Fundamental researches

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ENTROPY OF FREQUENCY DOMAIN OF HEART RATE VARIABILITY

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Introduction. The heart rate variability (HRV) is based on measuring (time) intervals between R-peaks (of RR-intervals) of an electrocardiogram (ECG) and plotting a rhythmogram on their basis with its subsequent analysis by various mathematical methods which are classified as Time-Domain (TD), Frequency-Domain (FD) and Nonlinear [1, 2]. There are a number of popular Nonlinear methods used in HRV analysis, such as entropy-based measures that mostly applied for TD. Spectral Entropy (SE) is using for Frequency-Domain: it is defined to be the Shannon entropy of the power spectral density (PSD) of the data. An important characteristic of Frequency-Domain studies is sympatho-vagal balance, which has been overlooked by entropy-based analysis. This is due to the fact that good entropy analysis restricted the number of existing HRV data, which is shrinking in FD and also in total spectrum parts.

Aim of the research. The goal of this paper is to provide a reliable formula for calculating entropy accurately for Frequency-domain of standard 5-min. HRV records and to show the advantages of such approach for analyzing of sympatho-vagal balance for healthy subjects (NSR), Congestive Heart Failure (CHF) and Atrial Fibrillation (AF) patients.

Materials and Methods. We used MIT-BIH long-term HRV records for Normal Sinus Rhythm (NSR), Congestive Heart Failure (CHF) and Atrial Fibrillation (AF).

The generalized form of the Robust Entropy Estimator (*EnRE*) for Frequency-domain of standard 5-min. HRV records was proposed and the key *EnRE* futures was shown.

The difference between means of the two independent selections (NSR and CHF, before and after AF) has been determined by a *t*-test for independent samples; discriminant analysis and statistical calculations have been done by using the statistical package IBM SPSS 27.

The results of the study. We calculate entropy for all valuable for HRV spectral interval, namely 0–0.4 Hz and to compare with existing results for Spectral Entropy: qualitatively we receive the same distribution number as [14] and significant difference ($p < 0.001$) between entropy averages for NSR and CHF or AF patients.

We define low-frequencies (LF) power spectrum components in the range of 0.04–0.15 Hz and high-frequencies (HF) power spectrum components in the range of 0.15–0.4 Hz [1]. The sympatho-vagal balance is a simple ratio LF/HF [1]. Then, we define an entropy eLF of the LF power spectrum components, an entropy eHF of the HF power spectrum components and entropy based sympatho-vagal balance as a ratio eLF/eHF.

The difference between NSR and CHF groups are significant in both cases LF/HF and eLF/eHF with $p < 0.001$, but in case of eLF/eHF the results are quite better ($t = -4.8$, compared to LF/HF where $t = -4.4$). The discriminant analysis shows total classification accuracy for eLF/eHF in 79.3 % ($\chi^2 = 19.4$, $p < 0.001$) and for LF/HF in 72.4 % ($\chi^2 = 16.6$, $p < 0.001$).

We applied entropy-based Frequencies-domain analyzing for AF patients and showed that ratio eLF/eHF is significantly higher during AF than before AF ($p < 0.001$). This is opposite to ordinary LF/HF where difference is insignificant due to high variation of this ratio.

Conclusion. Proposed in the article is generalized form for Robust Entropy Estimator *EnRE* for Frequencies-domain, which allows, for time series of a limited length (standard 5-min. records), to find entropy value of HRV power spectrum (total spectrum, low- and high- frequencies bands).

Using the proposed *EnRE* for MIT-BIH database of HRV records, we show for standard 5 min. HRV records the usage of *EnRE* of HRV power spectrum and entropy-based sympatho-vagal balance of Normal Sinus Rhythm (NSR) and Congestive Heart Failure (CHF) cases. It is demonstrated, that, entropy-based Frequencies-domain analyzing is applicable for case of Atrial Fibrillation (AF) even during AF episodes. We showed the significant difference ($p < 0.001$) before and during AF for entropy of total spectrum, as well as for sympatho-vagal balance in form of eLF/eHF.

KEY WORDS: *hearth rate variability, entropy, frequency-domain, congestive heart failure, atrial fibrillation*

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INTRODUCTION

The heart rate variability (HRV) is based on measuring (time) intervals between R-peaks (of RR-intervals) of an electrocardiogram (ECG) and plotting a rhythmogram on their basis with its subsequent analysis by various mathematical methods that are classified as Time-Domain (TD), Frequency-Domain (FD) and Nonlinear [1, 2]. There are a number of popular Nonlinear methods used in HRV analysis, such as entropy-based measures, like approximate entropy (ApEn) [3] and sample entropy (SampEn) [4]. SampEn is regarded as a modified version of ApEn, intended to solve such shortcomings as bias and relative inconsistency [4]. However, the traditional SampEn method is single-scale based and, therefore, fails to account for the multiple time scales inherent in cardiovascular systems [5–7]. Multiscale entropy (MSE) method was proposed in [7] and received much attention in the biomedical and mechanical fields [8–10]. Further MSE developing was transformed to multiscale multivariate entropy analysis [8, 10–13]. These entropy-based measures are all applied to original RRs, – that is mean their implementation for Time-Domain. Other hand the Spectral Entropy (SE) is using for Frequency-Domain: it is defined to be the Shannon entropy of the power spectral density (PSD) of the data. In article [14] the SE were estimated for healthy, thyroid and depression subjects, as well as for patients with Congestive Heart Failure (CHF) and Atrial Fibrillation (AF). It was shown the significant different of SE for all categories and ordered to increase of SE are: depression, thyroid, CHF, AF and healthy subjects. An important characteristic of Frequency-Domain studies is sympatho-vagal balance, which has been overlooked by entropy-based analysis. The reason for this was that good entropy analysis restricted the number of existing HRV data, which is shrinking in FD and also in total spectrum parts.

Prevalence of the effective methodology of entropy analysis of FD for standard 5-min HRV records is suppressed by unsatisfactory accuracy of available methods in case of short records as we shown in [15]. Therefore, it appears there is a necessity for building a robust formula for calculating entropy for each part of spectrum in Frequency-Domain with required accuracy for a limited series of RR-intervals observed in a standard 5-minute HRV record.

MATERIALS AND METHODS

We used long-term HRV records by Massachusetts Institute of Technology – Boston's Beth Israel Hospital (MIT-BIH) from [16] (http://www.physionet.org), a free-access, on-line archive of physiological signals. Normal Sinus Rhythm (NSR) RR Interval Database includes beat annotation files for 54 long-term ECG recordings of subjects in normal sinus rhythm (30 men, aged 28.5 to 76, and 24 women, aged 58 to 73). Congestive Heart Failure (CHF) RR Interval Database includes beat annotation files for 29 long-term ECG recordings of subjects aged 34 to 79, with congestive heart failure (NYHA classes I, II, and III). Subjects include 8 men and 2 women; gender of the remaining 21 subjects is not known. The original electrocardiography (ECG) signals for both NSR and CHF RR interval databases were digitized at 128 Hz, and the beat annotations were obtained by automated analysis with manual review and correction.

The MIT-BIH Atrial Fibrillation (AF) Database [17] was used for our entropy-based analyzing with long and short RR's subsets. This database includes 25 long-term ECG recordings of human subjects with atrial fibrillation (mostly paroxysmal). The individual recordings are each 10 hours in duration, and contain two ECG signals each sampled at 250 samples per second with 12-bit resolution over a range of ± 10 millivolts. The original analog recordings were made at Boston's Beth Israel Hospital (now the Beth Israel Deaconess Medical Center) using ambulatory ECG recorders with a typical recording bandwidth of approximately 0.1 Hz to 40 Hz.

A generalized form of the Robust Entropy Estimator (*EnRE*) for time series was proposed in [15] and adopted for power spectral density (PSD) of RR now:

$$EnRE = ln\left(\frac{A}{N^{l/2}}\sum_{i=1}^{N}\sum_{j=1}^{N}\left(\frac{\left(|B_i - B_j||B_j - MD|\right)^{1/k}}{(D_{ij})^{m/2}}\right)\right),$$

where *MD* is median of the sequence for *B* value of PSD; D_{ij}- distance between B_i and B_j; *A, l, m, k* – estimated coefficients. Search conditions for coefficients *A, l, m, k* is the following:

1/ accurate approximation for known distributions of a random value;

2/ independence of *EnRE* from *N* for initial time series and for series after sorting;

3/ independence of *EnRE* from additive changes of mean.

After numerical researches the following coefficient values had been found: $l = 3$, $m = 1$, $k = 2$.

The difference between means of the two independent selections (NSR and CHF, before and after AF) has been determined by a *t*-test for independent samples; discriminant analysis and statistical calculations have been done by using the statistical package IBM SPSS 27.

RESULTS AND DISCUSSION

First of all, let us calculate entropy for all valuable for HRV spectral interval, namely 0–0.4 Hz. That is give us possibility to compare with existing results for Spectral Entropy: qualitatively we receive the same distribution number as [14] and significant difference ($p < 0.001$) between entropy averages for NSR and CHF or AF patients. Quantitatively our result is not exactly the same to [14] because we used different entropy measures: SE is based on Shannon entropy and *EnRE* approximated the entropy of distribution or differential entropy.

Table 1

Entropy of all spectral interval of HRV

Entropy	Healthy (NSR)	CHF	AF
EnRE	$1.77 \pm 0.4^{*}$	1.13 ± 0.62	1.36 ± 0.09
SE [14]	1.95	0.85	1.15

According to [1] we define low-frequencies (LF) power spectrum components in the range of 0.04–0.15 Hz and high-frequencies (HF) power spectrum components in the range of 0.15–0.4 Hz. The sympatho-vagal balance is a simple ratio LF/HF [1]. We calculate an entropy of LF power spectrum components as eLF, entropy of HF power spectrum components as eHF and entropy based sympatho-vagal balance as a ratio eLF/eHF.

Many authors emphasize the importance of sympatho-vagal balance measures, but statistical significance makes it difficult to estimate the effects in CHF patients: for example, in [18] showed that LF/HF is significantly lower for CHF patients compare with healthy subjects, but in compare with [19], where difference in LF/HF between CHF and NSR groups is insignificant due to $p = 0.175$. The results of calculations of LF/HF and eLF/eHF for CHF and NSR groups are shown on the Fig. 1.

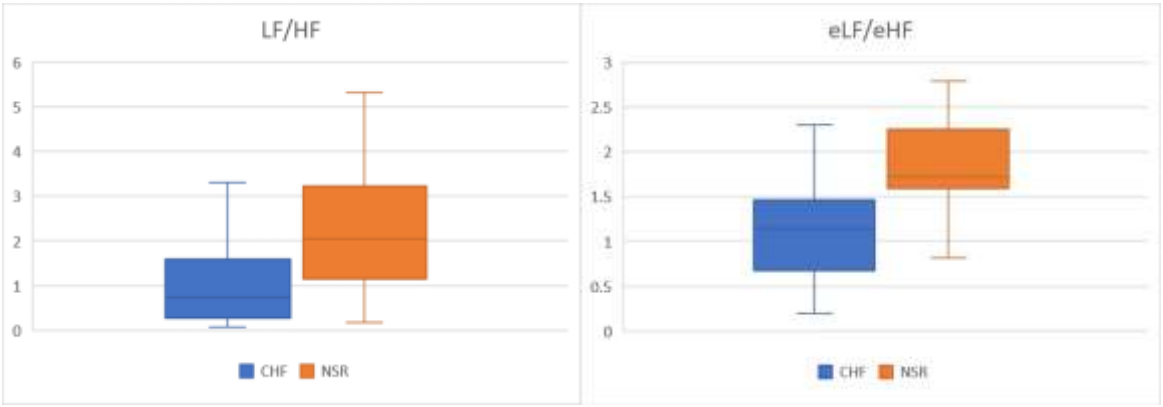

Fig. 1. Box & Whiskers plots of LF/HF and eLF/eHF for NSR and CHF groups

The difference between groups are significant in both cases LF/HF and eLF/eHF with $p < 0.001$, but in case of eLF/eHF it is something better with $t = -4.8$ in compare to LF/HF where is $t = -4.4$. The discriminant analysis shows total classification accuracy for eLF/eHF in 79.3% ($\chi^2 = 19.4$, $p < 0.001$) and for LF/HF in 72.4% ($\chi^2 = 16.6$, $p < 0.001$).

More interesting is applying such entropy-based Frequencies-domain analyzing for AF patients. There is an opinion that FD analysis is unsuitable for AF and this is true in case of LF/HF, because no significant difference before and during AF due to high variation of this ratio (see Fig. 2). The entropy-based ratio eLF/eHF is suitable much better for this case, – the eLF/eHF is significantly higher during AF than before AF ($p < 0.001$).

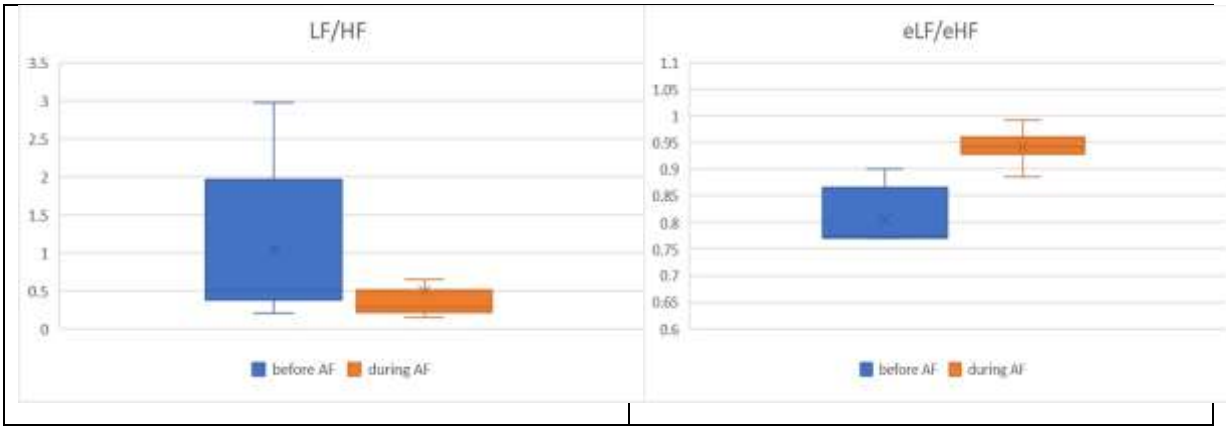

Fig. 2. Box & Whiskers plots of LF/HF and eLF/eHF for AF patents (before and during AF episodes)

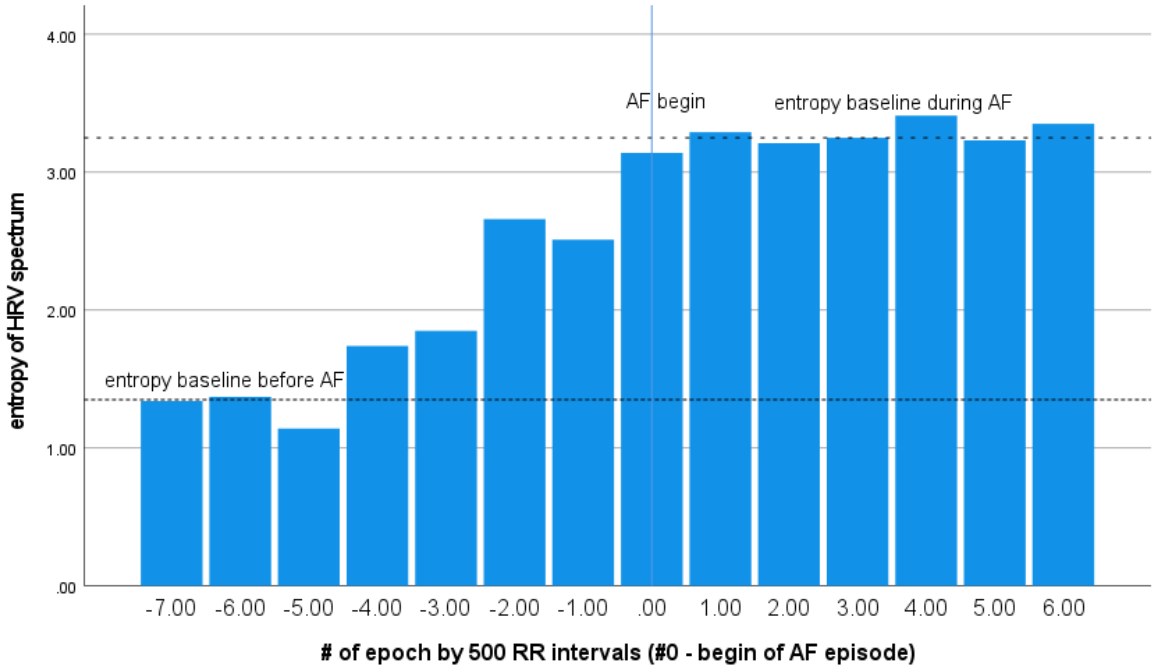

Fig. 3. Typical pattern of entropy of HRV power spectrum before and during atrial fibrillation episode (MIT-BIH AF Database [16]).

The Fig. 3. shows typical pattern of entropy of HRV power spectrum evolution before and during atrial fibrillation episode: each epoch on the Fig. 3. consists of short RRs records (N = 500); epoch with # '0' is the beginning of AF according to MIT-BIH reference rhythm annotations. Entropy of power spectrum does not have significant difference from mean record value under Normal rhythm intervals except 4–5 epochs before and after AF episodes: entropy begin significantly growth for about 20 minutes (or 4–5 epoch by N = 500 RRs) before AF and excides new maximal baseline during AF. The new baseline level is significantly different from previous one – before AF ($p < 0.001$).

Therefore, proposed generalized form for Robust Entropy Estimator *EnRE* for HRV power spectrum shows significant differences ($p < 0.001$) of total spectrum entropy and entropy-based sympatho-vagal balance for NSR and CHF groups in short records ($N = 500$), and presents additional advantages provided by *EnRE* in case of patients with atrial fibrillation.

CONCLUSIONS

Proposed in the article is generalized form for Robust Entropy Estimator *EnRE* for Frequencies-domain, which allows, for time series of a limited length (standard 5-min. records), to find entropy value of HRV power spectrum (total spectrum, low- and high-frequencies bands). Parameters in generalized form for *EnRE* have been derived from the following criteria:

1/ accurate approximation for known distributions of a random value in ranges that represent models of RRs for heart rate variability;

2/ independence of *EnRE* from *N* for initial time series and for series after sorting;

3/ independence of *EnRE* from additive changes of mean.

Using the proposed *EnRE* for MIT-BIH database of HRV records, we show for standard 5 min. HRV records the usage of *EnRE* of HRV power spectrum and entropy-based sympatho-vagal balance of Normal Sinus Rhythm (NSR) and Congestive Heart Failure (CHF) cases. It is demonstrated, that, entropy-based Frequencies-domain analyzing is applicable for case of Atrial Fibrillation (AF) even during AF episodes. We showed the significant difference ($p < 0.001$) before and during AF for entropy of total spectrum, as well as for sympatho-vagal balance in form of eLF/eHF.

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ЕНТРОПІЯ ЧАСТОТНОГО ДОМЕНУ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ

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A – концепція та дизайн дослідження; B – збір даних; C – аналіз та інтерпретація даних; D – написання статті; E – редагування статті; F – остаточне затвердження статті

Вступ. Варіабельність серцевого ритму (ВСР) базується на вимірюванні (часових) інтервалів між R-піками (RR-інтервалів) електрокардіограми (ЕКГ) і побудови на їх основі ритмограми з подальшим її аналізом різними математичними методами, які класифікуються як Часова область (TD), частотна область (FD) і нелінійна [1, 2]. Існує ряд популярних нелінійних методів, які використовуються в

аналізі ВСР, наприклад вимірювання на основі ентропії, які в основному застосовуються для TD. Спектральна ентропія (SE) використовується для частотної області: вона визначається як ентропія Шеннона спектральної щільності потужності (PSD) даних. Важливою характеристикою частотних досліджень є симпато-вагальний баланс, який раніше не враховувався в аналізі на основі ентропії. Причиною цього було те, що якісний ентропійний аналіз обмежено кількістю існуючих даних ВСР, які зменшуються у FD, а також у частинах загального спектру.

Мета. Метою цієї статті є надання надійної формули для точного обчислення ентропії для частотної області стандартних 5 хвилин запису ВСР та показати переваги такого підходу для аналізу симпато-вагального балансу у здорових суб'єктів (NSR), пацієнтів із застійною серцевою недостатністю (CHF) та фібриляцією передсердь (AF).

Матеріали і методи. Ми використовували довгострокові записи ВСР бази даних MIT-BIH для нормального синусового ритму (NSR), застійної серцевої недостатності (CHF) і фібриляції передсердь (AF).

Була запропонована узагальнена форма надійного оцінювача ентропії (EnRE) для частотної області стандартних 5 хв. записів ВСР і показані ключові ознаки EnRE.

Різниця між середніми значеннями двох незалежних вибірок (NSR і CHF, до і після AF) була визначена t-тестом для незалежних вибірок; дискримінантний аналіз і статистичні розрахунки виконано за допомогою статистичного пакету IBM SPSS 27.

Результати. Ми обчислювали ентропію для всього спектрального інтервалу ВСР, а саме 0–0,4 Гц, і порівнювали з існуючими результатами для спектральної ентропії: якісно ми отримуємо таке ж число розподілу, як у [14], і значущу різницю ($p < 0,001$) між середніми значеннями ентропії для NSR та пацієнтів із CHF або AF.

Визначаємо низькочастотні (LF) складові спектра потужності в діапазоні 0,04–0,15 Гц і високочастотні (HF) компоненти спектра потужності в діапазоні 0,15–0,4 Гц [1]. Симпато-вагальний баланс – це просте співвідношення LF/HF [1]. Ми обчислюємо ентропію компонентів спектру потужності LF як eLF, ентропію компонентів спектру потужності HF як eHF і симпато-вагальний баланс на основі ентропії як співвідношення eLF/eHF.

Різниця між групами NSR і CHF є значною в обох випадках LF/HF і eLF/eHF з $p < 0,001$, але у випадку eLF/eHF це дещо краще з $t = -4,8$ порівняно з LF/HF, де $t = -4,4$. Дискримінантний аналіз показує загальну точність класифікації для eLF/eHF у 79,3 % ($\chi^2 = 19,4$, $p < 0,001$) і для LF/HF у 72,4 % ($\chi^2 = 16,6$, $p < 0,001$).

Ми застосували частотний аналіз на основі ентропії для пацієнтів з AF і показали, що співвідношення eLF/eHF значно вище під час AF, ніж до AF ($p < 0,001$). Це протилежно звичайному НЧ/ВЧ, де немає статистичної значущості різниці через велику варіацію цього співвідношення.

Висновки. У статті запропоновано узагальнену форму надійного оцінювача ентропії EnRE задля частотного домену ВСР, що дозволяє для часових рядів обмеженої довжини (стандартні 5-хвилинні записи) знаходити значення ентропії спектра потужності ВСР (загальний спектр, низька і висока смуги частот).

Використовуючи запропоновану формулу EnRE для MIT-BIH бази даних записів ВСР, ми показали для стандартних 5 хв. записів ВСР використання EnRE спектра потужності ВСР та симпато-вагального балансу на основі ентропії у випадках нормального синусового ритму (NSR) і застійної серцевої недостатності (CHF). Продемонстровано, що ентропійний аналіз у частотній області застосований для випадків фібриляції передсердь (AF) навіть під час епізодів AF. Ми показали достовірну різницю ($p < 0,001$) до та під час AF для ентропії загального спектру, а також для симпато-вагального балансу у формі eLF/eHF.

КЛЮЧОВІ СЛОВА: *варіабельність серцевого ритму, ентропія, частотний домен, застійної серцевої недостатності, фібриляції передсердь*

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