale, study stage and mortality group.

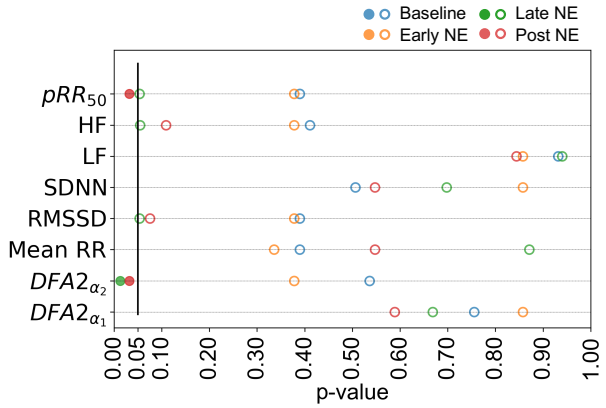

Figure 3. Multiple-comparison-corrected p-values for differences in conventional HRV parameters between patients who died in the ICU and those discharged from the ICU, calculated separately for each NE therapy stage.

We compared stratification groups at each study stage for continuous clinical and HRV-related variables using either the Student's t-test or the Mann–Whitney U test, depending on data distribution. We assessed normality using the Shapiro–Wilk test. To account for multiple comparisons across sDFA scales, p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) correction procedure. We applied the correction separately within each analysis stage. Adjusted p-values < 0.05 were considered statistically significant.

3. Results

The analysis included 243 patients receiving NE therapy, of whom 122 (50%) were female. Of these, 59 patients (24%) died in the ICU after the POST stage, while 184 were discharged alive. Patients who died were older than those discharged alive (66.1 $\pm$ 15.0 vs 61.4 $\pm$ 14.7 years, $p = 0.046$) and more frequently presented with respiratory failure (72.9% vs 52.7%, $p = 0.01$). We observed no significant between-group differences in SOFA score or shock distribution.

The biggest differences between outcome groups were observed in sDFA during the later stages of NE therapy. Survivors showed significantly higher sDFA exponents across a broad range of scales during Late NE ($s = 16$–100), with differences persisting during Post NE ($s = 21$–47). Differences were also observed during Early NE ($s = 45$–94) but did not remain significant after multiple-comparison correction. We found no significant differences during Baseline.

Analysis of changes relative to Baseline showed increasing sDFA exponents in survivors during later therapy stages, whereas values in non-survivors remained stable or decreased; however, these differences did not survive multiple-comparison correction.

Among conventional HRV measures, only pRR50 differed during Post NE, with higher values in non-survivors. Conventional DFA α_2 also differed between groups during Late NE and Post NE, supporting the scale-dependent sDFA findings.

4. Discussion

This study shows that scale-dependent HRV dynamics during NE therapy differ between ICU survivors and non-survivors. While sDFA profiles were comparable before treatment, survivors exhibited higher scaling exponents during the later stages of infusion and after its cessation, particularly across medium-to-long temporal scales. This

divergence may reflect differences in cardiovascular adaptability, suggesting that the physiological response to vasopressor therapy carries prognostic information beyond the pre-treatment state [9].

The observed pattern was more pronounced for sDFA than for conventional HRV measures, for which between-group differences were limited. Unlike conventional metrics describing the magnitude of RR variability, sDFA characterises its temporal organisation across multiple scales. The increase in sDFA observed in survivors may therefore indicate a greater capacity to maintain or restore coordinated cardiovascular regulation during haemodynamic stress. From this perspective, NE administration may also act as a physiological challenge that reveals differences in regulatory reserve between patients. Continuous assessment of these response trajectories could complement conventional haemodynamic monitoring and help identify patients at increased risk of adverse outcomes.

Several limitations should be considered. The retrospective design precludes causal interpretation, while uncertainty in infusion timestamps and residual confounding from concurrent ICU interventions may have influenced the observed HRV trajectories. Excluding patients with atrial fibrillation or paced rhythms also limits generalisability. Prospective studies with higher-resolution treatment and haemodynamic data and external validation are needed to determine whether sDFA-derived response patterns provide independent prognostic information and can support personalised monitoring during vasopressor therapy.

5. Conclusion

Norepinephrine therapy may act not only as haemodynamic support but also as a physiological challenge that reveals differences in cardiovascular adaptability. Scale-dependent HRV analysis identified distinct response trajectories between ICU survivors and non-survivors, with survivors showing higher sDFA exponents during the later stages of therapy and after infusion cessation. These findings suggest that sDFA may capture aspects of cardiovascular regulatory dynamics not reflected by conventional HRV measures and could contribute to non-invasive assessment of physiological adaptability and risk during critical illness.

Acknowledgments

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