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New Biophysical Approach in Analysis of Heart Rate Variability for Increasing its Predictive Value

Ludmila Sidorenko [1], ORCID: 0000-0003-0382-4542
Larisa Spinei [1], ORCID: 0000-0002-5370-9801
Gert Baumann [2],
[1] State University of Medicine and Pharmacy "Nicolae Testemitanu", Stefan cel Mare str. 165, Chisinau, RM
ludmila.sidorenco@usmf.md
[2] Charite University Clinic, Chariteplatz 1 10117 Berlin, Germany

***Abstract*—Background. Regarding the high incidence of cardiovascular diseases, it is critical to find predictors. The aim of this study is to appreciate the predivtive value of of recently-found parameters of cardiorhythmogram analysis applying the new biophysical approach for predicting the recurrence of atrial fibrillation. Material and methods. This is a case-series study, where 350 cardiorhythmograms were assessed. For assessment both methods were applied, the standard heart rate variability analysis and new approach by the parameters HF counterregulation and LF drops. Results. The both newly-found parameters predict reliably atrial fibrillation recurrence. The significance of the parameter HF counterregulation is $p < 0.0001$, in case of the parameter LF drops it is $p < 0.001$. Conclusions. In case if prediction is needed, the standard heart rate variability should be completed by the new biophysical approach, applying the parameters HF counterregulation and LF drops. Steady-state cardiorhythmograms with events of unstationarity can be realiably analysed just by these parameters. Events of unstationarity are informative sources for prediction.**

Keywords—cardiorhythmogram; atrial fibrillation; prediction; biophysics; unstationarity.

I. INTRODUCTION

Cardiovascular disease are in the top ten globally spread pathologies which affect the health and quality of life of millions of people worldwide [1]. This is the reason why relevant prediction methods in cardiology are of high importance. Reliable predicton can be elaborated just interdisciplinary, using therefore different physiological, electrophysiological, cardiological investigation tools, biophysical parameters, statistical analysis and mathematical models. The new biophysical approach described in this paper is applied with the aim to increase the predictive potential of heart rate variability (HRV) analysis. The HRV analysis is a well-known method. It is applied in different medical branches [2]. However, it still has its known limitations [2,3]. One of the limitations in the use of HRV in the cardiology is the problem of steady-state cardiorhythmograms [3]. The literature review shows that majority of the articles does not regard a very important biophysical parameter during their analysis of HRV – the appearance of non-stationar events in a steady-state cardiorhythmogram. In case of respecting all the recording condotions and excluding arrousels from body movement, the unstationarity is respresented by additional waves in the cardiorhythmogram. The problem is that these are cut out to make the classical analysis possible [4]. The reason is that a classical HRV analysis with automatically programmed analysis cannot be done with waves of unstationarity [4]. However, cutting out, the biosignal loses some of its quality and reliability [4, 5]. That is the main reason, why such cardiorhythmograms are mostly taken out of analysis or minimal information is extracted from such an HRV analysis. Furthermore, exactly the fragmetns of cardiorhythmograms before and following after the unstationar event reveal maximum of information regarding prediction during HRV analysis [5]. So just cutting them out in order to ensure a classical HRV analysis is a big mistake from biophysical and pathophysiological point of view [5]. That is why in this study the aim was to stydy cardiorhythmograms with unstationar events in steady-state cardiorhythmograms in order to extract maximum of information regarding the predictive value of HRV due to the application of a new approach to the analysis. The predictive value was applied to a concrete pathology – the prediction of atrial

fibrillation. The prediction of atrial fibrillation is of very high importance because it is the most common sustained arrhythmia in cardiology which affects remarkably the health state, is followed by a lot of consequences like stroke or arterial hypertension and effects the quality of life [6]. So the prevention of paroxysms of atrial fibrillation via finding relevant predictors is an important medical and social challenge.

II. MATERIAL AND METHODS

A. Analysis of cardiorhythmograms

The following study is a case-series study. It was written according to te STARD criteria. The new biophysic approach was assessed on 350 cardiorhythmograms. Inclusion criteria of the cardiorhythmograms was diagnosed paroxysmal atrial fibrillation, but at the moment of the biosignal recording has to be sinus rhythm. Exvlusion criteria was atrial fibrillation at the moment of biosignal recording. The biosignal was obtained by a 5-minute ECG recording using a specialized hardware (Polyspectrum-HRV-device, Neurosoft). The data obtained from the biosignal recording were further analysed with the software „Neuro-Soft“. 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 [4]. All the 350 cardiorhythmograms which were included in the study were included in the analysis. At the moment of biosignal recording the patients were paroxysm-free, so they had sinus rhythm. After the baseline recording every three months the biosignal was during follow up recorded. The follow-up lasted 18 moths. Every recording was analysed regarding the predictive value of non-stationr events in the steady-state cardiorhythmograms. The fragments of the cardiorhythmograms where the non-stationarity events occurred waere analysed separately. The non-stationar event was regarded as an “LF drop” and the fragment of cardiorhythmogram followed after the “LF drop” was regarded as “HF counerregulation”, descriebed in detailed elsewhere [5].

B. Standard Operating Procedure for obtaining a steady-state cardiorhythmogram

In order to obtain a steady-state cardiorhythmogram, a resting state probe is required. Therefore a 5-minute ECG in supine position is recorded. In the room all conditions for ensuring a calm state of the person shoul be respected. The person is alert, sleeping during biosignal recording is prohibited, important is the free spontaneous breathing. Recording just in sinus rhythm is possible. Before the beginning of the biosignal’s recording, a steady-state hast to be achieved. For that reason after having connected the electrodes, the investigator monitors the biosignal on the monitor until the moment when a steadystate signal is reached. Only after having achieved the corresponding indicators for that state, the biosignal recording which will be used further for analysis, starts. The time required for achieving the steady-state signal varies, it lasts individually. Usually it takes from 5 to 20 minutes [4]. It is important in order to exclude false positive reactions of an increased sympathetic or parasympathetic reaction of the vegetative nervous system. This is critical because the intension of this rest state biosignal recording, is a further assessment of the sympathetic, parasympathetic and the central modulations of the vegetative nervous system on the heart rhythm. Thus, a qualitative biosignal can be obtained only if all additional influences, which do not belong to rest state probe, are excluded [3, 4]. This is the only way to deliver a forther reliable assessment of the biosignal.

I. RESULTS AND DISCUSSION

Among the 350 cardiorhythmograms, in 280 paroxysms of atrial fibrillation during the 18 months of follow-up were observed. 70 cardiorhythmograms remained paroxysm-free. For that reason was the possibility to analyse both types of cardiorhythmograms, with and without paroxysm. It means, both pathophysiologic and biophysic conditions were reflected, those which indicate the prognosis of sinus rhythm and conditions, which indicate the appeareance of paroxysm of atrial fibrillation. Standard HRV analysis methods are not described in this paper as these are well known [2, 3, 4]. The new biophysic approach to cardiorhythmogram analysis is described. Several cardiophysiological biomarkers and biophysical parameters were taken for cardiorhythmogram analysis, 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) cunterregulation and increased central activity in rest state. These parameters describe in an appropriate way the biophysical aspect of unstationarity in steady-state cardiorhythmograms [5]. The pathophysiological background of these parameters is in detail described elsewhere [7]. In case that no unstationarity in a steady-state cardiorhythmogram occurs, it can be analysed according to the standard HRV analysis. In this case the classical prediction describes the high HRV as a predictive factor for keeping the sinus rhythm and the low HRV predicts the risk for appearance of atrial fibrillation paroxysm [2, 4]. The problem is that in patients with atrial fibrillation the functionl state of the regulatory systems of the heart is pathological [7, 8], so that seldom

cardiorhythmograms without unstationarity were analysed. In these cases standard HRV analyses are not possible [4]. From 350 cardiorhythmograms just 27 were without any stationarity In 323 cases unstationar events were present. In these cases the biophysical approach was useful. Therefore the LF drops and HF counterregulation were analysed. From 280 cardiorhythmograms with paroxysms of atrial fibrillation 263 were with LF drops in combination with a low HF counterregulation. In the 70 cases of paroxysm-free cardiorhythmograms 43 had LF drpos in combination with a high counterregulation, 27 had no LF drops, so were classiefied by the standard HRV as paroxysm-free. So from these data is clear that LF drops and HF counterregulation are reliable predictors for paroxysms of atrial fibrillation and for remaining in sinus rhythm, correspondingly. The combination LF drops with a low HF counterregulation predicts significantly paroxysm of atrial fibrillation ($p<0.0001$). The combination LF drops with a high HF counterregulation predicts significantly the maintanace of sinus rhythm ($p<0.001$).

A. Assessment of cardiorhythmogram

In this paper the following approach to the analysis of cardiorhythmograms, taking in account important biophysical and pathophysiological parameters, is proposed: first of all to recognize whether LF drops in the cardiorhythmogram are detected. In case that no LF drops are identified, the cardiorhythmogram can be analysed by the standard approach to HRV analysis [4]. Under this circumstances the cardiorhythmogram is regarded as a steady-state one, without unstationar events (fig. 1 and fig. 2). Correspondingly, in such cases the risk stratification says that the difference of wave structrure in the figure 1 and 2 is a standard important parameter to be taken in account [9]. In such a case like presented in cardiorhythmogram on figure 1 there is a low risk for paroxysm of atrial fibrillation. This cardiorhythmogram (fig. 1) is mainly modulated by HF waves. Physiologically it means that the parasympathetic nervous system works efficiently enough, so that the heart is regulated in calm state mainly by the medullar level [7, 8, 9]. As consequence, the prognosis for sinus rhythm was confirmed.

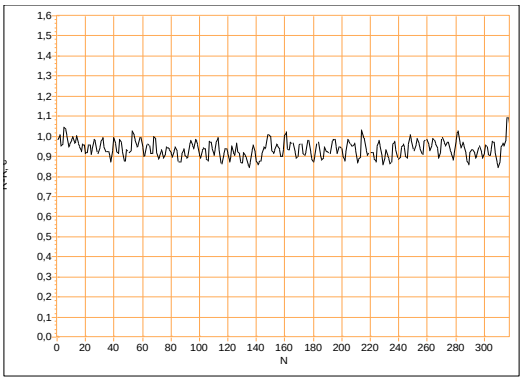
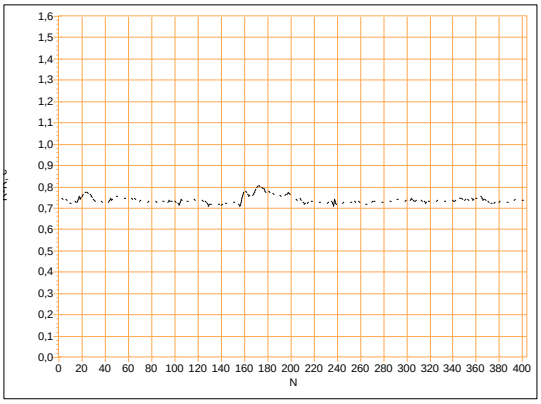


Figure 1. Cardiorhythmogram. In this cardiorhythmogram the HFwaves dominate. There are no LF drops.



Figue 2. Cardiorhythmogram. HRV is modulated predominantly by VLF and LF waves. There are no LF drops.

On the next figure (fig. 2) there is another extreme.
There are still no LF drops present, but the modulation of HRV is ensured mainly by VLF waves and LF waves. Pathophysiologically it means that the heart is modulated even at rest predominantly by the central level insead of the medullar level [5, 7]. In this case atrial fibrillation prognostically was expected. However, usually there are cardiorhythmograms when a prognosis cannot be made so obviously, just comparing LF or HF waves. This is the reason why respecting the biophysical parameter of ustationarity, analysing the cardiophysiological biomarkers in the cardiorhythmograms, like LF drops and HF counterregulation was proposed. The next example (fig. 3) represents a cardiorhythmogram with LF drops.

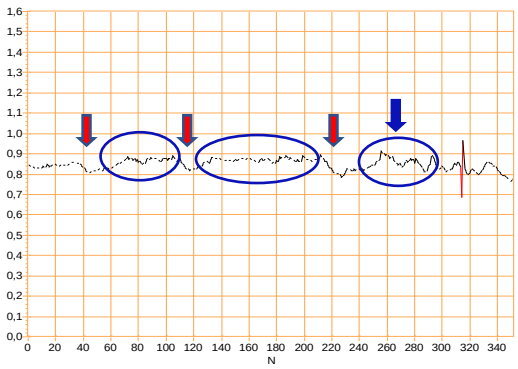


Figure 3. Cardiorhythmogram. By red arrows are marked the LF drops. The waves of counterbalancing are encircled blue. The latter are modulated mainly by LF waves instead of HF waves. A parasympathetic break-down is marked by the blue arrow, it occurs during the counterbalance of the LF drop.

The LF drop ia a nonsteady-state event evoked by unstationarity. As far as these are recognized, the standard HRV assessment is not possible [4]. LF drops represent waves on a cardiorhythmogram, which occur suddenly at the end part or in the middle part of VLF waves (fig. 3). Physiological low frequency (LF) waves on a cardiorhythmogram are driven usually by sympathetic inputs [4, 8]. The difference between LF physiological waves and LF drops is in the moment of appearance and in the morphology. LF dropps appear suddenly because of the sympathetic overflow of the heart, represented by LF waves of a high-amplitude drop-down on a rest-state cardiorhythmogram. The hight of the amplitude is taken relatively to the hight of the waves of every certain cardiorhythmogram. The sympathetically driven overflow of the heart rhythm modulation during rest state occurs when the medullar modulation of the heart rhythm is functionally insufficient and the central modulation of the heart is increased [7, 8, 10]. This pathophysiological state destabilizes the rhythm of the heart [8, 10]. As consequence, the LF drops in a cardiorhythmogram during rest state recording increase the risk for paroxysm of atrial fibrillation. The next parameter which should be analysed in cardiorhythmograms with LF drops, is the HF counterregulation. This is the fragment of the cardiorhythmogram following the LF drops (fig. 3 encircled blue). The HF counterregulation occurs with the aim to counterbalance the LF drops [5, 7]. It is important to analyse which waves' structure the fragmant of cardiorhythmogram which corresponds to the HF counterregulation has. Physiologically the counterbalancing has to be ensured by parasympathetic compensation [7, 10]. Under such conditions on cardiorhythmograms the HF waves should be detected [7]. During a pathological counterregulation the LF waves are detected. In this case a high risk for the recurrence of atrial fibrillation was observed. A pathological counterregulation you can see on figure 3. [7, 8]. Here the parasymphatetic counterreaction is not effectively enough in order to compensate the sympathetic overflow of the heart rhythm and the central overactivity in calm state. This state is a parasympathetic break-down (fig. 3 blue arrow). As consequence it resulted in atrial fibrillation recurrence until the next follow-up check. In case that a pathological counterregulation after the LF drops appeared, occurred recurrence of atrial fibrillation during the follow-up. LF drops can occur not only on cardiorhythmograms with a low HRV (fig. 3) but they also occur often on cardiorhythmograms with a high HRV (fig. 4).

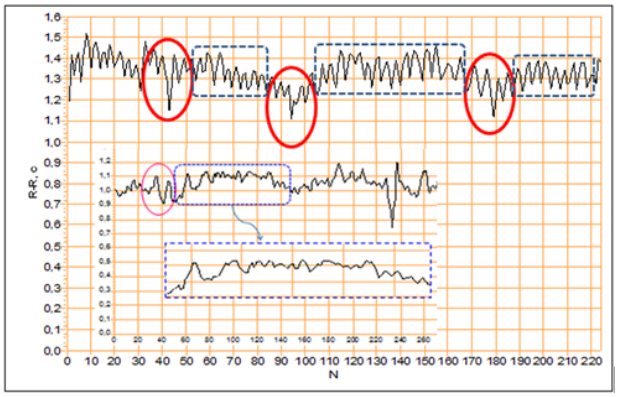


Figure 4. Comparison between two cardiorhythmograms with LF drops (encircled red). On the first (at the bottom of the figure) cardiorhythmogram the LF drops are followed by a sufficient physiological counterregulation (blue frame) by HF waves, whereas on the second one they are followed by a pathological counterregulation (blue frame): predominantly modulated by LF waves and with a dropdown of waves during counterreacting.

On figure 4 you can see two cardiorhythmograms with with a high HRV and in both cases LF drops (encircled red) are present. The difference is in the quality of the counterreaction. On the upper cardiorhythmogram it is ensured by physiological HF waves, meaning sinus rhythm in prognosis whereas the lower, the inseted cardiorhythmogram represents a pathological counterregulation (blue frame), so recurrence of atrial fibrillation occurs. The inseted one is ensured mainly by LF waves. It means, that the parasymphatetic counteractivity is functionally not sufficient to compensate for sympathetic central overactivity in calm state [8, 10]. This is connected with a high risk for atrial fibrillation recurrence. On the upper cardiorhythmogram on figure 4 there is an example when the LF drops are present, meaning an increased central modulation, but the counterregulation is modulated by HF waves (fig. 4, the upper cardiorhythmogram). That means, the

parasymphatetic counterbalancing activity is still sufficient to compensate for an increased central modulation of the heart in calm state [8, 9]. In case of such cardiorhythmograms a sinus rhythm during follow-up was observed.

B. Conclusions

1. The parameters LF drops and HF counterregulation predict significantly the recurrence of atrial fibrillation.
2. The standard heart rate variability should be completed by the new biophysical approach, applying the parameters HF counterregulation and LF drops.
3. Steady-state cardiorhythmograms with events of unstationarity can be realiably analysed just by the biophysical approach, apllying the parameters HF counterregulation and LF drops. parameters.

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