Characterization of Heart Rate Variability Dynamics in Heart Failure Patients Admitted to Intensive Care Unit

Maximiliano Mollura*[1], Christian Niklas*[2], Stefanie Messner[1], Markus A Weigand[2], Jan Larmann[2], Riccardo Barbieri[1]

[1] Politecnico di Milano, Milano, Italy
[2] Heidelberg University Hospital, Heidelberg, Germany

Abstract

Introduction: *The high mortality and difficulty of diagnosis make Heart failure (HF) a severe burden for the healthcare system, especially in intensive care units (ICU).* ***Goal:*** *This work proposes a method to characterize HF patients using autonomic indices from electrocardiogram (ECG) recordings in the ICU.* ***Methods:*** *We considered 52 ICU patients from the MIMIC-III database subjected to brain natriuretic peptide (NT-proBNP) laboratory measurement during their stay, of which 41 showed a positive reading for likely HF due to elevated levels of the peptide (NT-proBNP>300 pg/mL). RR intervals from 1 hour ECG recordings in the hour preceding NT-proBNP measurements were selected, and a point process framework was applied to extract time-varying estimates of indices related to autonomic nervous system activity. A general linear mixed-effects model was used to analyze the dynamics of the two populations.****Results:*** *Results showed an increasing average RR interval in the negative population ($p<0.001$). In parallel, RR variability increased in negative subjects ($p<0.001$) and decreased in positive patients ($p<0.001$). High frequency power ($p<0.001$) further showed different dynamics between the two populations.* ***Conclusions:*** *Results point at different autonomic cardiac control dynamics in patients with positive NT-proBNP test in the hour preceding the measurement.*

1. Introduction

The Intensive Care Unit (ICU) is the hospital ward devoted to the care of patients in critical conditions and requiring constant monitoring. These patients suffer from a wide range of acute pathologies as well as chronic comorbidities and are often in life threatening condition.

Heart failure (*HF*) is one of the most common cardiovascular conditions leading to ICU admission. It is a remarkable burden to the healthcare system and a complex illness, since it come with high rates of morbidity and mortality [1]. *HF* detection is a difficult task mainly because of unspecific symptoms [1] often concealed by the presence of underlying chronic conditions which further complicates its recognition and increases the impact of *HF*.

Echocardiography and brain natriuretic peptide (BNP) concentration measurement are commonly used to diagnose or quantify *HF* [1, 2]. The former estimates patient's ejection fraction (EF) as an index of cardiac performance, with a reduced EF being the predominant presentation of *HF*. BNP, together with N-Terminal proBNP (NT-proBNP), on the other hand are biomarkers of cardiac workload and stress, which are secreted by cardiomyocytes in case of increased wall tension. Natriuretic peptides (NPs) regulate the cardiovascular system by opposing the vasoconstriction, sodium retention, and anti-diuretic effects of the activated renin–angiotensin–aldosterone and modulate the sympathetic nervous system, leading to natriuresis, diuresis and vasodilation [2, 3].

Heart rate variability (HRV) is a well known proxy for the estimation of autonomic nervous system activity [4] which can be calculated from electrocardiographic (ECG) signals as the series of time intervals between successive heart beats, i.e. the time between two R-peaks in the ECG. Vital signals like ECG are continuously recorded from ICU patients and displayed on bedside monitors available to clinicians for assessing the overall patients conditions. This results in the collection of large amounts of data currently mainly used for temporary display and assessment of patients' condition. The information potential contained in these recordings is predominantly put to waste. Previous studies already assessed the potential of physiological waveform monitoring in ICU patients by exploring the association between autonomic control indexes and mortality [5, 6], the ability to identify patients with sepsis [7], and predict septic shock [8]. This study exploits routinely recorded ECG signals from the critically ill patients in or-

* These authors equally contributed to the manuscript

der to characterize the dynamic evolution of heart rate variability indices of the ICU patients with normal and abnormal N-Terminal proBNP (NT-proBNP) values and therefore at risk of HF. Through this, we demonstrate the potential diagnostic value of advanced signal processing in specific patient strata, when clinical demographic data and signals are used in combination.

2. Methods

2.1. Study Design and Cohort Selection

The data used in this study were extracted from the MIMIC-III database [10], a publicly available database on PhysioNet [11] collecting both clinical data from the electronic health records and physiological waveforms recordings of patients admitted to the intensive care unit at the Beth Israel Deaconess Medical Center in Boston, MA.

The first criterion for the cohort selection was the presence of a NT-proBNP test. A concentration of NT-proBNP $> 300pg/mL$ was chosen as a cut-off value to distinguish *HF* patients from the control population $\leq 300pg/mL$. [2] This criterion led to a starting population of 1110 distinct subjects with *HF* and 103 *Controls*. Successively, selection for patients with available ECG recordings in the 24 hours before the target time reduced the population to 139 *HF* patients and 22 *Controls*. Finally, only patients with available high-quality ECG recordings, without artifacts and ectopic beats, in the hour prior the NT-proBNP test were taken into consideration, resulting in a final population of 41 *HF* patients and 11 *Controls*.

Each patient's waveform was processed with an internally developed Pan-Tompkins based automatic annotation software which extracted the times of R-peak events on the ECG and underwent manual review and correction of missing beats and beats not belonging to the sinus rhythm.

2.2. Cardiovascular Data Modeling and Feature Extraction

The point process model presented by Barbieri et al. [12] was used to extract instantaneous R-R intervals and heart rate variability indices. A history-dependent Inverse Gaussian (IG) probability density function (PDF) was chosen as model describing the RR intervals distribution [12].

The instantaneous expected value of the IG PDF, $\mu_{RR}(t)$, was estimated by using an univariate p-th order (p=11) autoregressive model $\mu_{RR}(t) = a_0 + \sum_{i=1}^{p} a_i(t)RR_{t-i}$, whereas the instantaneous variability was estimated thanks to its relationship with the shape parameter $\theta(t)$ as follows: $\sigma^2_{RR}(t) = \mu^3_{RR}(t)/\theta(t)$.

In this work, 13 features extracted from clinical data and waveforms were used for analysis. All features had coverage for the clinical episode in focus, namely the ICU stay.

Characteristics	*HF* (41)	*Control* (11)
Age	66 (53;78)	54 (42;58.5)
Sex (F)	29% (12)	9% (1)
Length of stay (days)	8.1 (3.1;11.2)	10.5 (1.8;15.6)
30-day Mortality	22% (9)	9% (1)
Diabetes	2% (1)	18% (2)

Table 1. Clinical information for heart failure (*HF*) and *Control* populations. Population characteristics reported as median (IQR) or incidence (%) as appropriate.

The clinical features represented demographic information on the patients: age, gender and a history of diabetes. Extracted features include $\mu_{RR}(t)$, $\sigma^2_{RR}(t)$, and $\theta(t)$ in time domain, whereas, spectral domain features are extracted from the estimated time-varying power spectral density. The spectral domain features include: very low frequency power (P_{VLF}, range: $\leq$ 0.04Hz), low frequency power (P_{LF}, range: $0.04-0.15$Hz), high frequency power (P_{HF}, range: $0.15 - 0.45$Hz), total power of the power spectral density (P_{TOT}), normalized low frequency (P_{LFn}), normalized high frequency (P_{HFn}) and sympatho-vagal balance (P_{LF}/P_{HF}). The 1-hour time series of the features was divided in twelve blocks (5 minutes each), and for each timeblock the median was computed and used for analysis.

2.3. Statistical Analysis

The Mann-Whitney U-test to test for differences between the *HF* and the *Control* populations. Successively, a general linear mixed-effects model (GLMEM) was used as multivariate model to check for temporal trends in the two populations ($feature = \beta_0 + \beta_1 timeblock + \beta_2 HF + \beta_3 timeblock * HF + (1|subject)$). The considered expression summarizes the performed test, where *feature* represents the feature under test, *timeblock* indicates the twelve 5 minute blocks, *HF* is a binary variabile distinguishing *HF* patients (1) from *Controls* (0), *timeblock*HF* is an interaction describing the different temporal trends for each population, and *(1—subject)* represents the mixing effects to account for random variations due to inter-patient variability. Features showing non-Gaussian distribution ($skewness$ >3) where log-transformed to produce more reliable results. Significance was defined for $p < 0.05$.

3. Results

Univariate Analysis. Only the *VLF* power showed significant differences between the 5min block medians for the two populations. In particular, 30min before NT-proBNP measurement the *HF* population showed a median of $36.31ms^2$ with respect to $161.83ms^2$ of the control population with a p=0.02.

E[μ_{RR}]	β	95% CI	p-value
intercept	723.41	623.8 ; 822.93	<**0.001**
HF	0.37	-112.02 ; 112.77	0.99
timeblock	4.38	2.81 ; 5.95	<**0.001**
*timeblock*HF*	-4.19	-5.97 ; -2.42	**0.001**

Table 2. GLMEM coefficients for $E[\mu_{RR}]$ showing their estimate, 95% confidence interval (CI) and significance.

log(E[P_{HF}])	β	95% CI	p-value
intercept	2.56	1.59 ; 3.53	<**0.001**
HF	1.05	-0.06 ; 2.15	0.06
timeblock	0.14	0.13 ; 0.16	<**0.001**
*timeblock*HF*	-0.18	-0.20 ; -0.16	<**0.001**

Table 3. GLMEM coefficients for HF power (P_{HF}) showing their estimate, 95% confidence interval (CI) and significance.

General Linear Mixed-Effects Model. The GLMEM model approach resulted in interesting temporal trends which differed between the two populations. The average RR interval (μ_{RR}) showed significantly distinct trends between the two populations, summarized in Table 2. Specifically, an increase in RR interval was observed for the *Control* population (*timeblock*: $p < 0.001$) and a nearly constant temporal trend for the *HF* (*timeblock*HF*: $p = 0.001$), when approaching the laboratory test. Concerning σ^2_{RR}, the trend of the *Control* population increased (*timeblock*: $\beta_1 = 0.08$, $95\%CI = 0.07; 0.1$, $p < 0.001$), while it decreased for the *HF* population (*timeblock*HF*: $\beta_3 = -0.12$, $95\%CI = -0.14; -0.1$, $p < 0.001$). P_{VLF} showed a significantly different baseline value for both populations (*intercept*: $\beta_0 = 5.92$, $95\%CI = 5.45; 6.38$, $p < 0.001$ and *HF*: $\beta_2 = -1.13$, $95\%CI = -1.99; -0.27$, $p = 0.01$).A lower baseline was found for the P_{LF} in *HF* population at the limits of the significance threshold (*HF*: $\beta_2 = -2.22$, $95\%CI = -4.46; -0.03$, $p = 0.05$). Furthermore, P_{HF} resulted in statistically significant different trends while approaching the NT-proBNP measurement between the two groups, as shown in Table 3 (*timeblock* $p < 0.001$ and *timeblock*HF*: $p < 0.001$), as well as a higher baseline for the *HF* population close to the significance threshold (*HF*: $p = 0.06$). The *pTOT* resulted to be significantly different between the two populations when considering their time evolution (*timeblock*: $\beta_1 = 0.04$, $95\%CI = 0.02; 0.05$, $p < 0.001$, and *timeblock*HF*: $\beta_3 = -0.05$, $95\%CI = -0.08; -0.02$, $p < 0.001$) and on average it decreased for the heart failure population and increased for the *Control* population.

4. Discussion

This study shows a very low overall heart rate variability for critically ill patients which can be attributed to the acute and severe conditions of this population. This might be read as a sign of suppressed overall autonomic modulation. Similar results were also found in [5] and [6].
The two populations do not show differences in the absolute values of the autonomic indices, with the only exception of P_{VLF} that was lower in *HF* patients. This might be due to impaired hormonal systems, thermoregulation and/or circadian cycle states as well as to altered renin-angiotensin-aldosterone-system and parasympathetic system outflow [9]. Different dynamics in the hour preceding the NT-proBNP test can be demonstrated for the two populations distinguished by the result of the laboratory measurement. Specifically, *HF* patients show a smaller μ_{RR}, which is consistent with a persistent activity of the sympathetic ANS and impaired vagal activity, previously associated with worse clinical conditions [4]. In contrast to this, a progressive lengthening of inter-beat-interval duration is observed in *Control* subjects. RR intervals variability, σ^2_{RR}, increases when approaching the NT-proBNP test in the *Control* population and it decreased in *HF* population, thus suggesting a progressive recovery of vagal activity in *Control* patients. The *HF* population, on the other hand shows a progressive decrease in vagal response and total power which is coherent with previously observed results for heart failure patients [13]. It is worth highlighting that *Control* and *HF* populations were defined by thresholding NT-proBNP test results, and therefore the selected populations can be thought of as subjects with suspected heart failure. The secretion of brain natriuretic peptide is thought to modulate the sympathetic nervous system activity by inducing a vagal response, e.g. vasodilation to reduce systemic resistance and cardiac workload. However, the observed excessive production of BNP in heart failure patients may lead to the so-called BNP-paradox, i.e. alterations in physiological responses like increased vasoconstriction and decrease in diuresis. This phenomenon might be linked to the presence of altered and biologically inactive circulating molecular forms of BNP, which are not distinguishable from biologically active ones [14]. These mechanisms support the observed autonomic nervous system dynamics showing a progressive vagal recovery in *Control* patients and persistent sympathetic activity in *HF* patients.

This study has to deal with some limitations. The first and most important is the small sample size of the cohort, with only 52 patients considered, which represent only a small subset of the possible dynamics of heart failure patients and may therefore influence the proposed statistical analyses. Second, administration of medication within the care context was not considered in these analyses. Also, the criteria employed to select and identify *HF* patients rely on the presence of a NT-proBNP test, and therefore they focus on a specific population of patients with suspected heart failure.Finally, a multi-center valida-

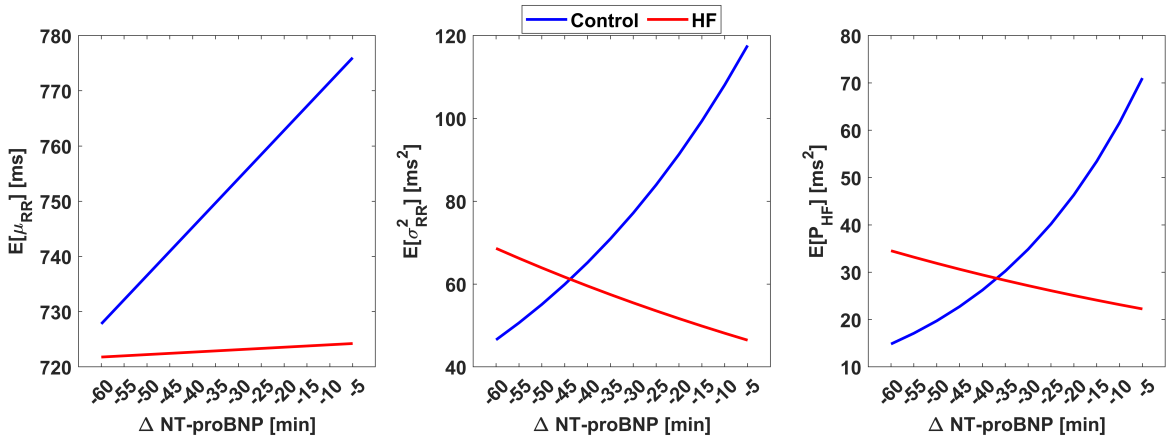

Figure 1. Trends of average RR interval (μ_{RR}), RR variability (σ^2_{RR}) and high frequency power (P_{HF}) in the hour preceding NT-proBNP measurement. (ΔNT-proBNP = Minutes from NT-proBNP measurement.)

tion would improve the generalizability of the results.

5. Conclusions

This study highlights the main differences in the dynamic evolution of autonomic activity of patients admitted to the ICU at risk of heart failure. The main findings suggest a recovered vagal activity in the control population rather than in the heart failure patients. This study paves the way for the inclusion of indices derived from the modeling of continuously recorded patients' vital signs as a valuable tool for ICU patient monitoring.

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Address for correspondence:

Maximiliano Mollura
Via Camillo Golgi, 39 Milano, Italy
maximiliano.mollura@polimi.it