World Applied Sciences Journal 19 (8): 1133-1139, 2012
ISSN 1818-4952

DOI: 10.5829/idosi.wasj.2012.19.08.661

Metabolic Rate Variability Impact on Very Low-Frequency of Heart Rate Variability

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Abstract: There is an opinion that the very-low-frequency (VLF) fluctuations of heart rate's variability (HRV) have been associated with energetic process in organism. The background of this study was the hypothesis that VLF variability of respiratory pattern (VRP) is influenced by oxygen consumption (VO_2) regulation. However, it is still unclear: is there a correlation between those processes? The goal of this study was to investigate the HRV, rhythms of pulmonary gas exchange and the variability of the respiratory pattern, as well as to find their possible relation. In search for periodicities in the variability spectral analysis was applied to breath-to-breath variables of oxygen consumption (VO_2), CO_2 production (VCO_2), end-tidal CO_2 ($FetCO_2$), lung ventilation (Ve) and breath frequency (f) in 19 healthy subjects at rest. Simultaneously HRV was investigated by pulse-oximetry method. The interbeat pulse intervals (Tpi) were calculated on-line using an R-wave peak detection algorithm. VRP was defined by pneumography method. Spectral analysis carried out using the fast Fourier transform (FFT) revealed two groups of peaks: the first one was in the range from 0.2 to 0.3 Hz (the time interval of 3-5 s), which was in good agreement with the breath frequency (f); the second was from 0.002 to 0.0075 Hz, which corresponded to the VLF band. Both groups of peaks were in same bands for all indices detected three different methods. The data makes it possible to draw a conclusion about the stability of the wave processes found that may be described as "metabolic rate variability". We are concluded that very-low-frequency variability of HRV and VRP are regulated by common mechanism of the metabolic control. It is possible that the mechanism has metabolic rate variability.

Key words: Heart Rate Variability · Variability of Respiratory Pattern · Pulmonary Gas Exchange · Vlf Band · Metabolic Rate Variability

INTRODUCTION

Analysis of the variability of biorhythms makes it possible to estimate the functional state of the system in total, especially during transient stages when qualitative changes take place. The heart rate's variability (HRV) in humans is well studied. Spectral analysis of the heartbeat time series using the fast Fourier transform showed wave modulation of the heart rate. Methods of dynamic analysis of bioelectrical signals related to a decrease in the variability of RR intervals and certain spectral power make it possible to detect the critical state of the myocardium [1, 2]. Four groups of major wave peaks were found in humans [3]. The high frequency band (HF band, 150 - 400 x 10^{-3} Hz), which corresponds to the respiratory rate, belongs to the first one. The other groups are as follows: the low-frequency (LF, 40 – 150 x 10^{-3} Hz) spectrum, very-low-frequency (VLF, 3.0 – 40.0 x 10^{-3} Hz) spectrum and ultra-low-frequency (ULF, 0.1 –3.0 x 10^{-3} Hz) spectrum. According to international standards [3], the spectral band was subdivided into three parts: VLF corresponds to time intervals from 25 s to 5.5 min; LF, to time intervals from 6.7 to 25.0 s; and HF, to time intervals from 2.5 to 6.7 s. The HF waves are supposed to

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be correlated to the respiratory rhythm and change in accordance with changes in the respiratory rate, but the physiological mechanisms of this phenomenon are still unclear [2, 4]. A theory of heart rate control was developed in studying the HF and LF formation [2, 5]. The relationship between HF and LF bands has been related regulation by the sympathetic and parasympathetic nervous systems [3].

However, there have been few purposeful studies of VLF phenomenon. There is assumption that VLF-band of HRV reflected regulatory rhythms of the hypothalamus and the endocrine system regulated metabolic rate [4, 6, 7]. Nevertheless, there is no direct proof of the existence of an "energy rhythm" at the level of the whole body. It is still unclear to which type of VLF-wave processes (chaotic or regular) these rhythm patterns belong to. In the previous study we concluded that the slow-wave dynamic periodicity of the pulmonary gas exchange indices (VO_2, Ve and VCO_2) reflects synchronization of oscillators with incommensurable frequencies when two-frequency periodicity is dominant. While the first oscillator is a chemoreceptor mechanism of the regulation of ventilation, the nature of the second one is still unclear. Taking into consideration that velocity of oxygen consumption (VO_2) depends on the energy demand, one can suppose that energy processes form another/other oscillator(s) of periodic processes [8]. The obtained results have allowed us to formulate a hypothesis that has two assumptions: 1) the central mechanism of metabolic rate (energetic consumption) regulation has VLF-band wave nature (time period is while 1-5 min) and there is metabolic rate variability (MRV); 2) metabolic rate variability can be one of oscillator of periodic processes for HRV and VRP.

Normally, regulation of energy processes in a healthy human at rest is probably based on self-organization principles. These principles may be seen in the rhythmic time course of a number of regulatory indices [9]. Ventilation and the blood circulation organs provide tissue respiration and their functioning will be determined by the time course of energy requirements. If this hypothesis is true then one can suppose that the intensity of pulmonary gas exchange directly reflects the velocity of oxygen consumption and the energy requirements is of a slow-wave type corresponding to the VLF band with a time interval from 100 to 300 s. Reflection of this variability in the respiratory rate pattern with HRV is able to be one more proof. Until now, however, the slow-wave type of the pulmonary ventilation indices has been shown only in several works on the variability of the spirometry indices [6, 7, 10]. The majority of researchers believe that the mechanism of maintaining the optimal pH and partial pressure of CO_2 in arterial blood underlies the variability of ventilation indices and lung ventilation adjustment through feedback regulation of the central regulator of breath [10-12]. Nobody has studied the variability of the respiratory pattern combined with HRV and the time course of pulmonary gas exchange in the VLF band using spectral analysis methods. This may be explained by methodical problems in respiratory records. Therefore, the goal of this study was to investigate HRV and the rhythms of pulmonary gas exchange and the variability of the respiratory pattern and find their possible relation.

MATERIALS AND METHODS

In order to analyze the variability of ventilation indices in the VLF band, a pneumogram was recorded for 30 min and then, without a pause, the pulmonary gas exchange indices were recorded for 30 min using the breath-by-breath method. Simultaneously the pulse oximetry was detected for HRV. A feature film with a neutral plot was shown to the subjects during the monitoring. The study was carried out in 19 healthy subjects (aged from 19 to 52 years) in a seated position at rest during the first half of the day. The variability of respiratory pattern (VRP) was recorded using pneumography reflecting the time course of air flow rate (AFR). A mouthpiece with a built-in NTC 833 termosensor (Higrosens Instruments) was used as a sensor of air flow. A Pneumoset device for airflow determination (DSS, Russia) connected with a computer was used to record the pneumograms and accumulate the data on the time course of air flow. A mouthpiece with a built-in termosensor was placed near the nasal passage and fixed using a communications earpiece. The Pneumoset Pro software (DSS, Russia) was used to record and analyze the pneumograms. The spectra of the pneumogram index (AFR - air temperature near the nasal passage) were calculated using the fast Fourier transform (FFT) with a 65636 calculating window and a spectral bandwidth of 3.0 x 10^{-3} Hz. Then, the spectrum was normalized using the maximal amplitude of the first harmonic taken as 100%. Spectral bands in the VLF (time intervals from 25 s to 5.6 min) were analyzed. The frequency of the main harmonic in the pneumogram in the ULF band was calculated using the spectra.

Recording of the pulmonary gas exchange indices for each respiratory cycle was carried out using an Ultima PFX Gas Exchange and Pulmonary Function System (United States). The subjects breathed through a face mask. Spectral analysis of the time course of the measured parameters was carried out using the following indices: oxygen consumption (VO_2); end-tidal concentration of CO_2 ($FetCO_2$); carbon dioxide production (VCO_2), lung ventilation or expired volume (Ve); breathing frequency (f). A pulse oximetry device (N200, Nellcor, United States) was used to measure the heart rate. The interbeat pulse intervals (Tpi) were calculated on-line using an R-wave peak detection algorithm and also stored on the PC for further off-line processing according to experience of other studies [13].

Spectral analysis of all parameters was carried out using the PowerGraph v. 3.3 software (DISoft, Russia). Frequency spectra with a spectral bandwidth of 3.0×10^{-3} Hz were calculated for all data sets of the mentioned indices. The peaks of the main harmonics for each index were calculated on the basis of these spectra. Using spectral analysis, the obtained pneumogram values and breath-by-breath results were resolved into wave components; and the contribution of each component was computed. The estimation of the area of the spectrogram in the three frequency bands (VLF, LF, HF) was carried out to compare the data of the spectral analysis of the pneumogram and pulmonary gas exchange.

Considering the sample size and the lack of fit to the Gaussian distribution of the recorded parameters, the ANOVA method was used for the statistical analysis of the data. The results were considered significant at $p < 0.05$.

RESULTS

Analysis of the Pneumogram Indices: Two sets of peaks were found in the entire spectrum in analyzing the variability of AFR in 30 min pneumograms using FFT (Fig. 1). The first (major) peak was in the $200 – 300 \times 10^{-3}$ Hz band (area of time interval, 3-5 s), which was in good agreement with the breath frequency, varying from 10 to 20 min^{-1}. The second one was in the $3.0 – 7.5 \times 10^{-3}$ Hz (VLF band). The major set of peaks was determined by the periodic changes dependent on the respiratory rate. A set of the second peak located outside of the respiratory rate area were found in all subjects. The same results were obtained in previous studies [8].

Two peaks (major and second) in the spectra of the pneumogram are separated by a "mute" range, in which the average value of spectra power does not exceed 2 % of the main harmonic power (at the breath frequency). At the same time, the maximal amplitude in the VLF band (as a percentage of the maximal amplitude in the HF band) varied from 3.5 to 66 %. These peaks were located within the interval from 1.9 to 6.1×10^{-3} Hz. Thus the time interval of the peaks found was between 163 and 526 s. The average maximal amplitude in the VLF band was 20.5 ± 19.3 % of the main harmonic; and the average frequency was $3.61 \pm 1.33 \times 10^{-3}$ Hz, which corresponded to a 4.6 -min period.

Analysis of the Pulmonary Gas Exchange Indices: The variability of all indices is similar to the analysis of the pneumography (Fig. 2). The same phenomenon of the second VLF band, which significantly differed from the long-term mute area, which separated it from the first area of the high amplitude spectrum in the HF band corresponding to the breath frequency, was found. The mean value of the frequency band of the second area containing the amplitude peaks was from 3.0 to 15.00×10^{-3} Hz. It should be noted that the location of the peaks of pneumogram in the VLF range corresponds to the location of the peaks of the indicators of gas exchange of the lungs. This is especially interesting, as a 30-minute pneumograms were recorded after pulmonary gas exchange tests. It is obvious that variability of recorded parameters has a steady character, at least in terms of the rest conditions.

Analysis of the Heart Rate Variability: The main peaks of the VLF frequency coincide with the peaks of pneumogram and parameters of gas exchange. On the panel of the Tpi are well marked as the VLF components intersect with the LF ones. It is known that the LF and the HF (high frequency) components account for approximately 5% of total power of the HRV recorded ECG method and a large part of the spectral power is on the VLF component [3]. In spite of the fact that this research was used another method, the power of the VLF component was significantly higher the LF component ($p<0.01$).

Comparison of the Results: Direct comparison of the spectral powers is impossible because of the different units of measure presented on the ordinate axis. However, one can estimate their distribution in the VLF band from

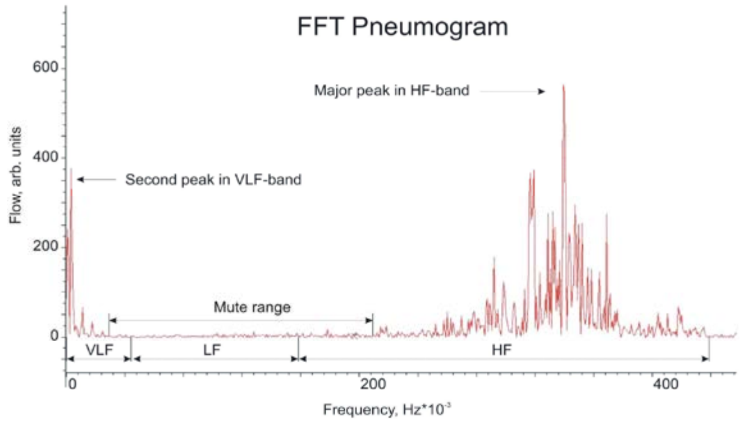

Fig. 1: Two peaks in the pneumogram spectrum obtained in spectral analysis using the FFT. The major peak stands in area of breath frequency from 10 to 20 min^{-1}.

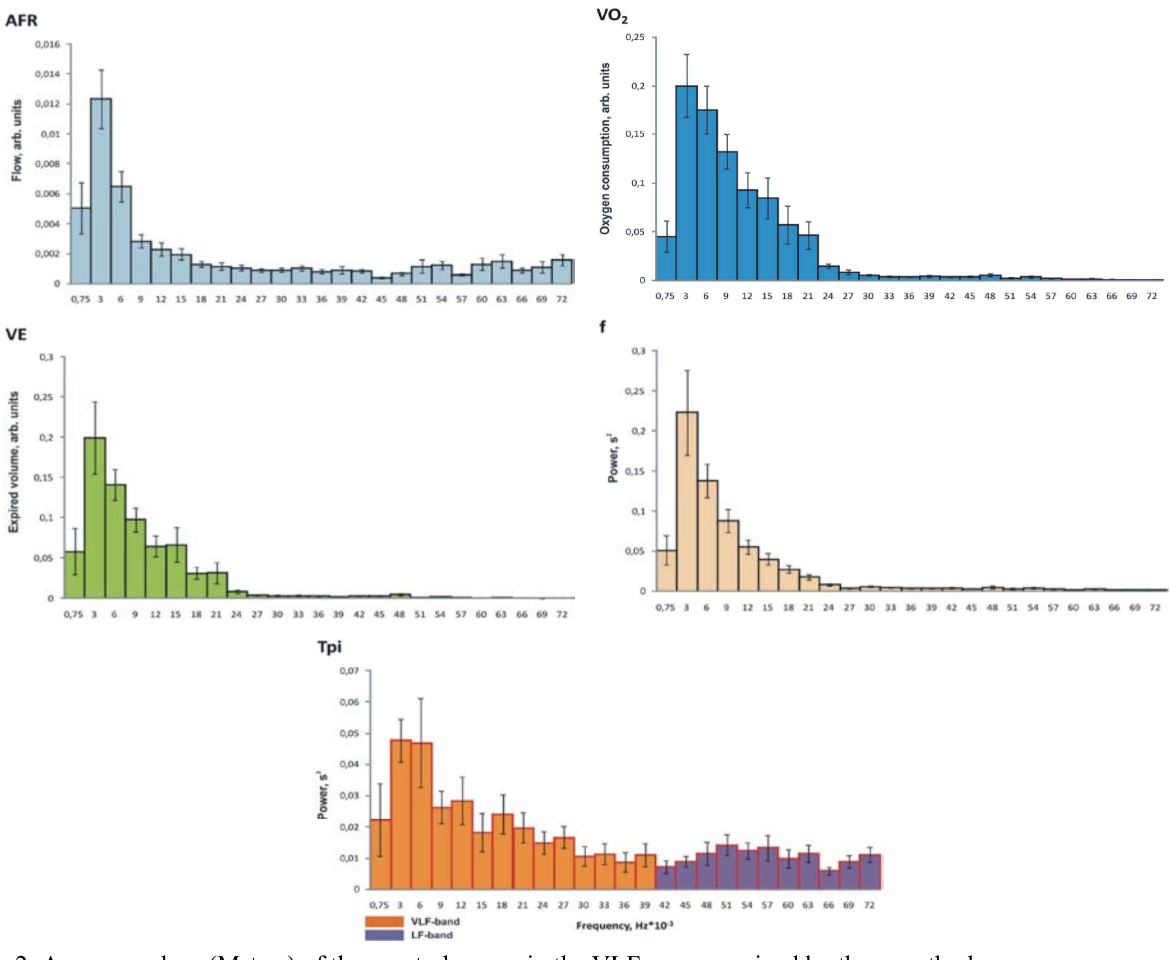

Fig. 2: Average values (M ± m) of the spectral power in the VLF range received by three methods:

- VO_2, Ve and f, indices recorded using the breath-by-breath method for 30 min;
- AFR recorded using pneumography;
- Tpi recorded using pulse oximetry.

Tpi and AFR panels have two areas: VLF band and part of LF band. VO_2, Ve and f panels have not LF band.
* The change in spectral power from the mute range is significant, $p < 0.05$

Table 1: Average values (M ± SD) of the frequency indices (Hz x 10^{-3}) of the peak value position for the indices of pneumography (AFR), pulmonary gas exchange and - interbeat pulse intervals (Tpi)

	Pulmonary gas exchange indices					
Pneumography AFR	VO_2	VCO_2	$FetCO_2$	Ve	f	Pulse oximetry Tpi
3.04±1.33	7.89±5.40	5.16±4.00	4.7±3,73	5.84±4.74	4.50±2.38	8.00±5.20
*	-	-	*	-	*	-
**	-	-	**	-	**	-

Notes: * A significant difference in Tpi, $p < 0.05$. ** - A significant difference in VO_2, $p < 0$

0.75 to 39 x 10^{-3} Hz. It should be noted that significant values of spectral power separating them from the noise level of the mute area are located from 1.9 to 9 x 10^{-3} Hz for pneumography and from 3 to 18 x 10^{-3} Hz for VO_2. This corresponds to a time interval of 1.5–8.5 min for AFR of pneumography and 1–3.5 min for VO_2. Thus, the rhythmic time course of the gas exchange function of pulmonary ventilation in the VLF band with an oscillation period of 1–3.5 min was found in analyzing the spectrum of the flow rate using a pneumogram and the pulmonary gas exchange indices.

The average values of the peak frequency characteristics of the analyzed indices are presented in the table. This comparison gives us the opportunity to estimate the significance of the coincidence of the spectral characteristics of VLF band for all the studied parameters. One can easily see that most peaks are located in one band. The analysis of variance (ANOVA) for significant differences between means showed the difference between the locations of the maximum peaks of some parameters of the gas exchange. It draws the attention of almost complete coincidence of places the VO_2 and the Tpi peaks, as well as the AFR and breath frequency (f) peaks. The coincidence of the spectra recorded by various methods indicates the existence of common physiological mechanism of regulating a respiration and a blood circulation.

DISCUSSION

Most studies on this problem have been carried out using variability analysis in the HF band corresponding to the respiratory rate. A theory was formed in the 1990s that the variability of the respiratory pattern found in both experimental animals and humans reflects the dynamic interaction between the chemoreflex and mechanoreflex feedback mechanisms regulating the ventilatory function of the external respiration [10, 14]. It was shown in a number of studies on the variability of the pulmonary ventilation function of the lung, estimated using statistical criterions of chaos, that the chemoreceptor regulation is the main factor determining the variability [15, 16]. This conclusion was based on the observation that the variability in healthy subjects increased under artificial hypercapnia, decreased under hypocapnia and did not change during breathing under additional load (up to 20 cm water column).

The slow-wave changes in the ventilation indices with a period from 60 to 120 s were first found in studying the breathing in the second phase of sleep [7]. Spirograms were recorded for 60 min using the breath-by-breath method in healthy subjects. The authors believed that the variability of the respiratory rhythm was of central origin or a result of the so-called noise in the respiratory chain of feedback chemical regulation. The presence of very low-frequency oscillations was explained by the instability of the chemical feedback loop. In other words, VLF processes were supposed to be a result of the noise effects of chemoregulatory mechanisms. However, in another study on the variability of the respiratory volume during sleep [17], the authors drew the conclusion that the regulation of the respiratory pattern did not depend on the sleep stage, was determined by metabolic control mechanisms and differed from simple rhythmogenesis.

The question now arises on whether the slow wave modulation of the pulmonary gas exchange indices is determined by the noise factors appearing in the interaction between the mechanisms of chemoregulation and mechanoregulation or whether it is a reflection of another unknown mechanism? In this study, the peaks in slow-wave bands display a number of features that suggest an additional mechanism of their formation. The first is the slow-wave spectra found for all measured parameters using different methods: 1) pneumography, 2) pulse oximetry, 3) spirometry –breath-by-breath method.

Second, these peaks remain unchanged in repeated tests (each test was carried out twice: pneumography for 30 min and then the study of spirometry and pulse oximetry simultaneously for 30 min). Third, the bands of spectral activity of the Slow-wave range coincided for all parameters measured regardless of the method used.

Specialists in the modern theory of nonlinear processes believe that these slow-wave events are typical of biological objects and belong to quasiiperiodic oscillations [18] that have two or more discrete components. These oscillations differ from periodic ones, which are represented, e.g., by the respiration rate formed by the chemoreceptor mechanism. They also differ from chaotic oscillations overlapping regular ones. Chaotic oscillations result from occasional changes in the external respiration apparatus (changes in the posture or body position) and the corresponding adjustment through the mechanoreceptor and other mechanisms. This also can be estimated by statistical methods, e.g., using the variation coefficient or calculation of mathematical characteristics of chaos [15, 16].

The most probable conclusion is that the slow-wave dynamic periodicity of the pulmonary gas exchange indices reflects synchronization of oscillators with incommensurable frequencies when two-frequency periodicity is dominant. It is well accepted that the first oscillator is a chemoreceptor mechanism of the regulation of ventilation. It is obvious, that the second oscillator may not be attributed to random noise. We conclude that VLF-phenomena reflects central mechanism for energy consumption regulation of whole organism. Therefore, the very-low-frequency variability of oxygen consumption, heart rate and respiration pattern fully coincide and support the hypothesis “metabolic rate variability”.

This work was supported by the Ministry of Education and Science of the Russia Federation (contract No 13.G25.31.0071).

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