Original Research Article

Analysis of heart rate variability as a predictor of mortality in cardiovascular patients of intensive care unit

Mohammad Karimi Moridani\textsuperscript{a,\ast}, Seyed Kamaledin Setarehdan\textsuperscript{b}, Ali Motie Nasrabadi\textsuperscript{c}, Esmaeil Hajinasrollah\textsuperscript{d}

\textsuperscript{a}Department of Biomedical Engineering, Science and Research Branch, Islamic Azad University, Tehran, Iran
\textsuperscript{b}Control and Intelligent Processsing Centre of Excellence, School of Electrical and Computer Engineering, College of Engineering, University of Tehran, Tehran, Iran
\textsuperscript{c}Department of Biomedical Engineering, Shaped University, Tehran, Iran
\textsuperscript{d}Logman Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

\textbf{A B S T R A C T}

Objective: Dynamic changes of heart rate variability (HRV) reflect autonomic dysfunction in cardiac disease. Some studies suggest the role of HRV in predicting intensive care unit (ICU) mortality. The main object of this study was analyzing the HRV to design an algorithm to predict mortality risk.

Methods: We evaluated 80 cardiovascular ICU patients (45 males and 45 females), ranging from 45 to 70 years. Common time and frequency domain analysis, non-linear Poincaré plot and recurrence quantification analysis (RQA) were used to study the HRV in two episodes. The episodes include 8–4 h before death, and 4 h before death to death. Independent sample t-test was used as statistical analysis.

Results: Statistical analysis indicates that frequency domain and Poincaré parameters such as LF/HF and SD2/SD1 show changes in transition to death episode \((p < 0.05)\). Moreover, \(L_{max}, v_{max}\) and RT measures showed meaningful changes \((p < 0.01)\) in closer segments to the death.

Conclusions: Analysis of physiological variables shows that there are significant differences in RQA measures in episodes close to death. These changes can be interpreted as more stability and determinism behavior of HRV in episodes close to death. RQA parameters can be used together with HRV parameters for description and prediction of mortality risk in ICU patients.

\begin{center}
\textcopyright 2015 Na\l{}cz Institute of Biocybernetics and Biomedical Engineering. Published by Elsevier Sp. z o.o. All rights reserved.
\end{center}

\textsuperscript{\ast}Corresponding author at: No. 29, Floor 4, Farjam St., Tehran-Pars, Tehran 1653989618, Iran.
E-mail address: mkarimi.bme@gmail.com (M.K. Moridani).

Abbreviations: HRV, heart rate variability; ICU, intensive care unit; RQA, recurrence quantification analysis; RP, recurrence plots; REC, recurrence rate; ENTR, entropy; TT, trapping time; RT, recurrence trend.

\url{http://dx.doi.org/10.1016/j.bbe.2015.05.004}

0208-5216/© 2015 Na\l{}cz Institute of Biocybernetics and Biomedical Engineering. Published by Elsevier Sp. z o.o. All rights reserved.
1. Introduction

Illness defined as a state of altered physiological function, which leads to reduction in the quality or quantity of life in patients whereas disease is an illness that has a sole and definable pathogenesis [1]. The main challenge of critical care is that the treated disorders are mostly illnesses rather than diseases. The physicians treat the specific signs and symptoms in patients, but there are lacks of information about how these signs combine as manifestations of a particular biological process. The behavior of critical illness is more complex because it arises through the interactions of the causative stimuli with multiple remedial and physiological responses.

Healthy state exhibits chaotic behaviors in physiological variables, such as heart rate. Loss of such variability means loss of complexity that accompanies critical illness [2,3]. It can be postulate that physiological systems consist of various components and small changes have significant effects on the behavior of the system [4]. Intensive care may extend the dying process in patients who do not show the possibility of retrieving an acceptable quality of life.

Experimental studies showed that large amounts of death in ICUs are receded by the prohibition or requisition of treatments. While a variety of the clinical parameters are associated with the decision to limit the treatments [5–12]. The frequencies of the prohibition or requisition of treatments and the degree of involvement of relatives in decision making are influenced by the cultural context [13,14].

Over the past decades, several studies focused on the data collected in the ICUs, especially in the field of data mining [15]. However, some reasons include lack of experts and busy physicians may lead to the elimination of important details while automated prediction methods could analyze the raw data and extract fundamental information for physicians to make a better decision [15]. Moreover, the data collected in the ICUs can be implemented to discover the relation of different types of illness, diagnosis, therapeutic and mortality risk factors.

However, it is hard to develop a clinically applicable prediction algorithm as there are several issues involved with data collection and various analysis methods. In recent years, numerous studies and methods attempted to predict the mortality risk of admitted patients in ICU [17–21]. However, these predictions are not accurate enough and still there is not any reliable tool to predict the dynamics leads to death in ICU patients.

Some research used machine learning algorithms, such as artificial neural networks and decision trees as a prediction algorithm in different critical care settings [22–28]. However, the evaluation of their performance is still under discussion. Mentioned methods include statistical analysis, machine learning algorithms and artificial neural networks require clinical inputs such as sodium, glucose, albumin, bilirubin, urine output, respiratory rates, etc. However, the issues in recordings of each input can lead to less accuracy in prediction algorithm. To the best of our knowledge, few studies considered the dynamics of HRV in death patients admitted in ICU.

In recent years, several techniques are used to describe the behaviors of complex systems such as autonomic nerve system. Heart rate variability analysis is a well-known method to measure the autonomic regulation of cardiac activity, which is mediated by the parasympathetic and sympathetic nerves, reflects the capacity for the parasympathetic inhibition of autonomic arousal and the coupling between the autonomic nervous system and the sinoatrial node. Increased HRV reflects a healthy autonomic nervous system [29–31] while decreased HRV is a marker of autonomic inflexibility [32,33] that may precede more systemic problems. There is mounted evidence that a strong association exists between low measures of HRV and severity of illness [33,29].

The support vector machine (SVM) is a relatively new classification or prediction method developed by Cortes and Vapnik in the 1990s as a result of the collaboration between the statistical and the machine learning research community. SVM tries to classify cases by finding a separating boundary called hyperplane. The main advantage of the SVM is that it can, with relative ease, overcome ‘the high dimensionality problem’. Moreover, SVM has demonstrated high performance in solving classification problems in bioinformatics [34].

Beside time and frequency analyses used for evaluation of HRV, nonlinear techniques enable us to describe the behaviors of complex systems such as ANS and HRV. Recurrence plots (RP) allow visualization of phase space trajectories using two-dimensional graph. It can be used to detect transitions between different states or to find interrelations between several systems. The structures created in RP represent the basis for RQA. Recurrence analysis, which is selected method in this study, is used in special cases such as evaluation of HRV before the onset of ventricular tachycardia or prediction of epileptic seizures [35].

In this paper, we analyzed the HRV of ICU patients by means of time and frequency domain, non-linear Poincaré plot analysis and RQA measures to find whether any significant changes can be seen in death episode.

This manuscript is organized as follows: Section 2 describes the database and feature extraction methods. Section 3 illustrates obtained results. Sections 4 and 5 represent the discussion and conclusions, respectively.

2. Materials and methods

Heart rate variability (HRV) analysis is affected by sinus pause and non-sinus beats. Sinus pause is a medical condition wherein the sinoatrial node of the heart transiently ceases to generate the electrical impulses that normally stimulate the myocardial tissues to contract and thus the heart to beat. It is defined as lasting from 2.0 s to several minutes. Since the heart contains multiple pacemakers, this interruption of the cardiac cycle generally lasts only a few seconds before another part of the heart, such as the atrio-ventricular junction or the ventricles, begins pacing and restores the heart action. This condition can be detected on an electrocardiogram (ECG) as a brief period of irregular length with no electrical activity before either the sinoatrial node resumes normal pacing, or another pacemaker begins pacing. If a pacemaker other than the sinoatrial node is pacing the heart, this condition is known
as an escape rhythm. If no other pacemaker begins pacing during an episode of sinus pause it becomes a cardiac pause. This condition is sometimes confused with sinoatrial block, a condition in which the pacing impulse is generated, but fails to conduct through the myocardium. Differential diagnosis of the two conditions is possible by examining the exact length of the interruption of cardiac activity [36].

Non-sinus beats, especially bradycardia with nodal rhythm or complete atrioventricular block, are serious complications during the cardiac resuscitation period after cardiac operations. They are rare, but still unavoidable nowadays. They can be classified as 2 types: anesthetic depression of the conduction system or myocardial edema due to traction and tension during surgical maneuvers; and permanent damage to the conduction system from surgical sutures.1 In the 1st type, non-sinus rhythm is transient and will generally revert to sinus rhythm after 48–72 h; but type 2 cannot recover. When non-sinus rhythm occurs, cardiac surgeons have no other choice but to insert a temporary pacemaker and wait anxiously for recovery [37].

An efficient method was proposed to deal with the ectopic beats. The method was based on trend correlation of the heart timing signal. Predictor of R-R interval (RRI) value at non-sinus beat time was constricted by the weight calculation and the slope estimation of preceding normal RRI. The type of non-sinus beat was detected and replaced by the predictor of RRI. The performance of the simulated signal after non-sinus correction was tested by the standard value using power spectrum density (PSD) estimation, whereas the results of clinical data with non-sinus beats were compared with the adjacent non-sinus-free data. The result showed the frequency indexes after non-sinus corrected had less error than other methods with the test of simulated signal and clinical data. It indicated our method could improve the PSD estimation in HRV analysis. The method had advantages of high accuracy and real time properties to recover the sinus node modulation [38].

2.1 Dataset

In this work, we have used physiological data streams from 80 patients collected in MIMIC-II (Multi-parameter Intelligent Monitoring in Intensive Care) database [39]. Data for each patient consists of several streams that include heart rate, mean arterial blood pressure, respiration rate and other vital indices. The traces for each patient are variable in length and typically span several days, corresponds the length of stay of the patient in the ICU. We selected cardiovascular admitted ICU patients include 40 males and 40 females with a mean (standard deviation) age of 64.5 (17.1) years and initial weights of 81.2 (23.8) kg. Table 1 represents the characteristics of studied subjects.

The sampling frequency is used 256 Hz by MIMIC II.

2.2 Time and frequency analysis

In current study, HRV was assessed by the traditional time and frequency domain analysis. The common features of HRV include RR intervals (RRI) and mean HR computed. Moreover, we extended the classical frequency domain parameters include the high frequency power (HF: 0.15–0.4 Hz), the low frequency power (LF: 0.04–0.15 Hz) and the low frequency to high frequency ratio (LF/HF), which determined from the power spectrum of RRI time series. It is well-known that vagal activity mainly contributes to HF while sympathetic activity influences LF and the LF/HF ratio [40].

2.3 Non-linear Poincaré plot analysis

The Poincaré plot is the most commonly used non-linear estimator of HRV function. Each successive RRI is plotted against its previous RRI. The popular technique used to quantify the Poincaré plot is fitting an ellipse and plotting two axes (perpendicular to each other) to the points, one can calculate the standard deviation of the distance of the points from each axis. The SD1 reflects short-term variability while SD2 reflects long-term variability. In case of heart rate variability, Poincaré plot reveals a useful visual pattern of the RRI by representing both short and long term variations of the signal [41].

2.4 Recurrence quantification analysis

Recurrence plots are indeed visualization of phase space trajectories using two-dimensional graph. As the state of a system usually changes in time, the vector in phase space describes a trajectory that represents dynamics of the system. In fact, the RQA detects patterns of recurrence in the data, which are one of the most important characteristics of dynamic systems. Although reconstructed phase space is not exactly the same as the original, with a large embedding dimension could maintain the same topological properties and helps us to interpret information more rigorously [42]. The first step in the analysis of a signal using RP theory is the reconstruction of the phase space of the signal. A frequently used method for the reconstruction is the time delay method. In this approach, the time series \( s_i \) \((i = 1,2,\ldots,N)\) of length N is embedded into a \( m \)-dimensional space with the time-delay (\( \tau \)) technique:

\[
x_i = [s_i s_{i+\tau} \cdots s_{i+(m-1)\tau}], \quad i = 1,2,\ldots,N-(m-1)\tau
\]

For the analysis, both embedding parameters, the dimension \( m \) and the delay \( \tau \), have to be chosen appropriately. Different approaches for the estimation of the smallest sufficient embedding dimension like the false nearest-neighbors algorithm, as well as for an appropriate time delay have

<table>
<thead>
<tr>
<th>Table 1 – Characteristics of studied subjects.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Sex (%Men)</td>
</tr>
<tr>
<td>Mean height (cm)</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
</tr>
<tr>
<td>Patient types:</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
</tr>
<tr>
<td>Heart failure (%)</td>
</tr>
<tr>
<td>Ischemic (%)</td>
</tr>
<tr>
<td>Arrhythmia (%)</td>
</tr>
<tr>
<td>Others (%)</td>
</tr>
<tr>
<td>Length of stay (h)</td>
</tr>
</tbody>
</table>
been proposed \[43, 44\]. The false nearest neighbor algorithm identifies the number of “false nearest neighbors” points that appear to be nearest neighbors because the embedding dimension is too small of every point in the phase space. When the number of false nearest neighbors drops to zero, we have embedded the time series to proper dimensional space \[43\].

Eckmann et al. have introduced a tool which can visualize the recurrence of states \(x_i\) in a phase space. Usually, a phase space does not have a dimension (two or three) which allows it to be pictured. Higher dimensional phase spaces can only be visualized by projection into the two or three-dimensional sub-spaces. However, Eckmann’s tool enables us to investigate the \(m\)-dimensional phase space trajectory through a two-dimensional representation of its recurrences. Such recurrence of a state at time \(i\) at a different time \(j\) is marked within a two-dimensional squared matrix with ones and zeros dots (black and white dots in the plot), where both axes are time axes. This representation is called recurrence plot (RP). Such an RP can be mathematically expressed as formula (2) \[42\].

For discontinuous signals such as RR-intervals extracted from the continuous ECG signals, the delay is best set to 1 \[45\]. After the state space reconstruction, the RP of a signal can be obtained. In this step, the \(M \times M\) recurrence matrix, the elements of matrix can be calculated using formula (2), is derived.

\[
R_{ij} = \Theta (|x_i - x_j|), \quad i, j = 1, 2, \ldots, M \tag{2}
\]

where \(M = N - (M - 1)\), \(\varepsilon\) is a threshold distance, \(||\) is the norm (e.g., the Euclidean norm) and \(\Theta (x)\) is the Heaviside function. This means that if two phase space vectors \(x_i\) and \(x_j\) are sufficiently close together, then \(R_{ij} = 1\); otherwise \(R_{ij} = 0\).

The RP is obtained by plotting the recurrence matrix, means that if the distance between \(x_i\) and \(x_j\) is less than a threshold, then a dot is placed at \((i, j)\) in the RP. A critical parameter of an RP is the threshold. Therefore, special attention required for its choice. If the threshold is chosen too small, there may be almost no recurrence points, and we cannot learn anything about the recurrence structure of the underlying system. On the other hand, if \(\varepsilon\) is chosen too large, almost every point is a neighbor of other points, which leads to a lot of artifacts. A too large \(\varepsilon\) includes also points into the neighborhood, which are simple consecutive points on the trajectory \[46\].

Several criteria for choosing the cutoff distance \(\varepsilon\) proposed \[47, 48\]. One approach uses a fixed number of neighbors, \(N_0\), for every point of the trajectory, called fixed amount of nearest neighbors \[49\].

In this approach, the cutoff distance, \(\varepsilon_i\) changes for each state \(x_i\) to ensure that all columns of the RP have the same recurrence density. Using this neighborhood criterion, \(\varepsilon_i\) can be adjusted in such a way that the recurrence rate (REC) has a fixed predetermined value (i.e., \(REC = N_0/N\)) \[46\].

In this study, six features were extracted from the RP of each segment with the duration of 5 min to characterize different patterns. The related features are as follows:

- **\(L_{\text{max}}\):** It measures the length of the longest diagonal line segment in the RP, excluding the main diagonal line:

\[
L_{\text{max}} = \max \{|l_i|; \quad i = 1, \ldots, N_1\} \tag{3}
\]

Formula (3) is related to the length of the longest diagonal line in recurrence plot. This is a very important recurrence variable because it inversely scales with the most positive Lyapunov exponent. Positive Lyapunov exponents gauge the rate at which trajectories diverge, and are the hallmark for dynamic chaos.

- **\(L_{\text{mean}}\):** It measures the average length of the diagonal lines whose lengths exceed the certain threshold \(L_{\text{min}}\):

\[
L_{\text{mean}} = \frac{\sum_{l > L_{\text{min}}} M \cdot p(l)}{\sum_{l > L_{\text{min}}} p(l)} \tag{4}
\]

where \(p(l)\) is the number of diagonal structures whose length is \(l\). \(L_{\text{mean}}\) represents the average time that two segments of the trajectory are close to each other and can be interpreted as the mean prediction time \[46\].

- **Entropy (ENTR):** The Shannon entropy of the probability distribution of the diagonal line lengths \(p(l)\):

\[
\text{ENTR} = - \sum_{l > L_{\text{min}}} p(l) \ln p(l) \tag{5}
\]

where \(p(l)\) is the probability density of the diagonal structure whose length is \(l\) and is defined as \(p(l)/\text{sum}(p(l))\). ENTR reflects the complexity of the RP in respect of the diagonal lines.

- **\(v_{\text{max}}\):** It measured the length of the longest line segment, which is vertical.

- **Trapping time (TT):** It measures the average length of vertical lines:

\[
\text{TT} = \frac{\sum_{j=1}^{N_0} u \cdot p(u)}{\sum_{j=1}^{N_0} p(u)} \tag{6}
\]

where \(p(u)\) is the number of diagonal structures whose length is \(u\). In current study, \(v_{\text{max}} = 2\). TT estimates the mean time that the system will resist at a specific state.

- **Recurrence trend (RT):** It measures the variation rate of the REC away from the main diagonal, which can reflect the drift and non-stationary in a time series.

In first step, the bottom right trigonal area of the RP is divided into \(k\) parts by \(k - 1\) equally spaced lines, which parallel to the 45° diagonal. Then the recurrence rate of the \(k\)th part REC\(_k\) is obtained and REC represents the mean of the sequence [REC\(_k\), \(k = 1, 2, \ldots, K\)]. RT is the linear regression slope of the sequence [REC\(_k\), \(k = 1, 2, \ldots, K\)] about \(\{k = 1, 2, \ldots, K\}\) and calculated as follows (7):

\[
\text{RT} = \frac{\sum_{k=1}^{K} [(k - (k + 1)/2)(\text{REC}_{k} - \text{REC})]}{\sum_{k=1}^{K} [(k - (k + 1)/2)^2]} \tag{7}
\]

2.5. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, version 19 (IBM, Armonk, NY, USA). To compare HRV parameters in different episodes far from and close to death; paired sample t test was used for normally distributed
variables. Values are given as the mean ± SD, and the p values less than 0.05 and 0.01 were considered statistically significant.

3. Results

We calculated the time and frequency domain analysis, Poincaré plot analysis and six measures of RQA include $L_{\text{max}}$, $L_{\text{mean}}$, $v_{\text{max}}$, $\text{TT}$, $\text{ENTR}$ and $\text{RT}$ to analyze the HRV of ICU patients in two episodes. The whole episode includes 8 h before death, which the first four hours considered as an episode far from death and the second four hours considered as an episode close to death. To evaluate the measures by detail, the whole episode of eight hours divided into 16 windows with the duration of 30 min. Therefore, the features were calculated for each window. The first to 8th window belongs to the episode far from death, and the 9–16th belongs to the episode close to death. The embedding dimension to reconstruct phase space was found to be about 4 for all subjects according to false nearest neighbor method. The time delay was considered 3, which determined by initial minimum points in mutual information function. The parameter ε was 5% of the maximum phase space diameter.

Tables 2 and 3 represent the mean and standard deviation of time and frequency domain analysis, non-linear Poincaré analysis and RQA parameters for two mentioned episodes, respectively. The statistical analysis results indicate that LF/HF and SD2/SD1 ratios of episodes close to death show significant changes ($p < 0.05$). Moreover, there are meaningful changes in $L_{\text{mean}}$, $v_{\text{max}}$ and RT measures of these episodes ($p < 0.01$).

Fig. 1 represents the comparison of three RQA measures that show the most statistical changes in both episodes. The blue lines represent the changes of each variable in episode far from death, which include the values of measures for first to 8th window with the duration of 30 min in 8–4 h before death,

| Table 2 – Time and frequency domain and Poincaré analysis measures for non-death and death episodes. |
| Features | Non-death episode (Mean ± SD) | Death episode (Mean ± SD) |
| RRI (ms) | 809.11 ± 106.2 | 900 ± 65.6 |
| Mean HR (bpm) | 74.2 ± 15.2 | 66.7 ± 3.21 |
| SD2/SD1 | 1.35 ± 0.23 | 1.1 ± 0.1 |
| LF/HF | 1.37 ± 0.18 | 1.23 ± 0.14 |
| $p$-Value | <0.05. |

| Table 3 – RQA variables’ values for non-death and death episodes. |
| Features | Non-death episode | Death episode |
| $L_{\text{mean}}$ | 0.18 ± 0.02 | 0.45 ± 0.04 |
| $v_{\text{max}}$ | 0.16 ± 0.02 | 0.25 ± 0.03 |
| $\text{RT}$ | 0.26 ± 0.02 | 0.40 ± 0.03 |
| $\text{TT}$ | 0.38 ± 0.02 | 0.45 ± 0.05 |
| $L_{\text{max}}$ | 0.60 ± 0.03 | 0.75 ± 0.05 |
| Entropy | 0.16 ± 0.02 | 0.18 ± 0.04 |
| $p$-Value | <0.01. |

Fig. 1 – Recurrence plot analysis of the time series of the RRI in: (a) 30 min and (b) 8–7:30 h before death.
Fig. 2 – Sample boxplots of the features of death episode (30 min before death) and non-death episodes (8–7:30 h before death), (a) $L_{\text{mean}}$, (b) recurrence trend (RT), (c) $v_{\text{max}}$, (d) trapping time (TT), (e) $L_{\text{max}}$ and (f) entropy.
and the red lines represent the measures for 9–16th belong to 4 h before death to death. As it can be seen, all measures have greater values in episodes close to death.

In Fig. 2, box plots of two sample episode for 8–7:30 h before death (first window) as non-death episode and 30 min before death (last window) as death episode is presented. Significantly higher values of RQA measures can be seen in episodes close to death compared with episodes far from death. Part (a), shows that $L_{\text{mean}}$, which reflect the average duration of a stable interaction in HRV exhibits higher value in death episodes. In part (b), RT which is an indicator to reflect the non-stationarity of HRV has a higher value in episode close to death. In part (c), $v_{\text{max}}$, which considered as one of RQA measures based on vertical lines structures, shows significant difference in episodes far from and close to death. Part (d), which shows the T\text{T}, has a higher value in episode close to death compared to the other episode. In part (f), ENTR shows a significant difference between two mentioned episodes. The value of ENTR were significantly higher in episode close to death compared to the episode far from death, which indicates more complexity and less deterministic behavior in episodes far from death. As it can be seen in part (e), $L_{\text{max}}$ represents higher value in death episodes, which can be interpreted that the death episode is less chaotic than episode far from death.

Fig. 3 illustrates the recurrence plot of the RRI in 30 min and 8–7:30 h before death. The differences were found in the structure of patterns within recurrence plot in two mentioned episodes. A higher proportion of points were grouped into diagonals in 30 min before death. As it can be seen in (b), horizontal and vertical black lines indicate that this episode has lower change. More points are predominant in the episode of 8–7:30 h before death compared to the 30 min before death. Moreover, there are more regular patterns in the recurrence plot of 30 min before death, which indicates that there is more rhythmicity with respect to episode far from death.

4. Discussion

Intensive care units provide care for patients with different injuries and illnesses. Various types of ICUs treat different types of problems. Patients admitted to ICUs require special
medical attention and support from an expert team of trained nurses and physicians to prevent organ injury and keep their bodies functioning. Monitors, intravenous tubes, breathing machines, catheters and other equipment also help to keep ICU patients alive. Although many patients admitted to ICUs recover, others do not. ICU specialists use scoring algorithms based on clinical signs and physiological measurements to predict their patients’ likely outcomes.

The primary goal of current study was to evaluate the abilities of linear and non-linear methods in mortality prediction of cardiovascular patients admitted in ICU. Our study represents the patterns of dynamic changes in episodes close to death based on non-linear analysis, whereas the parameters of time and frequency domain analyses were not as accurate. The results indicate that common time and frequency domain analyses are insufficient to detect changes in the heart rate dynamic in episodes close to death.

We evaluate the time and frequency domain analyses and non-linear methods include the Poincaré analysis and RQA parameters in mortality prediction of cardiovascular patients admitted in ICU. Although LF/HF and SD2/SD1 show some amount of changes in transition to death episode, these changes are not sensible as RQA measures. RQA is a sensitive method that provides complementary and independent information about HRV and could be applied to short and non-stationary time series, which distinguishes it from other non-linear methods. We demonstrated significant differences in values of RQA parameters for episodes far from death.

Statistical analysis shows higher values of $L_{mean}$, $v_{max}$ and RT in episode close to death. The $L_{mean}$ is diagonal, while $v_{max}$ is a variable with the vertical line structure. Increasing the value of determinism indicates that more episodes of signal are repeating. This will increases the number of diagonal lines and represents more stability in the behavior of the system. On the other hand, the lower value of $v_{max}$ implies high complexity in dynamic of the system because the state of the system stays for a short time in a state similar to the previous state.

Our results show higher value of $L_{mean}$ in episodes close to death.

It can be interpreted that the episodes close to death is more determinism and shows more stability. Moreover, due to increase of $v_{max}$ it can be conclude that the complexity of the episodes close to death is decreased. These results could strengthen the previous studies which reported that low heart rate variability is associated with mortality risk in cardiovascular patients [50,51].

5. Conclusion

We have verified the possibility of linear and non-linear analyses for evaluation of HRV in mortality prediction of ICU patients. The RQA parameters specially, $L_{mean}$, $v_{max}$ and RT showed potential for the evaluation of HRV in episodes close to death.

The present work gives an overview of non-linear analysis that is useful in prediction of mortality risk in patients suffering from cardiovascular diseases in ICU. The main finding of this study is that there are significant changes in RQA measures of HRV in cardiovascular patients admitted in ICU, from eight hours before death to death. Our results demonstrate that HRV at the period of 4 h before death is a strong predictor of mortality. However, future investigations should consider including this time point.

Our research showed that heart patients admitted to the intensive care unit, heart rate variability signal was reduced in all cases but the intensity of the changes in ischemic heart disease and heart failure is more than other patients. Therefore, the nonlinear features extracted of HRV signal in different episode showed when the patients become closer to the time of death; Obvious changes in these features can be further.

Short term and long term variations in HR are known to have different physiological origins and the magnitude of these variations has been shown to be indicative of the autonomic state of a patient. Different research have pointed out that cardiovascular diseases are associated with autonomic dysfunction, which can be quantified by measuring HRV. They showed that a reduction in HRV identifies patients at high risk of death and that HRV is a better predictor of death. For prediction of all-cause mortality, HRV is similar to that of left ventricular ejection fraction HRV is superior to left ventricular ejection fraction in predicting arrhythmic events such as sudden cardiac death or ventricular tachycardia.

Most cardiovascular drugs that improve morbidity and mortality, including beta blockers, Angiotensin-converting enzyme (ACE) inhibitor s, and statins, also increase HRV. Metoprolol, quinapril, captopril, enalapril, and atorvastatin have been shown in separate studies to increase HRV.

There is no information associated with drug injection and treatment of patients in this database. Certainly, the use of drugs during treatment can have a negative impact. Note that when the patient is near to death HRV is reduced, therefore infusions of the drug because increases the HRV cannot create special problems associated with the identifica-

tion of the patient’s condition. However, this issue will be examined more closely in future work.

In our presented method, we divided HRV to half-hour segments and non-linear features were extracted from each segment, then based on the features of each segment the risk status is determined is determined that nurses and doctors can pay more attention to patients. Since the HRV signal is one of the most important signals in the assessment of the risk of cardiovascular patients. In current research, we tried to find a relation between HRV signal and predict mortality of patients. The HRV signal used was very efficient to distinguish the episodes considered in this study. Other vital signs can be helpful that blood pressure is one of them. To increase the credibility of the results, more signals should be used. It can be expected that by increasing the number of recorded data, the results can better be judged. In future work, in order to achieve better results in cases are needed to study with more accurate can be used of this signal. Thus, in addition to examining HRV Signal of patients, blood pressure signal can be studied in each segment that we hope to achieve better results. Moreover, as Recurrence Plot as a non-linear features showed good results in discrimination of the episodes (8–7.5 h before death to 0.5 h to death) in this research, it is recommended to evaluate other non-linear features by means of this method.
There are limitations to this study that require discussion. Main limitation in this study was the small number of continuous ECG recordings for ICU patients. Moreover, in current study we focused on cardiovascular ICU patients. Therefore, results reflect outcomes of septic patients, which cannot be generalized to other types of ICU patients. Further studies require eliminating the shortcomings.

**Conflict of interest**

None declared.

**Financial support**

This research paper extracted from the PhD thesis of corresponding author, which performed in Department of Biomedical Engineering, Science and Research Branch, Islamic Azad University, Tehran, Iran.

**References**


