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New approach to heart rate variability analysis based on cardiophysiological biomarkers

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Abstract

Background: The heart rate variability (HRV) analysis is a well-known method demonstrating its value over the years in different medical fields. However, it still has its known limitations.
Material and methods: The new approach to HRV analysis is based on a complementary HRV standard analysis with new cardiophysiological biomarkers. The biomarkers are assessed on cardiorhythmograms obtained by a 5-minute ECG recording using a specialized hardware (Polyspectrum-HRV-device, Neurosoft).
Results: A possible applicative value of the biomarkers is shown on examples of how a prognosis for recurrence of atrial fibrillation (AFib) could be made. When in a rest-state cardiorhythmogram are observed LF drops and are followed by a pathological counterregulation, prognostically, recurrence of atrial fibrillation is expected. When in a cardiorhythmogram LF drops are observed and are followed by a physiological counterregulation, prognostically, sinus rhythm is expected. Physiological background of the biomarkers: increased central modulation of the heart in rest state of a patient, a sympathetic overflow of the heart in calm state and insufficiency of compensatory parasymphatetic counteractivation. Limitations of the paper: this is a methodological paper without description of patients. This paper will be followed by a clinical paper in which we are going to describe the validation of these cardiophysiological biomarkers on patients with AFib.
Conclusions: Complementary to the standard HRV analysis, cardiophysiological biomarkers should be assessed: LF drops and HF counterregulation could be used for prognosis construction in cardiology.
Key words: cardiophysiological biomarkers, heart rate variability.

Introduction

The new methodological approach described in this paper is based on heart rate variability (HRV) analysis. The HRV analysis is a well-known method which has been demonstrating its value over the years in different medical fields [1, 27]. However, it still has its known limitations [2]. Although from a physiological point of view it could offer much more information than offer classical statistical programs for an automatic HRV analysis. One of the limitations in use of HRV in the cardiologic field is the problem of steady-state cardiorhythmograms. Steady-state cardiorhythmogram means, that during the 5-minute measurement no extra waves are triggered from outside or even inside, i.e. the person should demonstrate a constant breathing pattern without hyperventilation, no extrasystoles should occur nor any other arrhythmias and all other standard conditions [3] to avoid the appearance of extra waves, should be respected. As far as additional waves occur in the cardiorhythmogram, i.e. triggered by a change of respiratory pattern, extrasystoles etc., it cannot be analysed using classical methods of HRV analysis. Sometimes, such additional waves are cut out to make the classical analysis possible at all. However, cutting out, the biosignal loses some of its quality and reliability [4]. That is the main reason, why such cardiorhythmograms are mostly just ignored or just minimal information is extracted from such a HRV analysis. For instance, to determine whether the HRV is high or low – from a physiological point of view – there is only a minimum of information that could be extracted from a HRV analysis when applying also physiological skills for a HRV analysis. In cardiology, there are very common cardiorhythmograms which do not at all correspond to a steady-state cardiorhythmogram. That is why in this field there are a lot of limitations in the application of HRV analysis. Mathematicians are trying to solve this problem by using an analysis of non-steady-state cardiorhythmograms with non-linear methods of HRV analysis [5, 27, 31]. Another possible way to solve this problem is described in this paper. It is proposed to assess the standard HRV analysis using additionally cardiophysiological biomarkers for a more advanced physiological HRV interpretation.

Material and methods

The biomarkers are assessed on cardiorhythmograms obtained by a 5-minute ECG recording using a specialized hardware (Polyspectrum-HRV-device, Neurosoft). The biosignal was obtained from a one-channeled ECG, the first derivative was applied. It is important to mention, that the biosignal for further HRV analysis was obtained not from a Holter ECG. In order to obtain a reliable biosignal and to ensure the reproducibility of the data, all standard conditions during measurement were regarded [3].

Standard operating procedure for heart rate variability recording

Resting state probe includes a 5-minute ECG recording which is done in supine position. During the recording the person lies quietly but is alert with free spontaneous breathing. The person has to be in sinus rhythm. Before starting with the recording itself, a steady-state was achieved. Therefore, the person lies with connected electrodes and is checked on the monitor until the moment when a steady-state signal is reached. Only then starts the recording of the ECG signal which will be used for further HRV analysis. The length of the transition phase needed for achieving a steady-state signal is very individual and usually takes from 5 to 20 minutes [6]. This is to avoid false positive reactions of an increased level of the sympathetic or parasympathetic part of the vegetative nervous system. In the rest state probe, there should be an assessment of the functional activity of the regulatory systems of the heart including the medullar level and the central one. It can be concluded that a reliable and qualitative assessment can only be effected, if all additional influences, not belonging to the rest state condition, are excluded.

Results and discussion

The data were analysed by the use of „Neuro-Soft"-software which is working with biosignals and is specialized on HRV analysis. Additionally the data were analysed by using cardiophysiological biomarkers. Standard HRV analysis methods are not described in this paper as these are well known [3, 12]. The new physiological approach to HRV analysis by using cardiophysiological biomarkers will be described. These are applied when evaluating cardiorhythmograms and spectrograms. Were applied several cardiophysiological biomarkers but in this paper are described only the most informative, most important and most convenient ones for the data analysis: Low frequency (LF) drops, high frequency (HF) counterregulation and increased central activity in rest state.

HRV is applied for risk determination in different cardiovascular diseases [5, 28]. In order to illustrate a possible way of applying cardiophysiological biomarkers, there are given examples of how a prognosis for atrial fibrillation and sinus rhythm can be made. Hence, we analysed different cardiorhythmograms and spectrograms using the cardiophysiological biomarkers.

Below are presented cardiorhythmograms and spectrograms, where prognostically a sinus rhythm (SR) is expected by applying the biomarkers' analysis:

1.A. On the rhythmogram no LF drops are recognized and the HRV is predominantly modulated by HF waves (fig. 1).

1.B. On the spectrogram dominates the HF spectrum area (blue) with a physiological peaks' distribution (fig. 2).

2.A. On a rhythmogram LF drops are present but are followed by a physiological counterbalancing via HF waves (fig. 3).

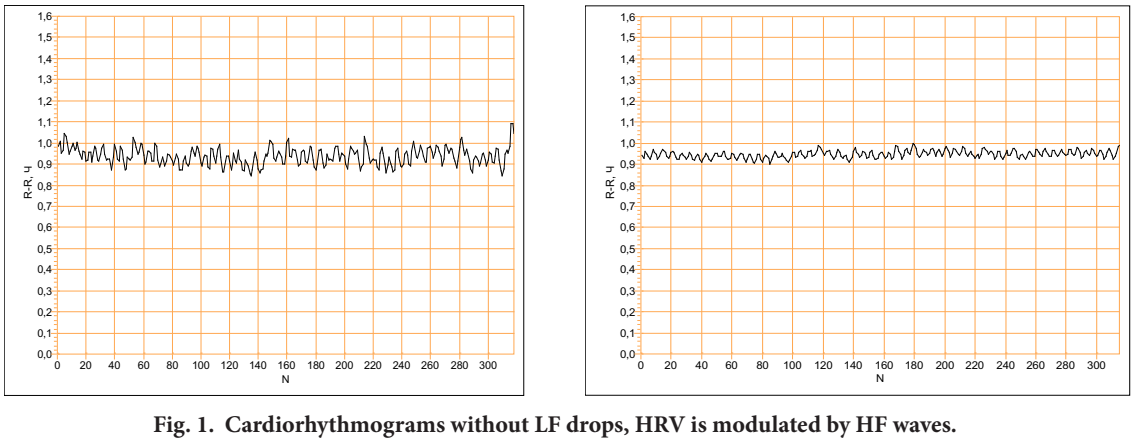

Fig. 1. Cardiorhythmograms without LF drops, HRV is modulated by HF waves. On the left side – rhythmogram of a younger person, on the right side – of an older person.

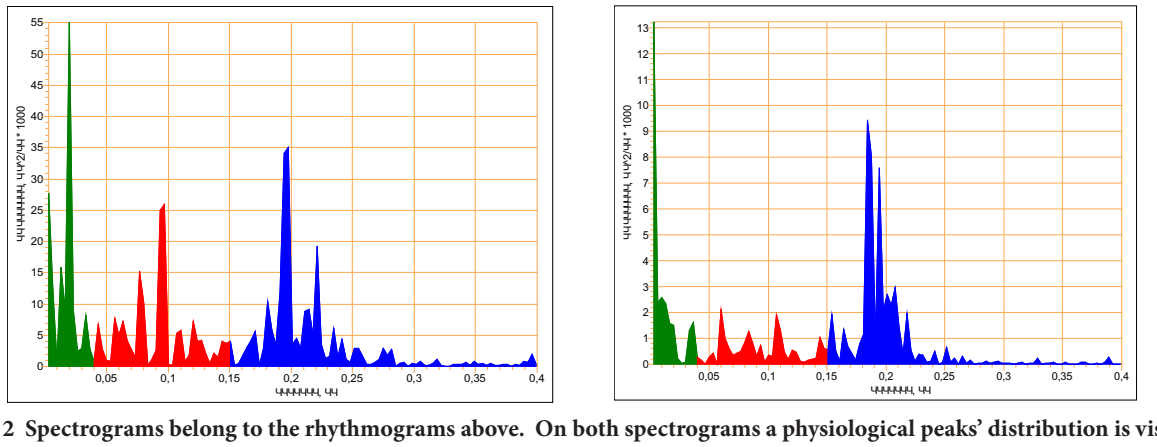

Fig. 2 Spectrograms belong to the rhythmograms above. On both spectrograms a physiological peaks' distribution is visible.

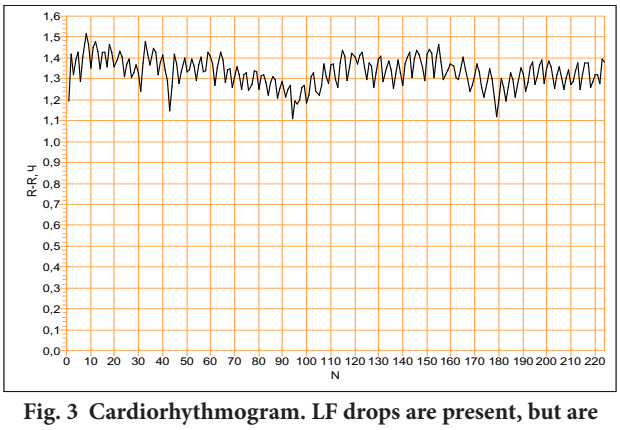

Fig. 3 Cardiorhythmogram. LF drops are present, but are followed by a physiological counterbalancing via HF waves.

2.B. The VLF component is increased on the spectrogram but the HF spectrum has a physiological HF peaks' distribution, sufficient to compensate the increased VLF component (fig. 4).

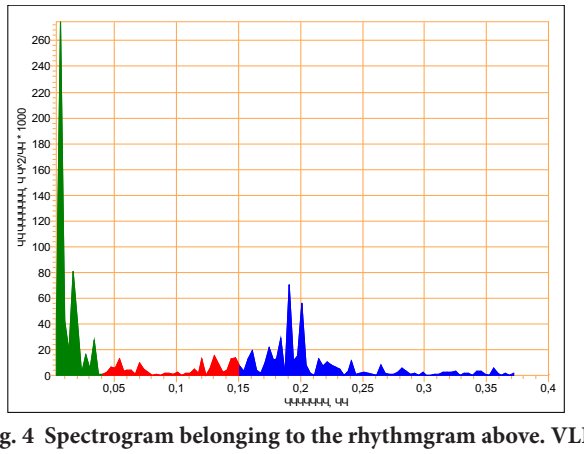

Fig. 4 Spectrogram belonging to the rhythmgram above. VLF (green colour) is increased but the HF spectrum (blue colour) has a physiological HF peaks' distribution.

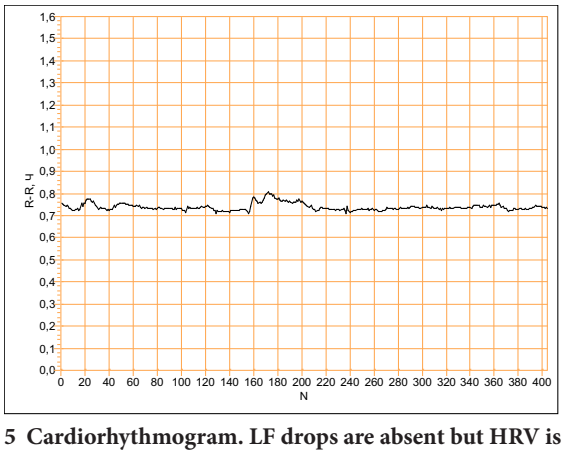

Fig. 5 Cardiorhythmogram. LF drops are absent but HRV is low and is in its modulation dominated by VLF and LF waves.

Below are presented cardiorhythmograms and spectrograms where prognostically AFib is expected by applying the biomarkers' analysis:

1.A. On a rhythmogram, even without LF drops, the HRV is low and is in its modulation dominated by VLF and LF waves (fig. 5).

1.B. On a spectrogram the VLF component dominates in the total power spectrum. Pathological peaks' structure in the HF spectrum area, representing parasympathetic break-down (fig. 6).

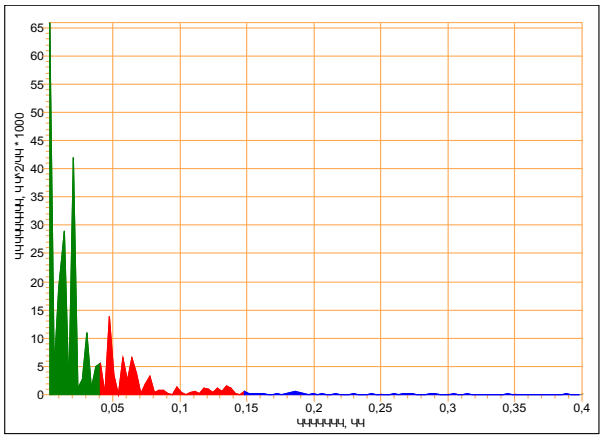

Fig. 6 Spectrogram which belongs to the cardiorhythmogram above. VLF component dominates in the total power spectrum. Pathological peaks' structure in the HF spectrum area, representing parasympathetic break-down.

2.A. On the rhythmogram LF drops are present, followed by a pathological counterregulation: predominated by LF waves (fig. 7).

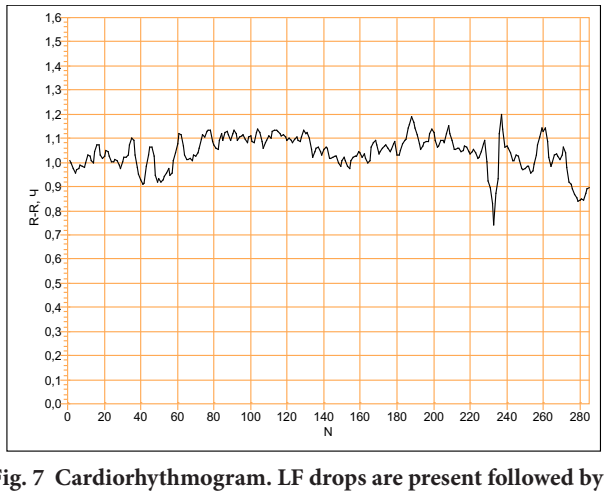

Fig. 7 Cardiorhythmogram. LF drops are present followed by a pathological counterregulation: predominated by LF waves.

2.B. On the spectrogram (fig. 8) the VLF and LF components are dominating in the total power spectrum and at the same time, there is evidence of a pathological peaks' structure in the HF spectrum area, it means a parasympathetic insufficiency, which is unable to compensate for the dominant VLF (central) component and increased LF component (sympathetic overflow in calm state).

The HRV analysis with an additional application of biomarkers, made on the figures above, requires a certain algorithm. Below is presented a simplified algorithm, which is proposed for the use by physicians in the daily practice but still should be validated clinically afterwards. It is based on cardiophysiological biomarkers described in this paper. The algorithm is used for the prognosis regarding sinus rhythm maintenance or AFib recurrence.

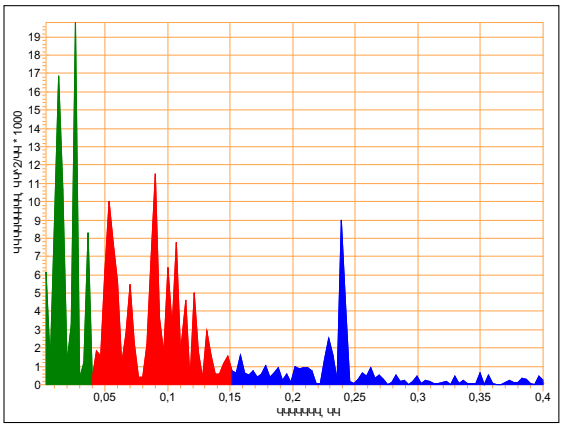

Fig. 8 Spectrogram which belongs to the cardiorhythmogram above. VLF and the LF components are dominating in the total power spectrum. Pathological peaks' structure in the HF spectrum area.

1. In the rhythmogram:
– Are LF drops present or not?
– If there are no LF drops, it is necessary to assess: is the HRV high or low?
– If LF drops are present, it is necessary to assess: is it parasympathetic or sympathetic counterregulation?
2. In the spectrogram:
– Do the peaks in the HF spectrum have a physiological structure?
– Is the VLF component pathologically high in the whole spectrum or in the physiological normal range?
– Is there evidence of a VLF + LF coupling in the transition?

Risk stratification for AFib using the questions described above:

1. In the rhythmogram:
– If LF drops are absent and the HRV is high –the risk is low
– If LF drops are absent, but the HRV is low – the risk is high
– LF drops are present – it is a risk factor. Parasympathetic counterregulation after LF drops – the risk is low, sympathetic counterregulation after LF drops – the risk is high.
2. In the spectrogram:

– Peaks in the HF spectrum – in case of a physiological structure: a main peak with two or three side peaks – the risk is low. Pathological peaks' distribution in the HF spectrum: several main peaks / no major peak/ only low-amplitude peaks scattered in the spectrum – the risk is high.

– VLF component: in case of a physiological VLF proportion in the entire spectrum (not dominating over the HF and the LF components of the total spectrum) – low risk; if pathological (VLF component proportion in the total spectrum is increased and dominates over the HF and LF spectra) – high risk.

– VLF + LF coupling in transition not present – low risk; VLF + LF coupling present in transition – high risk.

Below are given explanations on how to assess the cardiorhythmograms and spectrograms illustrated in the text above. Also, it is described how the cardiophysiological biomarkers are identified, by assessing a cardiorhythmogram or spectrogram and the physiological background of the cardiophysiological biomarkers.

Assessment of cardiorhythmogram

For a more convenient understanding of all cardiorhythmograms in the paper, is given a brief explanation: on the abscissa there is the number of the R peaks deriving from ECG, marked by the letter "N". On the ordinate is shown the beat-to-beat interval measured in seconds.

Now the approach to the cardiorhythmogram analysis proposed in this paper: first of all, it is important to recognize whether any LF drops in the cardiorhythmogram are present (what exactly is considered to be LF drops will be explained in detail later in the text). If there are no LF drops present, it means this is a steady-state cardiorhythmogram (fig. 9 and fig. 10), it can be analysed according to standard HRV analysis procedure [7]. According to the risk stratification, there is a difference between the figure 9 and 10. The cardiorhythmogram represented on figure 9 reflects a low risk for developing AFib. For the risk stratification and prognosis it is important to recognize whether the HRV is modulated by the medullar or by the central level of heart regulation. This physiological background is seen on a cardiorhythmogram recorded in calm state: when it is predominantly modulated by HF waves (fig. 9), then it can be assumed, that the parasympathetic nervous system works physiologically sound and the heart is regulated mainly by the medullar level [8]. Thus this supports a prognosis for SR.

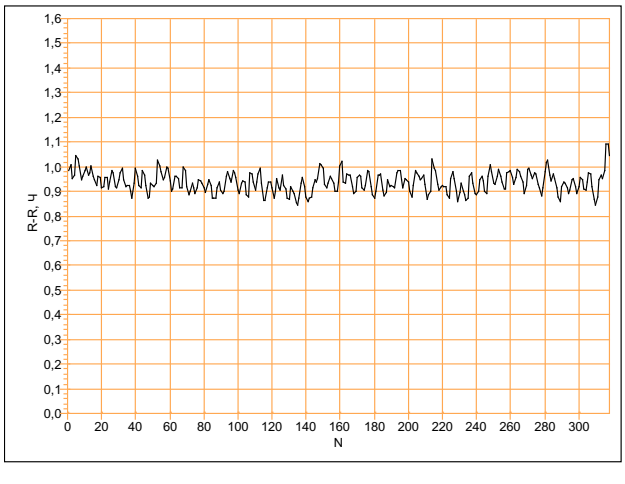

Fig. 9. Cardiorhythmogram. In this cardiorhythmogram the HF waves dominate. There are no LF drops.

On the next figure (fig. 10) there is another extreme. There are still no LF drops present, but the HRV is modulated predominantly by VLF and LF waves. From a physiological point of view, this is a dangerous situation, because the heart is modulated in rest state not by the medullar level but mainly by the central level [8, 9, 24]. This supports that prognostically AFib is expected.

However, examples presented on figure 9 and 10 represent two extreme cases, but there are fluent phases in be-

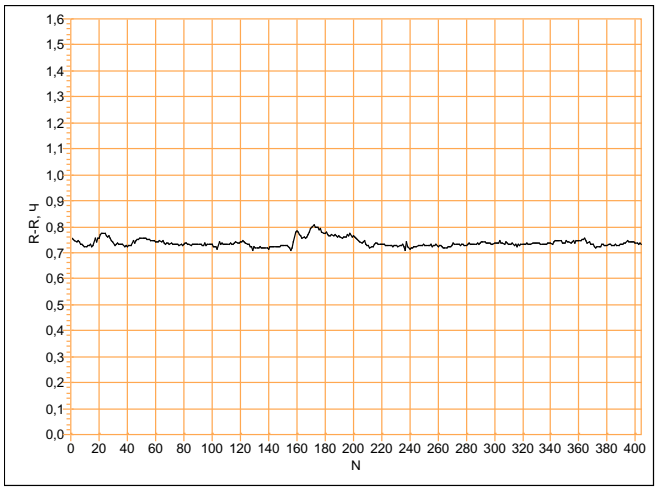

Fig. 10. Cardiorhythmogram. HRV is modulated predominantly by VLF and LF waves. There are no LF drops.

tween, when a prognosis cannot be made so obviously. That is why the use of cardiophysiological biomarkers, in order to apply them in addition to the standard HRV analysis, are proposed. On the next example (fig. 11) you can see a cardiorhythmogram with LF drops. LF drops represent non-steady-state events. As far as these are recognized, the HRV cannot be assessed by standard HRV analysis [3, 25]. How can it be analysed then? Assessing the LF drops as being one cardiophysiological biomarker and the HF counterregulation as another one. What are the LF drops? LF drops are waves on a cardiorhythmogram, occurring suddenly at the end or in the middle of a VLF wave (fig. 11 LF drops are marked by red arrows). They drop down towards the beat-to-beat interval shortening, that is why we called them LF drops, it means low frequency drops. Low frequency (LF) waves on a cardiorhythmogram are normally physiologically driven by sympathetic inputs [10]. But the difference between physiological LF waves and LF drops consists in a sudden appearance of sympathetic overflow represented by LF waves of high intensity on a rhythmogram. That is why we called them LF drops. Taking into account that these are rest-state cardiorhythmograms, it is a pathological condition. A sympathetic overflow of the heart in rest state it is observed, when the medullar heart modulation is working insufficiently, thus the central modulation of the heart increases compensatory [8, 11]. Such a state destabilizes the heart rhythm [10, 26]. As a result, the appearance of LF drops on a cardiorhythmogram in rest state is connected with an increased risk for AFib.

As a second step of analysis of cardiorhythmograms with LF drops, the HF counterregulation should be assessed. The HF counterregulation is represented by the waves following the LF drops (fig. 11 encircled blue) in order to counterbalance them [12]. Under physiological conditions it is expected that the counterbalancing reaction is to be ensured by a parasympathetic compensatory reaction [12]. In this case on cardiorhythmograms HF (high frequency) waves will be observed, which correspond to parasymphatetic modulation of the heart. In case of a pathological counterregulation, LF waves will be seen. A pathological counterregulation is

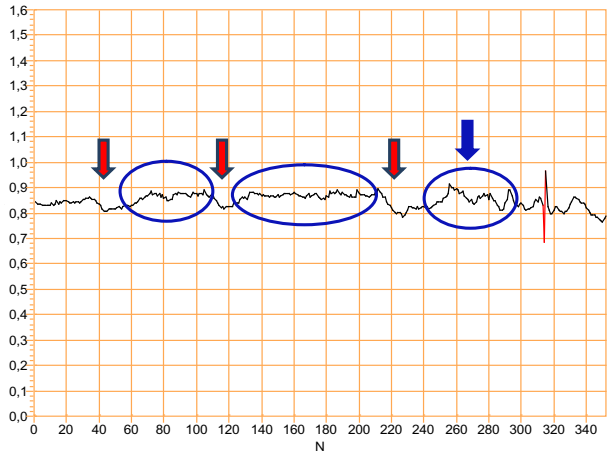

Fig. 11 Cardiorhythmogram. The heart regulation is predominantly ensured by the central level: LF drops are marked with red arrows. The counterbalancing waves (encircled blue) are present predominantly by LF waves instead of HF waves. A parasympathetic break-down (blue arrow) reaction, when counterbalancing the LF drop, is visible.

connected with a high risk for AFib recurrence. Figure 11 represents an example of a pathological counterregulation. It is classified pathological, because it is ensured mainly by LF waves instead of HF waves. It takes place when the counterregulation after LF drops is exerted not by the medullar level of heart regulation, but predominantly, by the central level [8, 14, 32]. In other words, the parasymphatetic activity is responding not effectively enough in reacting to sympathetic activations driven by the increased central regulatory activity in calm state. It is a parasympathetic break-down reaction during answering to LF drops (fig. 11 blue arrow). This is connected with a high risk for AFib recurrence.

LF drops followed by a pathological counterregulation can occur not only on cardiorhythmograms with a low HRV (fig. 11) but they also occur often on cardiorhythmograms with a high HRV (fig. 12).

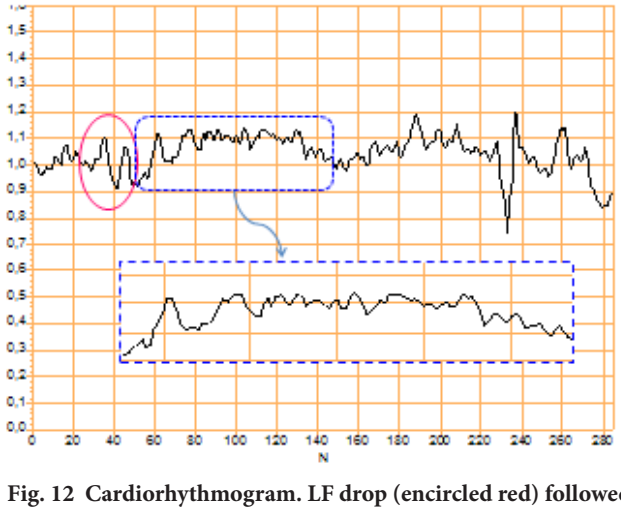

Fig. 12 Cardiorhythmogram. LF drop (encircled red) followed by a pathological counterregulation (blue frame): predominantly modulated by LF waves, instead of HF waves and with a drop-down of waves during counterbalancing.

On figure 12 you can see the LF drop (encircled red) followed by a pathological counterregulation (blue frame). On this cardiorhythmogram the HRV is high, but if you look at the counterregulation, you can recognize, that it is ensured mainly by LF waves. It means, that the parasymphatetic counteractivity is functionally not sufficient to compensate for sympathetic central activity in calm state [15, 32]. This is connected with a high risk for AFib recurrence.

Below, there is an example of a cardiorhythmogram, where the LF drops are present, meaning an increased central modulation, but the counterregulation is modulated by HF waves (fig. 13). That means, the parasymphatetic counterbalancing activity is sufficient to compensate for an increased central modulation of the heart in calm state. In such a situation, a sinus rhythm is expected.

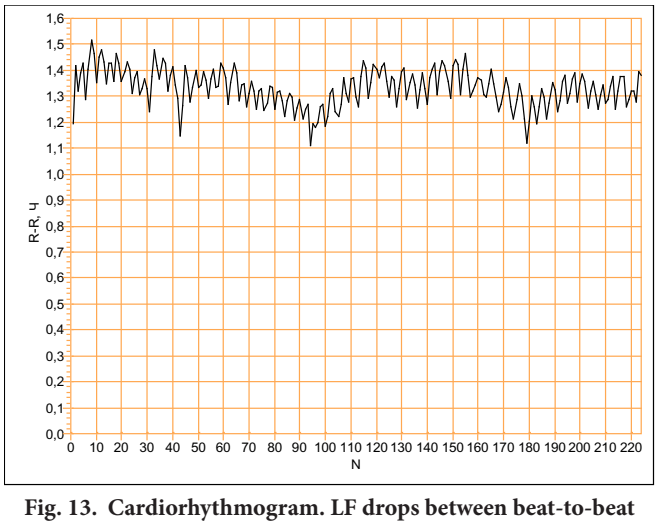

Fig. 13. Cardiorhythmogram. LF drops between beat-to-beat interval 40 – 50, 90 – 100, 170 – 180 (abscissa), followed by a counterregulation by HF waves.

In addition to the rhythmograms, the corresponding spectrograms can also be assessed. On the spectrograms it is also possible to apply the physiological background of the cardiophysiological biomarkers. The influence of the central heart modulation can be analyzed by the VLF component and the vagal activity can be analyzed by the HF spectrum (more in detail in the following text).

Assessment of the spectrogram

For a more convenient assessment of spectrograms it should be briefly noted what is shown on the abscissa and ordinate. On the abscissa you can see three groups of frequencies (obtained from cardiorhythmograms) in Hertz [16]. Marked by blue colour is the HF – high frequency spectrum area, which represents the parasympathetic part of the vegetative nervous system. By the red colour the low frequency (LF) spectrum area is marked, which represents the influence of the sympathetic part of the vegetative nervous system, acting by noradrenaline. The green colour in the spectrogram represents the VLF component of the spectrum. It is the very low frequency component. It represents the central modulation of the heart (cortex, limbic system, hypothalamus) [8, 9, 32]. Important to mention as well is that the VLF component represents the central heart modulation in case of a rest-state probe in 5-minute ECG recordings under steady-state conditions [8, 17]. In case of HRV analysis from a Holter ECG, the VLF component has other characteristics and origin, it does not represent the central modulation of the heart. These three groups of frequencies are measured in Hertz in the spectrogram. All these three spectra make up the total power spectrum in amplitudes, which is represented on the y-axis.

When assessing the spectrogram, it is important to note what the spectral distribution looks like and what proportion of each spectrum is in the overall spectrum. First, the peaks' distribution in the HF area is considered: if a main peak is observed and accompanied side by side by one or two smaller secondary peaks (they should be half-sized or one quarter of the size of the main peak), then it is assumed that the parasympathetic heart modulation physiologically works well and a sinus rhythm is most probably predicted (fig. 14).

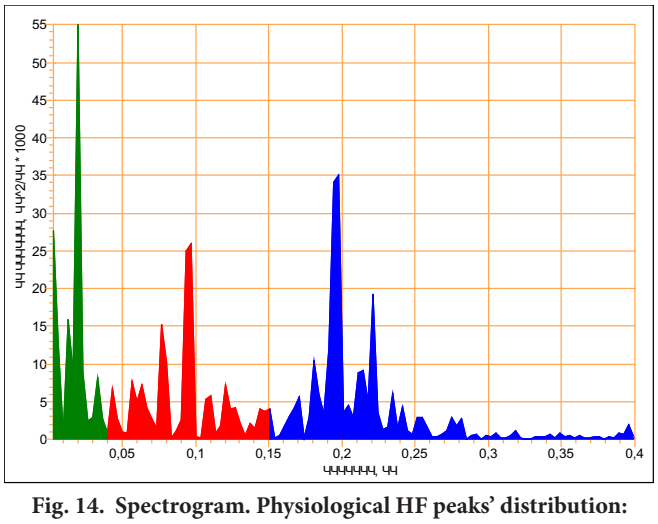

Fig. 14. Spectrogram. Physiological HF peaks' distribution: there is the main peak on frequency about 0.2 Hz (abscissa) and laterally smaller side peaks are seen.

It should be noted that the distribution of the peaks on the frequencies depends on the individual respiratory rate [18, 30]. The closer the main peak is to 0.4 Hz (see abscissa fig. 14), the higher the respiratory rate. The closer the main peak shifts in the opposite direction, closer to the green spectrum area, the slower the person's breathing. As can be seen (fig. 14), the main peak is at the frequency value 0.2. Thus, the respiratory rate is about 10 breath cycles per minute.

In spectral analysis it is also important to estimate the VLF component. This gives information about the central input of the VNS in the cardiac regulation. [17]. Under physiological conditions predominantly the medullar level modulates the heart at rest [8, 9] (fig. 14), opposite to the central level (VLF area). In the spectrogram you can see it well: the majority is made up of the blue and the red spectra. However, the green portion does not dominate over the blue and the red spectra. Under these circumstances we expect a SR.

In pathological situations, when a dominant green spec-

trum area on a spectrogram (fig. 15) during rest-state probe is observed, it is considered that the central level of heart modulation is more involved than the medullar one. This is a dangerous state from a physiological point of view [19, 29], as it represents risk factors for the development of AFib.

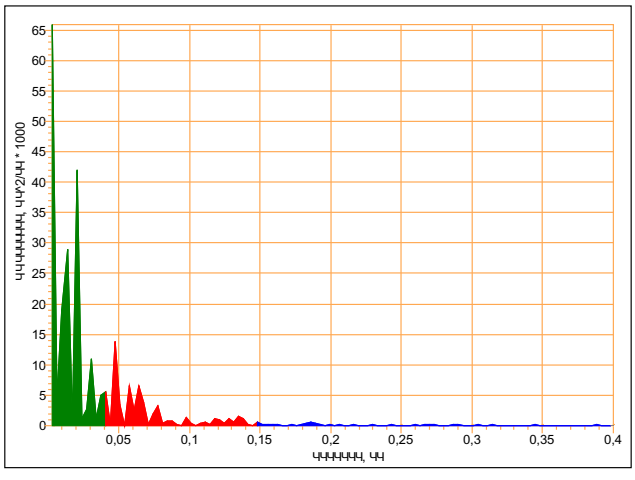

Fig. 15. Spectrogram. Pathological regulation of the heart: an increased central modulation – VLF (green) component in the total power spectrum and a pathological – HF spectrum area (blue) – a parasympathetic break-down.

On the next spectrogram (fig. 16) you can see an increased VLF spectrum (green) followed by a marked increased LF spectrum (red). That means, an increased central modulation of the heart parallel with an increased sympathetic overflow [20, 21, 32] of the heart. It is important to keep in mind, that it was a rest-state ECG registration, so it is an increased sympathicotonia in calm state. In such conditions, it is important to have an effective vagal compensation [8, 31]. But if you look at (fig. 16) the HF spectrum (blue) corresponding to the parasympathetic functional activity, you recognize a lack of functional parasympathetic activity. In the blue spectrum there is a pathological wave distribution: only one peak without side peaks, instead there

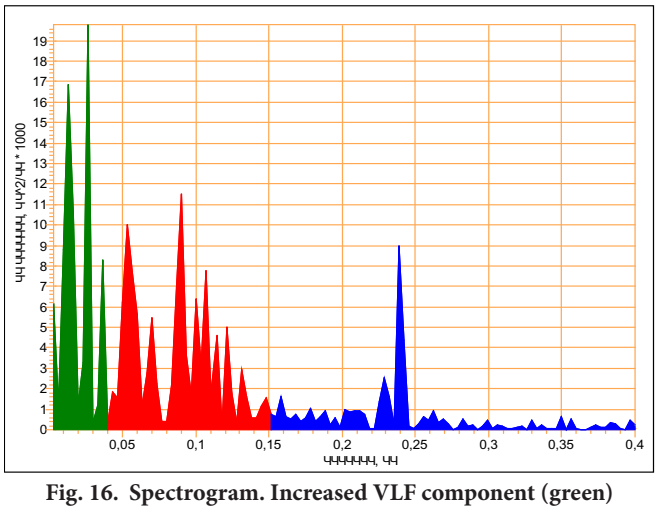

Fig. 16. Spectrogram. Increased VLF component (green) in the total power spectrum and a marked high LF component (red). HF spectrum area: only one main peak without side peaks, just low-amplitude distributed peaks through the whole spectrum area.

are very low amplitude peaks distributed through the whole HF spectrum area. It is obvious, that such a vagal counterbalance is not able to compensate effectively enough such a high central modulation and sympathetic overactivity of the heart [23, 31]. This represents a parasympathetic insufficiency, so the vagus is able to counterbalance only for short-term reactions but is not able to fulfill effectively enough its counterregulatory function against sympathetic central overflow. Hence, prognostically, AFib is expected.

It is important to note, that in case the VLF component is increased in the total power spectrum, the HF component should also be assessed in order to make a correct qualitative prognosis. When VLF is increased, but the HF spectrum has a physiological peaks' distribution, it can be concluded that the parasympathetic functional activity is sufficient in order to compensate for an increased central input to the heart in rest state (fig. 17) [32].

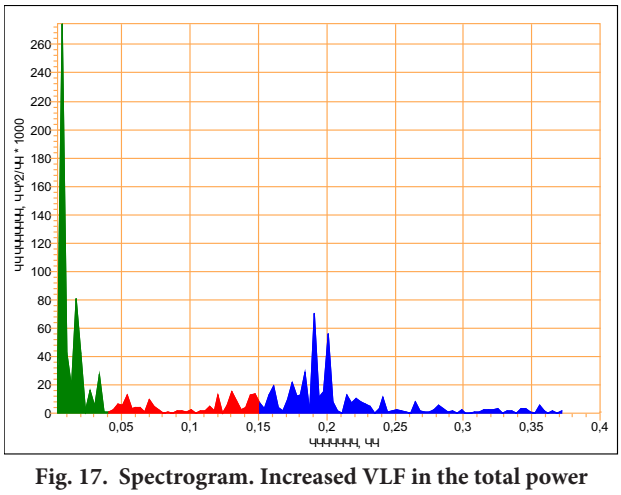

Fig. 17. Spectrogram. Increased VLF in the total power spectrum compensated by a physiological HF spectrum.

Conclusions

1. In addition to the standard HRV analysis, cardiophysiological biomarkers should be assessed: LF drops and HF counterregulation. On the example of prognosis construction for atrial fibrillation based on the biomarkers a possible applicative value of them is explained.

2. When in a steady-state cardiorhythmogram LF drops are observed followed by a pathological counterregulation, prognostically atrial fibrillation recurrence is expected.

3. When in a steady-state cardiorhythmogram LF drops are observed followed by a physiological counterregulation, prognostically, sinus rhythm is expected.

4. Additionally to the cardiorhythmogram the biomarkers can be assessed in a spectrogram using the VLF and the HF components.

5. When the VLF component is pathologically high in rest state and the structure of the HF spectrum is pathological, prognostically the recurrence of atrial fibrillation is expected.

6. When the VLF component is pathologically high in rest state but the structure of the HF spectrum is physiological, prognostically sinus rhythm is expected.

7. Physiological background of the biomarkers: increased

central modulation of the heart in rest state (LF drops present, increased VLF) is a risk factor for atrial fibrillation but if the parasymphatetic modulation is sufficient to compensate for it (HF counterregulation by HF waves, physiological HF spectrum), sinus rhythm is expected. If the parasympathetic modulation is not sufficient to compensate for it (counterregulation by LF waves, pathological HF spectrum), atrial fibrillation is expected.

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