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AGE-BASED ANALYSIS OF HEART RATE VARIABILITY (HRV) FOR PATIENTS WITH CONGESTIVE HEART FAILURE

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Abstract

It is known that heart activity changes during aging. In this paper, we evaluated alterations of heart activity from the complexity point of view. We analyzed the variations of heart rate of patients with congestive heart failure that are categorized into four different age groups, namely 30–39, 50–59, 60–69, and 70–79 years old. For this purpose, we employed three complexity measures that include fractal dimension, sample entropy, and approximate entropy. The results showed that the trend of increment of subjects' age is reflected in the trend of increment of the complexity of heart rate variability (HRV) since the values of fractal dimension, approximate

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entropy, and sample entropy increase as subjects get older. The analysis of the complexity of other physiological signals can be further considered to investigate the variations of activity of other organs due to aging.

Keywords: Heart Rate Variability; Congestive Heart Failure; Complexity; Aging; Fractal Dimension; Approximate Entropy; Sample Entropy.

1. INTRODUCTION

Analysis of the heart activity due to the variations of conditions is an important category of research. Because of the biological changes in the human heart due to aging,[1] there should be some changes in the heart rate. By referring to the literature, we can find many studies on analyzing the variations of heart rate due to aging.[2–6]

Since heart failure is an important condition for the human heart with a similar mortality risk with some cancers,[7] analyzing the variations of heart activity for these patients is important. An exciting topic of research is to investigate how heart activity changes for these patients during aging. For the first time, we studied the variations of heart rate for patients with heart failure during aging by employing complexity methods.

Since R-R time series as Heart Rate Variability (HRV) have a chaotic structure, therefore, complexity measures are suitable for our analysis. Fractal theory, sample entropy, and approximate entropy are popular methods for the analysis of the complexity of time series.

The fractal theory is a popular technique that has been widely applied to analyze complex objects. Self-similar fractals can be detected easily since they have obvious repeating patterns. However, self-affine fractals do not follow the same scaling exponent in different directions and, therefore, should be analyzed mathematically to quantify their complex structures.[8] For this purpose, the fractal dimension is calculated, which quantifies the complexity, where its bigger values indicate higher complexity.[9] The applications of fractal theory in the analysis of different complex signals such as Electroencephalography (EEG) signals,[10] Electromyography (EMG) signals,[11] Phonocardiogram (PCG) signals,[12] respiration signals,[13] eye movements,[14] GSR signals,[15] voice signals,[16] and human genome walk[17] are very extensive. Similarly, several studies have analyzed the variations of the human heart rate using fractal theory. The reported works that predicted sudden cardiac death[18] showed the effects of the vagal blocker atropine on the variations of fractal structure of heart rate,[19] demonstrated the variations in the fractal dimension of heart rate under different postural stress,[20] showed the changes in the integrative autonomic control of circulation in paraplegic individuals by fractal analysis of HRV,[21] found out the significant changes in the fractal dimension of HRV between waking and sleeping,[22] showed that the fractal dimension of HRV decreases significantly in people with diabetes compared to healthy subjects,[23] demonstrated the significant variations in the fractal structure of fetal HRV during pregnancy,[24] and decoded the correlation between the complexities of HRV and walking path[25] are worthy of being mentioned.

Approximate entropy is another measure that has been used widely to characterize the amount of irregularity and the unpredictability of physiological signals such as EEG,[26] EMG,[27] MEG,[28] speech,[29] and respiration signals.[30] We can also call the studies that applied approximate entropy to HRV to investigate its changes in different scenarios. The studies that compared the approximate entropy of HRV between rest and regular walking,[31] showed the changes in the approximate entropy of HRV for people with the major depressive disorder,[32] predicted heart failure by the application of approximate entropy to HRV,[33] predicted fetal HRV during pregnancy using approximate entropy,[34] demonstrated the effect of type of visual stimuli on alterations of approximate entropy of HRV,[35] differentiated awake versus sleep by analysis of approximate entropy of heart rate and heart period,[36] and analyzed the variations of approximate entropy of 24-h HRV for diabetic patients[37] can be mentioned.

Sample entropy is a modification of approximate entropy that is utilized to quantify time series complexity. The advantage of using sample entropy is that it is not dependant on the length of the signal. Therefore, since the extracted R-R time series from different subjects have various lengths (even

for the same period of recording), sample entropy is a suitable technique for our analysis. Similarly, a significant number of studies have reported the investigations on the analysis of different physiological signals[38–41] using sample entropy. We can also find some works on the HRV analysis using sample entropy. We can call the research studies that compared the HRV's sample entropy between rest and regular walking,[31] demonstrated greater sample entropy of HRV in normal subjects than patients with obstructive sleep apnea syndrome,[42] analyzed the variations of sample entropy of RR signal between rest and exercise conditions,[43] showed the differences in the HRV's sample entropy between cognitive tasks, stress, and consuming alcohol,[44] investigated the effects of ectopic beats editing by analysis of HRV,[45] showed the difference in the multiscale sample entropy of HRV between healthy subjects and aortic stenosis patients,[46] and analyzed the HRV for neonatals using sample entropy.[47]

Besides the conducted studies that analyzed the variations of heart rate in different conditions, no work has investigated the effect of aging on HRV for patients with congestive heart failure from a complexity view. Therefore, for the first time, we employ complexity methods to understand how the heart rate changes as these patients get older.

In the next section, we discuss the methodology. Then, the database that we used and the steps of analysis will be discussed. After that, the results will be presented that lead to the discussion.

2. METHOD

We study the variations of heart rate for patients with congestive heart failure according to their age. As it is known, ECG signals contain QRS complexes, and the heart rate is generated by extracting R peaks and measuring the time difference between every two consecutive R peaks. In this study, subjects have divided into four groups. As Table 1 shows, subjects in the first to the fourth group are 30–39, 50–59, 60–69, and 70–79-year-old.

Table 1 Different Age Groups.

Group No.	Age Range
First group	30–39 years old
Second group	50–59 years old
Third group	60–69 years old
Fourth group	70–79 years old

As the first index, we use the fractal dimension. Different methods calculate the fractal exponent of a complex object. We employ the box-counting method in this research. In this algorithm, the fractal object (R-R interval time series in this study) is covered with boxes that have the same size (μ). Then, the number of boxes (n) is counted. This algorithm repeats this procedure in different steps with various box sizes, and finally, it computes the fractal exponent using the following equation:

$$\mathrm{FD} = \lim_{\mu-0} \frac{\log n(\mu)}{\log 1/\mu}. \tag{1}$$

The general form of fractal exponent with the order of e is formulated as Eq. 2(Ref. 48):

$$\mathrm{FD}_e = \lim_{\mu-0} \frac{1}{e-1} \frac{\log \sum_{i=1}^{n} p_i^e}{\log \mu}. \tag{2}$$

For a time series with the total duration of T, the probability of occurrence in ith bin is formulated as:

$$p_i = \lim_{T-\infty} \frac{t_i}{T}. \tag{3}$$

In Eq. (3), t_i stands for the number of occurrences in the ith bin.

We also analyze the variations of heart rate using approximate entropy. Approximate entropy is widely utilized to investigate the irregularity of physiological time series. Since more irregular objects are more complex, therefore, approximate entropy is a suitable technique to analyze the complexity of HRV in this research. Considering a time series that contains n sample points $(k(1), k(2), \ldots, k(n))$, each vector is defined as:

$$f(i) = [k(i), k(i+1), \ldots, k(i+m-1)], \tag{4}$$

where h stands for embedding dimension. For each i, $1 \le i \le n-h+1$, $S_i^h(r)$ is formulated as:

$$S_i^h(r) = \frac{\text{number of } f(j) \text{ such that } d[f(i), f(j) \le r]}{n-h+1}. \tag{5}$$

The difference (d) in Eq. (5) is defined as:

$$d[f, f^*] = \max_c |k(c) - k^*(c)|. \tag{6}$$

By averaging $S_i^h(r)$ in Eq. (7), the approximate entropy is formulated using Eq. (8).

$$\varphi^h(r) = \frac{\sum_{i=1}^{n-h+1} \log(S_i^h(r))}{n-h+1}, \tag{7}$$

$$\mathrm{ApEn} = \varphi^h(r) - \varphi^{h+1}(r). \tag{8}$$

As another measure, we compare the sample entropy of HRV between different age groups. Sample entropy is similar to approximate entropy, but

it is not dependent on the length of data, and since the heart rate in the case of different patients had different lengths, we benefit from sample entropy to verify the obtained results from approximate entropy. Considering a time series with n sample points $(k(1), k(2), \ldots, k(n))$, the sample entropy is formulated as[49]:

$$\mathrm{SamEn}(h, r, n) = -\log \frac{E}{W}. \quad (9)$$

In Eq. (9), h and r indicate the embedding dimension and tolerance, respectively. Also, E is defined as the number of template vector pairs that:

$$d[f_{h+1}(i), f_{h+1}(j)] < r \quad (10)$$

and W is specified as the number of template vector pairs that:

$$d[f_h(i), f_h(j)] < r, \quad (11)$$

where $f_h(i)$ is formulated as:

$$f_h(i) = \{k(i), k(i+1), \ldots, k(i+h-1)\}. \quad (12)$$

We calculate the complexity of HRV using the complexity measures, and then we will discuss their variations based on the age of patients.

3. DATABASE AND ANALYSIS

We utilize the database[50,51] that was prepared by Krum *et al.*, which contains heartbeat annotation files for long-term ECG recordings from 29 subjects aged 34–79 years old with congestive heart failure. These data were recorded at the Heart Failure Center at Columbia-Presbyterian Medical Center to evaluate chronic heart failure. The recording has been done at 128 Hz by 24-h ambulatory electrocardiographic Holter recordings, and then R peaks were selected by an automated analysis based on template matching. For more information about the data collection procedure, please refer to Ref. 52.

To analyze this data, firstly, we generated R–R interval time series using a code that we wrote in MATLAB. This code calculated the time difference between every two consecutive R peaks and then generates the R–R interval time series. This code also removed the values of R–R intervals that were bigger than 200. These out-of-range values were caused due to errors by the algorithm which extracted R peaks.

Then, we calculated the fractal dimension, sample, and approximate entropies of HRV. The embedding dimension of 2 and tolerance of $0.2 \times \mathrm{std}_{\mathrm{data}}$ were selected for running the calculation of entropies.

We conducted the posthoc Tukey test ($\alpha = 0.05$) to analyze the variations of complexity measures between different age groups. We also analyzed the effect of different ages on the variations of the complexity of HRV by calculating Cohen's d.

4. RESULTS

We should state that some computed values for three subjects showed outliers values and therefore were removed from further analysis. Figure 1 shows the fractal exponent of the R–R interval signal (mean value between different subjects) in the case of various age groups. Error bars indicate the standard deviation of data.

As this figure shows, subjects in the first group have the smallest fractal exponent. Contrarily, subjects in the fourth group have the biggest value of the fractal dimension. Therefore, we can indicate that by increasing the age of subjects, the fractal dimension of the R–R interval time series increases. Therefore, by increasing the age of subjects, the complexity of their HRV increases.

Besides, the comparison of the fractal dimension between different groups indicates that as the age of subjects increases, the difference among the values of the fractal exponent increases. It means the HRV for older subjects changes more significantly than the HRV for younger subjects.

The results of pairwise comparisons that are listed in Table 2 indicate the insignificant variations of the fractal dimension of HRV between different age groups. However, the obtained results in this table verify the presented results in Fig. 1. As can be seen in this table, the P-values are getting smaller when the difference between the age groups increases. For instance, the smaller P-value

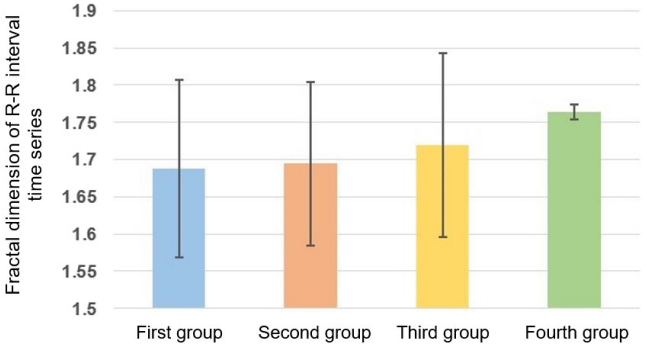

Fig. 1 The fractal exponent of heart rate in different age groups.

Table 2 Comparison of the Fractal Exponent of HRV Between the Age Groups.

Comparison	*P*-Value	Cohen's *d*
First and second groups	0.9996	−0.0571
First and third groups	0.9598	−0.2590
First and fourth groups	0.8595	−0.8885
Second and third groups	0.9641	−0.2130
Second and fourth groups	0.8644	−0.8808
Third and fourth groups	0.9604	−0.5008

Table 3 Comparison of Approximate Entropy of HRV Between the Age Groups.

Comparison	*P*-Value	Cohen's *d*
First and second groups	0.9801	−0.2160
First and third groups	0.9368	−0.3085
First and fourth groups	0.7970	−0.5707
Second and third groups	0.9946	−0.1200
Second and fourth groups	0.8896	−0.4410
Third and fourth groups	0.9413	−0.3358

between the first and fourth groups compared to the P-value between the first and second groups demonstrates the smaller changes in the complexity of HRV between the first and second groups compared to the first and fourth groups. Besides, the computed values of Cohen's d in this table indicate that increasing the age causes greater effects on the variations of the complexity of HRV. Therefore, the first and fourth age ranges had the smallest and biggest effect on the variations of the HRV.

Figure 2 shows the approximate entropy of HRV (mean value between different subjects) in the case of various age groups. Error bars indicate standard deviation.

According to Fig. 2, by increasing the age of subjects, the approximate entropy of HRV increases. In other words, the R–R interval time series become more irregular as subjects get older. This irregularity has a direct relationship with complexity. In other words, the complexity of the R–R interval time series increases as subjects get older. Therefore, this obtained result validates the obtained result for the fractal dimension of the HRV in Fig. 2.

The presented results from the post-hoc test that are brought in Table 3 show the insignificant alterations of the complexity of HRV among various age groups. However, the trend of calculated values demonstrates the greater alterations in the HRV's complexity as patients get older. In addition, the computed values of Cohen's d in this table indicate that increasing the age causes greater effects on the variations of the complexity of HRV. Therefore, the first and fourth age ranges had the smallest and biggest effect on the variations of the HRV.

To validate the obtained results for the approximate entropy of HRV, the calculated values of sample entropy of the R–R interval time series (mean value between different subjects) for different age groups are brought in Fig. 3. Error bars indicate standard deviation.

As it is clear from this figure, the first and fourth groups have the smallest and biggest values of sample entropy. The trend of sample entropy variations indicates that by increasing the age of subjects, the sample entropy of the R–R interval time series increases. Since sample entropy is the indicator of the complexity of the process, therefore, we can indicate that the complexity of HRV increases as the age of subjects increases. Therefore, the trend of variations of sample entropy validates the shown results in Figs. 1 and 2.

The result of the post-hoc test in Table 4 indicates no significant difference between the values of sample entropy. Besides, the computed effect sizes in this table indicate that increasing the age causes greater effects on the variations of the complexity

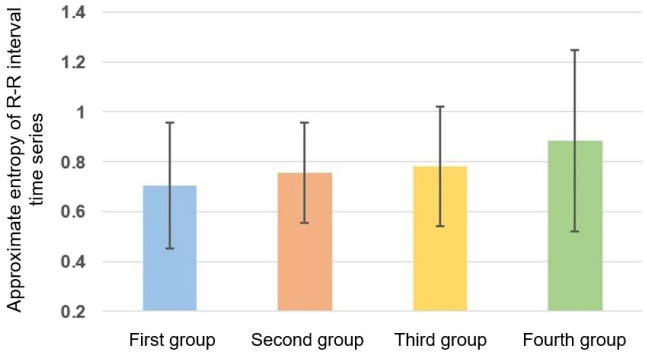

Fig. 2 Approximate entropy of HRV in different age groups.

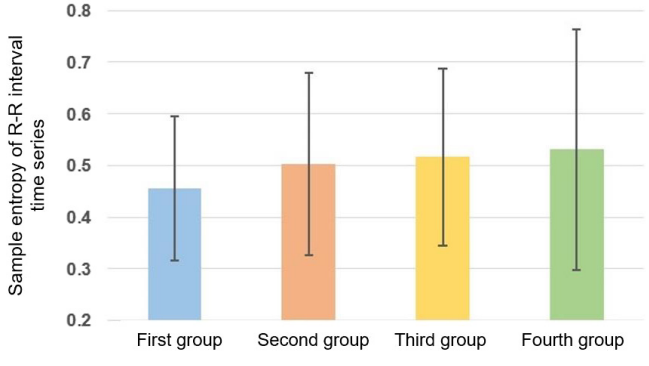

Fig. 3 Sample entropy of HRV in different age groups.

Table 4 Comparison of Sample Entropy of R–R Interval Time Series Between the Age Groups.

Comparison	*P*-Value	Cohen's *d*
First and second groups	0.9580	−0.2961
First and third groups	0.9220	−0.3844
First and fourth groups	0.9532	−0.3905
Second and third groups	0.9983	−0.0748
Second and fourth groups	0.9967	−0.1342
Third and fourth groups	0.9995	−0.0717

of HRV. Therefore, the first and fourth age ranges had the smallest and biggest effect on the variations of the HRV.

Overall, according to our analysis of three complexity measures in this research, the complexity of HRV increases as subjects get older. Therefore, the fractal dimension, approximate, and sample entropies are reliable measures to investigate the effect of aging on HRV.

5. CONCLUSION AND DISCUSSION

In this study, we focused on the analysis of HRV for patients with congestive heart failure. Based on the design of our study, we analyzed how the HRV of these patients changes as they get older. For this purpose, we benefited from three complexity measures. The result demonstrated that the fractal dimension, approximate entropy, and sample entropy of HRV increase with the increment of patients' age. In other words, the complexity of the HRV increases as patients get older. Therefore, we concluded that the complexity measures work well to decode the variations of heart rate during aging. We can claim that our study is comprehensive since it analyzed the variations of heart rate using three complexity measures and specifically used sample entropy to validate the results from the fractal analysis and approximate entropy.

The trend of variations of Cohen's d and p-values among different age groups supported the variations of heart rate between them. In general, we can state the obtained results from this study are according to the investigations[1] that mention the variations in the heart activity due to aging. On the other hand, the outcome of this research is interesting since the investigations in the case of healthy subjects[53,54] indicated the decrement in the complexity of HRV. In contrast, our findings for patients with heart failure indicate the increment in the complexity of HRV during aging.

In further works, a similar analysis can be conducted for healthy subjects or patients with other heart diseases (e.g. Coronary Artery Disease (CAD), Heart Arrhythmias, cardiomyopathy) to investigate how their heart rate changes with the variations of their age. Also, we can work on the analysis of the other physiological signals recorded from humans to investigate their variations with aging. For example, EEG signals as the indicator of brain activity can be analyzed using the introduced complexity measures in this study to evaluate how brain activity changes with the age of subjects. Since sample entropy,[55] approximate entropy,[56] and fractal dimension[57] of EEG signals are reactive to the changes in the status of the brain, we should be able to see their variations based on the age of subjects. Also, we can apply different stimuli (e.g. auditory, olfactory, etc.) on subjects and investigate how different organs of the body react to the stimuli based on the variations of the age. Based on the obtained results, we can understand how aging affects the body's responses to external stimuli.

Since fractal theory also can be employed in the analysis of images,[58] we can analyze the changes in medical images (e.g. MRI images) to evaluate the alterations of different organs (e.g. brain) in relation to aging.

To make a mathematical relationship between the variations of heart rate (or other organs activities) and age of subjects, we can benefit from modeling. The modeling will help us to understand the future variations of heart activity based on its current status. For this purpose, we can benefit from different mathematical (e.g. fractional diffusion equations[59]) or computational[60,61] models. Overall, all these efforts enable us to understand the activities of the human body.

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