

Linear and nonlinear heart rate dynamics in elderly inpatients. Relations with comorbidity and depression

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Key words: heart rate variability; comorbidity; depression; elderly; inpatients.

Summary. Background. Hospitalization processes are known to increase depressive symptoms arising among elderly population. Meanwhile, dysregulation of cardiac autonomic function has been suggested to link depression and cardiovascular mortality. In this context, analysis of heart rate variability (HRV) is emerging as a powerful mortality risk stratifier clinical tool. The purpose of the study was to examine the relationship among HRV, depression, and comorbidity risk among an elderly inpatient population.

Material and methods. Twenty-six subjects (aged 78 ± 9 years) were recruited from the Short-Term Stay Unit at the Hospital General de Alicante. Before joining a Physical Activity Program aimed to prevent functional impairment and after medical selection and written consent, inpatients were tested for heart rate variability, Yesavage Geriatric Depression Scale, and Charlson comorbidity index score.

Results. Men compared to women showed a significantly larger CCI score. Short-term scaling exponent (α_1), derived from detrended fluctuation analysis, showed a negative correlation with Charlson comorbidity index. Conversely, a positive correlation was found between sample entropy (SampEn) and Yesavage Scale.

Conclusions. On the one hand, fractal analysis of HRV confirms to be useful as a risk stratifier tool. On the other hand, SampEn is proposed to be reflecting a non-neurally generated complexity when accompanied with low values of α_1 . Accordingly, in this regime, it would be indicative of a paradoxical gradual reduction in cardiac autonomic control, accentuated with the severity of depressive symptoms.

Introduction

Aging is an irreversible multifactorial and stochastic impairment process. Since the second or third decade of life, the functional capacity of our systems begins to decrease progressively. Irrespective of our health status, emotional or cognitive state, age causes significant losses in our physical condition motor capacities (1, 2); metabolic, cardiovascular, respiratory, and endocrine functions (3–5); nervous system and neural-motor control (5, 6), and others.

At the same time, depression is known to cause not only personal suffering, but to be also related with higher morbidity and mortality due to its association with an increased risk of cardiovascular disease (7, 8). Moreover, hospitalized elderly people are at higher risk for the development of depression (9). Specifically, prevalence of depressive symptoms

has been described to rise up to 27% among elderly inpatients (10).

Similarly, the loss of functional capacities resulting from hospitalization is a matter of fact among elderly inpatients. Hospitalization often results in a severe restriction of activity that leads to a great impairment of mobility, a potentially loss of independence, and an increased morbidity risk, in all cases the greater, the longer the stay in hospital (11, 12). Eventually, this functional impairment is clear even 48 hours after admission (12).

In order to minimize those negative consequences of hospitalization processes and to avoid as much as possible the rising of the aforementioned depressive symptoms, the Short-Term Stay Unit (STSU) at the Hospital General de Alicante together with the Department of Physical Education and Sports, University of Valencia, launched a physical activity

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program specifically designed to be done during the hospitalization period. Before the admission into the program, patients went through a multimodal initial assessment jointly conducted by the medical team and the geriatric personal trainers (GPT), within an interdisciplinary approach. The above-mentioned evaluation included information on demographics, comorbidity, cognitive status, physical health, functional abilities, depressive symptoms, and recording of resting heart rate (HR). In the present paper, comorbidity and depression assessment together with the analysis of the resting HR recording are presented.

Heart rate variability (HRV) analysis is commonly used as an index of cardiac autonomic functioning. Decreased HRV, measured in any time or frequency domain, has been associated with a poor health status in numerous clinical studies. Moreover, recent investigations suggest that abnormal values for nonlinear HRV measures, reflecting augmented randomness of the HR, are even more strongly associated with increased mortality (13–15).

Therefore, because elderly population is at high risk of developing depressive symptoms, and this risk is highly increased when becoming embedded patients at a hospital, an examination of the relationship among heart rate dynamics, depression, and comorbidity among this group seems to be of clinical interest.

Material and methods

Twenty-six subjects (17 males and 9 females, age 78 ± 9 years) were recruited from the STSU at the Hospital General de Alicante, as a part of a larger study aimed to prevent functional impairment in elderly hospitalized patients. Only in the event of patients' extremely weakness, cardiovascular shock risk or communication incapacity, cases were excluded. All participants and their relatives gave their written consent after being informed about the research purposes, test and training procedures. This investigation is currently being jointly conducted by the aforementioned institution and the Department of Physical Education and Sports of the University of Valencia. The protocol was approved by the Research Ethics Committee of the Hospital General de Alicante.

Charlson Comorbidity Index (CCI) was developed in 1987 based on 1-year mortality data from internal medicine patients admitted in a New York Hospital (16). The index encompasses 19 medical conditions (i.e., myocardial infarction, congestive heart failure, dementia, diabetes mellitus, cancer, AIDS, etc.) weighted 1–6 depending on the risk of dying associated with this condition, with total scores ranging from 0–37 (17). Depression was evaluated by means of the 15-question Spanish Version

of the Yesavage Geriatric Depression Scale (GDS), a scale aimed to diagnose depression in population aged 65 years and more (18). This short version contains 15 dichotomous questions; each is valued with 1 point.

Resting HR measurements were performed under a standardized protocol between 9:30 AM and 10:30 AM, in a quiet environment with stable temperature. Subjects were asked to remain still, with eyes closed but without falling asleep, and to avoid disruptive movements of the head or hands throughout the recording period. Participants were equipped with an electrode transmitter belt (T61, Polar Electro, Kempele, Finland) fitted just above the chest muscles, after application of conductive gel as recommended by the manufacturer. Resting heart rate was continuously monitored and recorded for 10 min using a Polar RS800 HR monitor set to R-R interval mode (Polar Electro, Kempele, Finland). This instrument was previously validated for the accurate measurement of R-R intervals and for the purpose of analyzing HRV (19, 20).

Data were transferred to the Polar Pro Trainer 5 software (Polar Electro, Kempele, Finland) through an infrared interface, and each downloaded R-R interval file was then exported as a *.txt file and further analyzed by means of Kubios HRV Analysis Software 2.0 (The Biomedical Signal and Medical Imaging Analysis Group, Department of Applied Physics, University of Kuopio, Finland). The whole analysis process was carried out by the same researcher to ensure consistency. After proper artifact inspection and correction, time domain and spectral analysis was performed on 5-min artifact-free epochs. For the time domain, the standard deviation of normal R-R intervals (SDNN) and the root-mean-square difference of successive normal R-R intervals (rMSSD) were calculated. Before the power frequency analysis, R-R data were detrended (21) and resampled at 4 Hz. The fast Fourier transform spectrum was then calculated using a Welch's periodogram method. Low-frequency power (LF, 0.04–0.15 Hz), high-frequency power (HF, 0.15–0.4 Hz), and total power (TP, 0–0.4 Hz) were calculated as integrals of the respective power spectral density curve. LF/HF ratio was also retained for statistical analysis.

Besides time domain and spectral analysis, HR dynamics was nonlinearly analyzed using measures of fractal scaling properties and complexity. Detrended fluctuation analysis (DFA) technique was applied to the R-R interval data in order to quantify self-similarity correlations. A detailed description of this technique has been previously provided by Peng et al. (22). Briefly, the root-mean-square fluctuations of the integrated and detrended data are measured in observation windows of different sizes and then plotted against the size of the window on a log-

log scale. The result of this calculation is the scaling exponent α , which represents the slope of this line and relates (log) fluctuation to (log) windows size. Typically, in DFA, the correlations are divided into short-term and long-term fluctuations. Based on previous research (14, 23) and because of our relatively short recording time, we decided to utilize the short-term (4 to 11 beats) scaling exponent (α_1) to analyze our R–R interval data. HR complexity analyses provide a general indication of predictability of a time series. In this study, complexity was calculated using sample entropy (SampEn), which has been previously described in detail (24). By definition, SampEn is a negative natural logarithm of an estimate for the predictability in finding specific matches in a short-time series. To characterize the stringency of match recognition, the length (m) of the subseries and the tolerance (r) of the matches are previously set. Those adjustable parameters were fixed at $m=2$ and $r=20\%$ of the SD of the datasets, as previously described in the literature (25–27).

All statistical analyses were carried out using the Statistical Package for the Social Sciences software (SPSS version 15.0, SPSS Inc., Chicago, USA). The distribution of each variable was examined with the Kolmogorov–Smirnov normality test. When data were skewed, as it was the case for spectral measures, data were transformed by taking the natural logarithm to allow parametric statistical comparisons that assume a normal distribution. Therefore, TP, HF, LF, and LF/HF variables will henceforth be referred as \ln TP, \ln HF, \ln LF, and \ln LF/HF respectively.

Gender differences in CCI and GDS scores were evaluated using a Student's t test model for two samples of unequal variance. Homogeneity of variance was verified by the Levene's test. A one-way ANCOVA model was employed to elucidate differences in linear HRV indices (i.e., SDNN, rMSSD, \ln TP, \ln HF, \ln LF, \ln LF/HF) and nonlinear measures (i.e., α_1 and SampEn), between males and females, using CCI and age as covariables.

Partial correlations were used to assess the relationship between linear and nonlinear HRV indices, CCI and GDS scores, controlling for age. Moreover, gender-specific partial correlations (controlling for age and CCI) between linear and nonlinear HRV indices and GDS score were conducted. The purpose of this further analysis was to verify whether the association between depressive symptoms and cardiac autonomic regulation differed between elderly males and females, as recently proposed by Chen et al. (28). The magnitudes of correlations were defined according to Cohen (29), whereby correlations >0.5 are considered large, 0.3 – 0.5 are considered moderate and 0.1 – 0.3 are considered small.

A P value of <0.05 was considered statistically significant. Data are presented as means and standard deviations (\pm SD).

Results

Three subjects (3 males) were excluded from the analysis due to an excessive number of artifacts in their HR recordings. Men as compared to women showed a significantly larger CCI score (8.07 ± 2.49 vs. 6.33 ± 1.12 , $P=0.034$). On the contrary, women displayed a higher, although insignificant, GDS score (4.78 ± 2.95 vs. 3.36 ± 3.01 , $P=0.277$). Table 1 shows differences in linear and nonlinear HRV indices between men and women. No significant gender differences were found either in linear HRV indices (SDNN, rMSSD, \ln TP, \ln LF, \ln HF, \ln LF/HF) or amongst nonlinear measures (α_1 and SampEn).

Table 1. Gender differences in measures of linear and nonlinear heart rate dynamics

	Men	Women	P
SDNN, ms	17.98 \pm 10.50	26.57 \pm 29.69	0.635
rMSSD, ms	21.16 \pm 12.54	31.39 \pm 33.78	0.535
\ln TP, ms ²	5.09 \pm 1.33	4.99 \pm 2.35	0.566
\ln HF, ms ²	4.20 \pm 1.45	4.14 \pm 2.55	0.723
\ln LF, ms ²	4.07 \pm 1.51	3.93 \pm 2.54	0.514
\ln LF/HF	-0.11 \pm 0.87	-0.24 \pm 0.99	0.471
α_1	0.87 \pm 0.30	0.86 \pm 0.20	0.717
SampEn	1.44 \pm 0.36	1.41 \pm 0.26	0.456

Values are provided as means \pm SD. SDNN, standard deviation of R–R intervals; rMSSD, root-mean-square difference of successive R–R intervals; \ln TP, total-frequency power of R–R intervals; \ln LF, low-frequency power of R–R intervals; \ln HF, high-frequency power of R–R intervals; \ln LF/HF, ratio of low-frequency to high-frequency power; α_1 , short-term fractal scaling exponent; SampEn, sample entropy.

No significant correlations between any time or frequency domain indices and CCI or GDS scores were found. Nevertheless, α_1 displayed a negative moderate significant correlation with the CCI score ($r=-0.42$, $P<0.05$). Conversely, a positive moderate significant correlation was found between SampEn and GDS score ($r=0.57$, $P<0.01$). The results of all partial correlations (i.e., controlling for age) considering the sample as a whole are presented in Table 2.

When analyzing separately (i.e., men and women) the abovementioned relationships, amongst women, both linear and nonlinear measures failed to correlate significantly with the GDS score. On the contrary, among men, SampEn showed a positive strong significant correlation with the GDS score ($r=0.80$, $P<0.01$). The results of all gender-specific partial correlations (i.e., controlling for age and CCI score) are presented in Table 3.

Table 2. Results of partial correlations (r), controlling for age and considering the sample as a whole, between linear and nonlinear HR dynamics measures, CCI and GDS.

	SDNN		rMSSD		lnTP		lnLF		lnHF		lnLF/HF		α_1		SampEn	
	r	P	r	P	r	P	r	P								
CCI	-0.26	0.236	-0.16	0.467	-0.25	0.257	-0.26	0.231	-0.10	0.653	-0.34	0.119	-0.42	0.049*	0.20	0.379
GDS	0.21	0.342	0.20	0.375	0.22	0.317	0.18	0.434	0.29	0.191	-0.26	0.245	-0.14	0.524	0.57	0.006**

CCI, Charlson comorbidity index; GDS, Yesavage Geriatric Depression Scale; SDNN, standard deviation of R-R intervals; rMSSD, root-mean-square difference of successive R-R intervals; lnTP, total-frequency power of R-R intervals; lnLF, low-frequency power of R-R intervals; lnHF, high-frequency power of R-R intervals; lnLF/HF, ratio of low-frequency to high-frequency power; α_1 , short-term fractal scaling exponent; SampEn, sample entropy. * $P < 0.05$, ** $P < 0.01$.

Table 3. Results of gender-specific partial correlations (r), controlling for age and CCI score, between linear and nonlinear HR dynamics measures, and GDS

	SDNN		rMSSD		lnTP		lnLF		lnHF		lnLF/HF		α_1		SampEn	
	r	P	r	P	r	P	r	P	r	P	r	P	r	P	r	P
Men	0.02	0.942	0.08	0.801	0.26	0.406	0.20	0.541	0.41	0.184	-0.47	0.128	-0.23	0.473	0.80	0.002**
Women	0.39	0.384	0.32	0.0485	0.36	0.422	0.41	0.365	0.33	0.471	0.27	0.552	0.43	0.332	0.04	0.933

SDNN, standard deviation of R-R intervals; rMSSD, root-mean-square difference of successive R-R intervals; lnTP, total-frequency power of R-R intervals; lnLF, low-frequency power of R-R intervals; lnHF, high-frequency power of R-R intervals; lnLF/HF, ratio of low-frequency to high-frequency power; α_1 , short-term fractal scaling exponent; SampEn, sample entropy. * $P < 0.05$, ** $P < 0.01$.

Discussion

Fractal scaling properties of HR dynamics have been shown to yield powerful prognostic information compared with conventional measures of HRV. Specifically, a growing body of evidence is emerging regarding prognostic power of short-term fractal scaling properties analyzed by means of the DFA technique. Eventually, a breakdown of short-term fractal organization in human HR dynamics, expressed as a reduced scaling exponent α_1 , has been observed in various disease states, and it has been indicative of an increased risk of mortality and life-threatening arrhythmias in patients with and without structural heart disease. Moreover, in non-heart-diseased elderly population, α_1 has been suggested to be an specific risk marker of cardiac death (23). Interestingly, in the above-mentioned study, α_1 displayed an association with overall mortality, whereas ApEn showed no prognostic power. Similarly, in our study, α_1 displayed a significant correlation with the CCI score ($P=0.049$), but SampEn was far from significantly correlating with the CCI score ($P=0.524$). It may imply that among nonlinear measures, those addressed to assess fractal correlation properties, are more accurate as risk stratifiers than those analyzing HR complexity.

Some authors have already advocated for generalizing the application of α_1 as a risk stratifier of sudden cardiac death beyond the patient populations considered at increased risk of fatal arrhythmias to the general elderly population (14, 23). Notwithstanding, as pointed out by Huikuri et al. (13) in a recent review article, DFA of HR dynamics is not yet in widespread clinical use. Unlike the above-mentioned approach, CCI is worldwide and commonly utilized for risk adjustment. Therefore, our statically significant correlation between α_1 and CCI further reinforces the application of α_1 as a mortality risk stratifier and should encourage its widespread clinical use, especially among elderly populations and/or pluripathologic patients.

A positive correlation between severity of depressive symptoms and HR complexity (see Table 2) found in the present study is in complete disagreement with some previous investigations concerning this relationship (30, 31). However, this contradiction may be simply due to a methodological issue. Unlike the above-mentioned authors, who used an approximate entropy (ApEn) algorithm, we employed a SampEn algorithm to measure the complexity of our RR interval data. SampEn was proposed by Richman and Moorman (24) to overcome limitations associated with ApEn. Specifically, SampEn excludes counting self-matches and does not employ a template-wise strategy for calculating probabilities as ApEn does. Therefore, SampEn is widely accepted as a more consistent and less biased

complexity measure. And accordingly, ApEn results should be interpreted with caution (32). However, irrespective of methodological considerations, larger values of HR complexity are usually associated with a healthier cardiac autonomic functioning (26, 33, 34).

Notwithstanding, this unidirectional view of changes in HR complexity has been thoroughly discussed (35), and it remains an open and somewhat controversial question (32, 36). As proposed for linear HRV indices, it could be that larger values do not necessarily mean “better” values (15). Platisa and Gal (37) interestingly assessed resting HR dynamics, by means of both SampEn and DFA, in four groups of people: young healthy subjects, elderly individuals, congestive heart failure subjects, and a patient with transplanted heart. They found that illness was characterized by concomitant loss of regularity (i.e., high SampEn) and short-term fractal correlation properties of RR interval dynamics (i.e., low α_1). Similar HR dynamics has been described during high intensity exercise (38, 39). Hence, it may be suggested that high values of SampEn should be interpreted bidirectionally. On the one hand, together with “good” values of α_1 (i. e., nearing 1), larger values of SampEn should be interpreted as healthier. On the other hand, when accompanied with low values of α_1 , high values of SampEn might be indicative of a gradual reduction in cardiac autonomic control via the sinus node. In this regime, SampEn would be reflecting a non-neurally generated complexity (i.e., intrinsic heart control mechanisms) (32, 37, 40, 41). In alignment with this notion, Greiser et al. (42) suggested that increasing HRV in men aged 75 years and more might be explained by a higher prevalence of sinus node disease (compared to women).

Our α_1 results (0.87 ± 0.26) are far from those considered as “healthy”; on the contrary, they are indicative of an increased risk of cardiac mortality in our sample (14, 23). Accordingly, a positive correlation showed between severity of depressive symptoms and HR complexity leads us to conclude that depression, even in an already frail population (78 ± 9 years, CCI 7.39 ± 2.21), further impairs cardiac autonomic regulation. Interestingly, in the unique depression-related study, to the best of our knowledge, in which HR dynamics was analyzed by means of SampEn (43), patients with major depressive disorder (compared to healthy subjects) showed higher, although insignificant statistically, values in that variable (1.77 vs. 1.92). Moreover, in Chen et al. study (28), although SampEn was not measured, a concomitant decrease in HF and LF/HF among severe depressed elderly participants was interpreted as a “pervasive decline of their cardiac autonomic function.”

Therefore, the present investigation contributes further to previous investigations examining depression-related cardiac autonomic dysregulation, especially those using HR complexity measures in their analysis (30, 31, 43). Moreover, consistent with previous research (39, 44–46), nonlinear approaches (compared to linear indices) showed superior for detecting subtle changes in HR behavior in an already poor HRV background. Nevertheless, further studies with larger samples are needed to confirm our hypothesis and clarify the underlying mechanisms of the “non-healthy” higher SampEn-RR proposed in the present paper. At the same time, a reanalysis of our RR interval data using the recently developed Multiscale Sample Entropy technique would enable us to reach more robust conclusions (47, 48).

Similarly to us, Rozzini et al. (49) findings pointed to a higher prevalence of depressive symptoms among female inpatients, while comorbidity risk was greater amongst males (i.e., higher values of CCI). Notwithstanding, these gender differences were attenuated from 70 s to 90 s, almost disappearing in the last decade. Meanwhile, differences in resting HRV between men and women among elderly population have been thoroughly examined; however, results are partly contradictory. Within a large community study (1742 participants), Felber Dietrich et al. (50) showed that women aged 65–73 had a significantly higher HF but lower LF and LF/HF than men of the same age group. In a similar size sample (1779 participants), Greiser et al. (42) corroborated these gender differences in resting HRV (higher HF but lower LF and LF/HF in women), furthermore including subjects up to 83 years of age. Notwithstanding, even recently, Chen et al. (28) showed no significantly gender differences in LF, HF, and LF/HF ratio in a homogeneous sample of 606 participants aged 65 or more.

Besides, only a handful of studies concerning gender differences among elderly population have included nonlinear HRV measures in their analysis. Kojima et al. (30) measured α_1 and ApEn in a sample of 119 hemodialysis patients aged 55.2 ± 10.5 years. By using an ANCOVA model, where age and serum albumin were entered as covariables, they found that both variables displayed significantly lower values in women compared to men. We utilized a similar statistical approach in our study, covarying for age and CCI score in our analysis. Nevertheless, we failed to find any significant gender differences (see Table 1). This difference may be explained not only by our smaller sample (23 vs. 116 subjects), but also because of our participants were much older (78 ± 9 vs. 55.2 ± 10.5 years), and gender differences are known to disappear as a function of time (51, 52).

Despite finding no gender differences in all HR dynamics measures (included SampEn), we decided to conduct stratified (i.e., separating men and women) partial correlations between linear and nonlinear HRV indices and GDS. The purpose of this further analysis was to examine whether gender plays an interactive role on the relationship between depression and cardiac autonomic regulation. Interestingly, we found a stronger correlation between SampEn and GDS score when considering only men than when considering the entire sample ($r=0.80$ vs. $r=0.57$). Meanwhile, among women, SampEn failed to correlate with GDS score (see Table 3). This more robust association between depression and cardiac autonomic dysregulation in elderly males compared to females is in accordance with Chen et al. (28). Assuming that increased complexity of RR interval data at rest may be indicative of reduced cardiac autonomic control in some cases (i.e., when it is accompanied with low values of α_1), the absence of relationship between severity of depressive symptoms and HR complexity among females could be due to women (compared to men) lagging behind several years in developing cardiovascular diseases (i.e., sinus node impairment) (42).

Conclusions

In the present study, two major findings should be highlighted. Firstly, measurement of fractal properties of heart rate dynamics kept a significant relationship with CCI score, thus emphasizing their use as a risk stratifier tool. Secondly, exceedingly higher values of SampEn among severely depressed elderly may be reflecting a progressive loss in cardiac autonomic control. This latter observation further reinforces depression deleterious effect on inpatients' health and utterly justify interventions aimed to avoid or reduce the appearance of depressive symptoms associated with hospitalization processes. However, as above-mentioned, further studies with larger samples and a reanalysis of the RR interval data using the recently developed multiscale sample entropy technique are needed to delve into this phenomenon.

Nevertheless, as a main conclusion, according to the results here presented, interventions aimed to avoid or reduce the appearance of depressive symptoms associated with hospitalization processes are fully justified.

Acknowledgments

Special thanks to Arturo Ruíz, chief-responsible of the Delegation of the Consell Valencià de l'Esport in Alicante, and to Dr. Raúl P. Garrido, Dr. at the General Hospital de Alicante, for their help and support in the building up of this project.

Vyresnio amžiaus žmonių tiesinė ir netiesinė širdies dažnio dinamika Ryšys tarp sergamumo ir depresijos

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Raktažodžiai: širdies ritmo variabilumas, sergamumas, depresija, vyresnio amžiaus žmonės, ligoniniai.

Santrauka. Žinoma, jog hospitalizacijos procesas didina depresijos simptomus vyresnio amžiaus žmonėms. Tuo tarpu širdies autonominės funkcijos išsiregulavimas turi ryšį su depresija bei mirštamumu sergant širdies kraujagyslių ligomis. Taigi, širdies dažnio variabilumo (HRV) analizė tampa efektyviu mirtinumo rizikos vertinimo klinikiu įrankiu. *Tyrimo tikslas* – ištirti ryšį tarp HRV, depresijos ir sergamumo vyresnio amžiaus asmenims.

Tirtųjų kontingentas ir tyrimo metodai. Ištirti 26 asmenys (amžius 78±9 metai), gydyti trumpalaikio gydymo skyriuje Alicantės ligoninėje. Siekiant išvengti funkcinų sutrikimų, prieš įtraukiant į fizinio aktyvumo programą ir po medicininės atrankos bei rašiško sutikimo, ligoniniai tirti: atlikta HRV analizė pagal Yesavage geriatrinę depresijos skalę, apskaičiuotas Chalson sergamumo indeksas (CCI).

Rezultatai. Vyrai, lyginant su moterimis, parodė patikimai didesnę CCI. Trumposios skalės eksponentė (α_1), gauta iš betrendinės svyravimų analizės, parodė neigiamą koreliaciją su CCI. Priešingai, teigiama koreliacija rasta tarp imties Entropijos (SampEn) ir Yesavage skalės.

Išvada. Pirma, HRV fraktalinė analizė yra geras rizikos vertintojo įrankis. Antra, SampEn gali rodyti nenerviniu keliu sukuriama kompleksiskumą, kai randama drauge su mažomis α_1 reikšmėmis. Atitinkamai šioje situacijoje gali būti naudingas α_1 dydis, esant ūminiam širdies autonominės reguliavimo sistemos įtakos sumažėjimui, kartu esant sunkių depresijos simptomų.

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Received 17 May 2010, accepted 7 June 2010

Straipsnis gautas 2010 05 17, priimtas 2010 06 07