

Autonomic control of heart rate in patients with chronic cardiorespiratory disease and in healthy participants at rest and during a respiratory sinus arrhythmia maneuver

Controle autonômico da frequência cardíaca de pacientes com doenças cardiorrespiratórias crônicas e indivíduos saudáveis em repouso e durante a manobra de acentuação da arritmia sinusal respiratória

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Abstract

Objective: To evaluate the autonomic modulation of heart rate (HR) at rest in the supine position and during a respiratory sinus arrhythmia maneuver (M-RSA) among participants with chronic obstructive pulmonary disease (COPD) or with chronic heart failure (CHF). **Methods:** Twenty-eight men were divided into three groups: ten with COPD, aged 69±9 years; nine with CHF, aged 62±8 years; and nine healthy participants aged 64±5 years (controls). At rest, the R-R interval of the electrocardiographic signal was obtained in the following situations: 1) 15 min in the supine position; and 2) 4 min during M-RSA in the supine position. The data were analyzed in the time domain (RMSSD and SDNN indices) and the frequency domain (LFab and HFab). During M-RSA, the expiratory/inspiratory ratio (E/I) and the inspiratory/expiratory difference (Δ IE) were calculated. **Results:** The main findings showed that the CHF patients presented lower RMSSD (12.2±2.6 vs. 20.4±6.5), LFab (99.2±72.7 vs. 305.3±208.9) and HFab (53.4±29.9 vs. 178.9±113.1), compared with the controls. The LFab band was significantly lower in the COPD group than in the controls (133.8±145.5 vs. 305.3±208.9). Additionally, both CHF patients and COPD patients showed lower E/I ratios (1.1±0.06 vs. 1.2±0.1 and 1.1±0.03 vs. 1.2±0.1) and Δ IE values (7.0±3.5 vs. 12.7±0.1 and 4.9±1.6 vs. 12.7±0.1), respectively, compared with the controls during M-RSA. **Conclusion:** The results from this study suggest that both COPD and CHF have a negative impact on the autonomic control of heart rate. Article registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) under the number: ACTRN12609000467235

Key words: chronic obstructive pulmonary disease; chronic heart failure; autonomic control of heart rate; respiratory sinus arrhythmia.

Resumo

Objetivo: Avaliar a modulação autonômica da frequência cardíaca (FC) em repouso, na postura supina e durante a manobra de acentuação da arritmia sinusal respiratória (M-ASR) de pacientes com doença pulmonar obstrutiva crônica (DPOC) ou com insuficiência cardíaca crônica (ICC). **Métodos:** Vinte e oito homens foram subdivididos em três grupos: 10 com DPOC (GD) e 69±9 anos; 9 com ICC (GI) e 62±8 anos; e 9 saudáveis (GC) com 64±5 anos. Em repouso, os intervalos R-R a partir do sinal eletrocardiográfico foram obtidos nas seguintes situações: 1) 15 minutos na posição supina e 2) 4 minutos durante M-ASR na posição supina. Os dados foram analisados nos domínios do tempo (índices RMSSD e SDNN) e da frequência. Durante M-ASR, foram calculadas a razão expiração/inspiração (E/I) e a diferença inspiração/expiração (Δ IE). **Resultados:** Os principais achados mostraram que os pacientes com ICC apresentaram menores valores de RMSSD (12,2±2,6 vs 20,4±6,5), BFab (99,2±72,7 vs 305,3±208,9) e AFun (53,4±29,9 vs 178,9±113,1) quando comparados ao controle. Além disso, a banda de BFab foi significativamente reduzida no grupo DPOC quando comparado ao controle (133,8±145,5 vs 305,3±208,9). Adicionalmente, pacientes com ICC e DPOC mostraram menor razão E/I (1,1±0,06 vs 1,2±0,1 e 1,1±0,03 vs 1,2±0,1) e Δ IE (7,0±3,5 vs 12,7±0,1 e 4,9±1,6 vs 12,7±0,1), respectivamente, comparados ao GC durante a M-ASR. **Conclusão:** Os resultados deste estudo sugerem que tanto a DPOC como a ICC produzem impacto negativo sobre o controle autonômico da FC. Artigo registrado no Australian New Zealand Clinical Trials Registry (ANZCTR) sob o número: ACTRN12609000467235

Palavras-chaves: doença pulmonar obstrutiva crônica; insuficiência cardíaca crônica; controle autonômico da frequência cardíaca; arritmia sinusal respiratória.

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Introduction

It has been reported that chronic cardiopulmonary diseases cause imbalance of the sympathovagal balance of heart rate (HR) control¹⁻³. In chronic obstructive pulmonary disease (COPD), the coexistence of expiratory flow limitation and loss of elastic recoil of the lung causes progressive changes in the respiratory pattern and in lung volume and capacity. Accordingly, a series of hemodynamic adjustments occurs, especially in the autonomic control of HR to maintain homeostasis⁴.

In patients with COPD, there is inconsistency in the changes in autonomic modulation of HR. By observing the indices of the time domain, some authors found that these individuals have a reduced heart rate variability (HRV), however the values of spectral analysis showed a predominance of vagal action (reflecting the vagal hyperactivity observed in the airway)⁵⁻⁸. Other authors^{9,10} found an increase in sympathetic activity in HR control, although they agree that there is a reduction in HRV in patients with COPD.

With regard to chronic heart failure (CHF), the reduced ejection fraction has a significant impact on the respiratory system, leading to congestive phenomena. Thus, through the sympathetic hyperactivity and reduced vagal action, there is an increase in HR and vasoconstriction of capillaries and veins with flow redistribution¹¹. Musialik-Lydka, Sreidniawa and Pasyk¹², Tulppo and Huikuri¹³ and Rosen et al.¹⁴ suggest the predominance of sympathetic activity in the sinus node. In contrast, van de Borne et al.¹⁵, Ponikowski et al.¹⁶ and Mortara et al.¹⁷ observed the sympathovagal imbalance of the autonomic control of HR without evidence of sympathetic hyperactivity.

The autonomic control of HR is also modulated by respiratory cycles. During spontaneous respiration, there is a synchronous interaction between the inspiratory phase and the increase in HR, due to vagal withdrawal, and between the expiratory phase and the reduction in HR, due to the resumption of vagal activity in the sinus node¹⁸. This phenomenon is called respiratory sinus arrhythmia (RSA), which is characterized by physiological HR oscillations in synchrony with respiration^{19,20}. Under experimental conditions, the RSA can be enhanced through controlled breathing maneuvers (M-RSA). Based on the processing of the HR values and RR intervals (RRI), it is possible to extract the M-RSA indices, which reflect the modulatory effect of respiration on the sinus node, caused primarily by the parasympathetic efferent²¹. Given that the analysis of HRV has been very useful in the prognosis of several chronic cardiopulmonary diseases, the analysis of the interaction between respiratory cycles and periodic HR oscillations through this maneuver can also provide an important prognostic index. In this sense, it would be reasonable to

assume that certain disorders that cause changes in respiratory cycles may indirectly produce autonomic changes in HR. Given these considerations, the study aimed to evaluate the autonomic modulation of HR at rest in the supine position and during the M-RSA of patients with COPD or CHF and in healthy individuals.

Methods

Observational and cross-sectional study with three groups.

Participants

Participants with the following profiles were recruited: 1) COPD group (DG) - moderate to severe COPD and forced expiratory volume in 1s (FEV₁) <60% of the predicted value (GOLD Scientific Committee, 2001), clinically stable and without exacerbations of disease, ex-smokers, non-alcoholics, not involved in a regular exercise program over the last six months, and with symptoms of dyspnea on low or moderate exertion; CHF group (FG) - documented CHF in the past six months, with echocardiography showing ejection fraction (EF) of the left ventricle <50% and classification of the disease from I to III according to the New York Heart Association (NYHA)²², no hospitalization in the last month, non-smokers, non-alcoholics, without COPD (FEV₁/FVC >70% and FEV₁ >70% of the predicted value), unstable angina at rest or a history of myocardial infarct within the last six months; and finally 3) control group (CG) - apparently healthy individuals who served as controls and who were screened with a clinical evaluation.

All participants underwent the following evaluations: a clinical evaluation (full medical history, family history, lifestyle, physical examinations) with the cardiologist, pulmonologist or general physician; a physical therapy evaluation (postural evaluation and muscle tests); a dyspnea evaluation using the scale developed by the British Council of Modified Medical Research (Medical Research Council - MRC)²³ for patients with COPD and using the NYHA classification²² for CHF; laboratory tests (full blood test, triglycerides, total cholesterol and fractions, urinalysis); spirometry; 12-lead electrocardiogram (ECG) and maximal or symptom-limited incremental exercise test. Individuals were excluded if they were not clinically stable, had electrocardiographic changes that prevented HRV collection, refused to participate in the study or did not fulfill the abovementioned inclusion criteria.

The participants were informed about the experimental procedures to which they would be submitted and signed an

informed consent form to take part in the research. The study was approved by the Research Ethics Committee of Universidade Federal de São Carlos under approval number 238/2005.

Medication

The participants with COPD routinely used short-acting (n=10) and long-acting (n=6) bronchodilators. In contrast, all CHF participants made use of beta-blockers (n=9), furosemide (n=3), digoxin (n=5), nitrates (n=2), angiotensin-converting enzyme inhibitors (n=6) and acetylsalicylic acid (n=2).

Spirometry

The pulmonary function tests were performed using a hand-held spirometer (Vitalograph Spirometer 2120, Ennis, Ireland). Slow vital capacity (SVC) and forced vital capacity (FVC) maneuvers were carried out to determine the FEV₁ and the FEV₁/FVC ratio. The technical procedures and the acceptability and reproducibility criteria followed the standards recommended by the American Thoracic Society²⁴.

Experimental procedure

The research was conducted in a laboratory with controlled temperature between 22°C and 24°C and relative air humidity between 50% and 60% at the same time of day (between 8 a.m. and 12 p.m.). The participants were familiarized with the experimental environment and with the examiners. The participants were instructed to avoid stimulating beverages on the day before the test and on the test day and to avoid exercise 24 hours before the tests. Light meals and adequate sleep (at least eight hours) were also recommended.

Initially the participants remained at rest in the supine position for about 10 minutes for the HR to reach baseline values. Next, the ECG and instantaneous HR were collected for 15 minutes in this position. The collection was then repeated during the performance of M-RSA in the same position in the following order: 1 minute at rest with spontaneous respiration, 4 minutes performing M-RSA, and 1 final minute at rest. During M-RSA, the participants were instructed to perform a series of deep and slow inspirations and expirations, varying the lung volume from total lung capacity (maximal inspiration) to residual volume (maximal expiration). Therefore, each respiratory cycle was performed in 10 seconds (5 seconds of inspiration and 5 seconds of expiration) with a total of five to six respiratory cycles per minute, during which maximum RSA was expected to be reached²¹. The participants were also instructed to monitor their respiratory rate by the time displayed on an analog

clock, while the examiner used the ECG signals on the computer monitor to give positive feedback if the cycle matched the previous cycle. At the end of the maneuver, the participants were instructed to breathe spontaneously, remaining at rest for a period of 1 minute. During all experimental procedures, the participants were monitored using the bipolar MC5 lead. The ECG signal was recorded on a one-channel heart monitor (TC 500, Ecafix, São Paulo, Brazil) and processed by a Lab-PC+ multifunction I/O board (National Instruments Co., Austin, TX, USA), which is an interface between the cardiac monitor and a personal computer (Pentium III). The HR was obtained and calculated from the intervals between the RRIs that were recorded at a sampling frequency of 500 Hz and stored by a specific software²⁵.

Data analysis

HRV was analyzed in the time and frequency domains using a specific routine developed in MatLab 6.1 (Release 12.1). The selection of the analysis interval of the supine rest conditions was done through visual inspection of RRI distribution (ms) within a 15-minute period. We selected the most stable signal period that produced a frequency sampling of, at least, 256 points as recommended by the Task Force¹. The noise caused by ectopic beats, heart rhythm disturbances or interference in the signal was manually removed because it could interfere with the analysis and interpretation of the data.

The analysis of the time domain was based on the RMSSD (ms) and SDNN (ms) indices^{1,26}. In contrast, the analysis of the frequency domain consisted in the application of the fast Fourier transform (FFT) with Hanning windowing of the RRI of the time series and cubic spline interpolation. By applying this model, the total spectral density (TSD) and its three frequency bands were identified: very low frequency (VLF), low frequency (LF) and high frequency (HF)^{1,26}. These components were determined in absolute values (ms²; LFab and HFab) and normalized units (nu; LFnu and HFnu), obtained by dividing the spectral component in question by the TSD, subtracting the VLF component and multiplying by 100. Additionally, the components were expressed as the ratio of low to high frequency bands (LF/HF ratio), reflecting the sympathovagal balance.

The analyses of the time and frequency domains were also performed in the RRIs acquired during the performance of M-RSA. Another specific routine developed in MatLab was then used to calculate the indices of HR and RRI obtained from the M-RSA²⁷: expiration/inspiration ratio (E/I; mean of the highest RRI values achieved during the expiration phase divided by the mean of the lowest RRI values of the inspiratory phase of the

M-RSA); inspiration-expiration difference (ΔIE ; difference between the mean of the highest HR values obtained during the inspiratory phase and the mean of the lower HR values in the expiratory phase of the M-RSA).

Statistical analysis

For the statistical tests, the data were transformed into decimal logarithms. Parametric statistical tests were used because the data showed normal distribution (Shapiro-Wilk test) and homogeneity of variances (Levene's test). One-way ANOVA with Tukey's post-hoc test was used in the intergroup comparisons (DG vs. FG vs. CG). The analyses were performed in SPSS Release 10.0.1 (1999) with the significance level set at $p < 0.05$.

Results

Twenty-eight participants were studied: 10 patients with COPD (DG), 9 patients with CHF (FG) and 9 control participants (CG). Table 1 shows the demographic, anthropometric and clinical data of the participants at rest. There were no significant differences between groups for the anthropometric measures, however the DG values were significantly lower than the CG values for body mass, even though the CG individuals were classified as healthy²⁸.

The DG showed a moderate stage of disease (Stage IIB)²⁹. In addition, the FEV_1 and FEV_1/FVC ratio for this group

were significantly lower than the CG ($p < 0.05$). The functional capacity of the DG by the MRC scale showed that the participants belonged to classes I (N=1), II (N=3) and III (N=6). The FG was composed of participants with systolic dysfunction of idiopathic etiology (N=5) due to myocardial infarction (N=4) and with functional class I (N=2), II (N=4) and III (N=3) by the NYHA²². According to the MRC and NYHA scales for functional class, the DG and FG showed similarities in the degree of dyspnea, i.e. limitation in the performance of activities of daily living that require light or moderate effort. Additionally, the SpO_2 was lower in the DG than in the CG ($p < 0.05$), but the DG and the FG did not differ (Table 1).

Regarding the HRV indices at rest (Table 2), it was observed that the DG showed lower LFab when compared to the CG ($p < 0.05$). In contrast, the FG showed lower values of RMSSD, LFab and HFab than the CG ($p < 0.05$). No significant differences were observed between the DG and the FG. In the comparisons during the M-RSA (Table 3), the DG and FG showed lower values for the E/I ratio and ΔIE when compared to the CG ($p < 0.05$). For the HRV indices in the M-RSA in the time domain, the participants in the DG and FG showed significantly lower values for RMSSD and SDNN than the CG. Similarly, in the frequency domain, the DG and FG showed lower LFab and HFab values compared to the CG ($p < 0.05$). Additionally, Figure 1 illustrates the spectral behaviour that represents each group. The DG and FG showed lower values of total spectral density compared to the CG.

Table 1. Demographic, anthropometric and clinical characteristics for all groups.

Variables	DG (N=10)	FG (N=9)	CG (N=9)
Demographics / Anthropometrics			
Age (years)	69±9	62±7	64±5
Height (m)	1.67±0.08	1.68±0.06	1.71±0.05
Body mass (kg)	64±9.0	69±8.5	75±6.3*
BMI (kg/m ²)	23±3.3	25±3.1	25±1.2
Echocardiogram			
EF (%)	---	41±6	---
Spirometry			
FEV_1 (% of predicted value)	41±11	80±9	91±20*
FEV_1/FVC	59±12	82±11	101±7*
Clinical characteristics			
SpO_2 (%)	92±3	96±2	96±1*
RF (rpm)	15±4	14±4	12±3

Values are means±SD. DG=COPD group; FG=CHF group; CG=control group; BMI=body mass index; EF=ejection fraction of the left ventricle; FEV_1 =forced expiratory volume in the first second; FEV_1/FVC = FEV_1 to forced vital capacity ratio; SpO_2 =peripheral oxygen saturation; RF=respiratory frequency in respirations per min. * $p < 0.05$ =DG vs. CG; (one-way ANOVA with Tukey's post-hoc test).

Table 2. Comparison of heart rate variability at rest in the time and frequency domains for all groups.

	DG (n=10)	FG (n=9)	CG (n=9)
Time domain			
HR (bpm)	73±12	64±7	68±9
RRI (ms)	838±122	878±19	900±116
RMSSD (ms)	17.7±6.1	12.2±2.6	20.4±6.5 [†]
SDNN (ms)	23.2±9.2	18.4±4.5	30.2±9.1
Frequency domain			
LFab (ms ²)	133.8±45.5	99.2±72.7	305.3±208.9 [†]
HFab (ms ²)	114.3±98.3	53.4±29.9	178.9±113.1 [†]
LFnu	0.5±0.3	0.6±0.4	0.6±0.2
HFnu	0.5±0.3	0.4±0.2	0.4±0.2
LF/HF	2.3±4.1	2.1±1.6	2.2±1.7

Values are means±SD. DG=COPD group; FG=CHF group; CG=control group; HR=heart rate; RRI=RR intervals in the ECG; RMSSD=root mean square of successive differences between adjacent RRI; SDNN= standard deviation of normal to normal RRI; LFab=low frequency in absolute values; HFab=high frequency in absolute values; LFnu=low frequency in normalized units; HFnu=high frequency in normalized units; [†] $p < 0.05$ =FG vs. CG and * $p < 0.05$ =DG vs CG (one-way ANOVA with Tukey's post-hoc test).

Table 3. I/E ratio, IE-differences and heart rate variability during respiratory sinus arrhythmia maneuver of the groups studied.

	DG (n=10)	FG (n=9)	CG (n=9)
Time domain			
E/I ratio	1.1±0.06	1.1±0.03	1.2±0.1*†
ΔIE (bpm)	7.0±3.5	4.9±1.6	12.7±4.2*†
RMSSD (ms)	18.3±15.6	17.6±4.1	43.5±27.9*†
SDNN (ms)	32.1±21.2	28.2±10.1	63.8±29.1*†
Frequency domain			
LFab (ms ²)	1052.7±1538.3	463.2±403.4	3551.2±3581.2*†
HFab (ms ²)	93.9±153.8	65.3±37.4	626.8±906.8*†
LFnu	0.9±0.03	0.7±0.2	0.8±0.07
HFnu	0.8±0.03	0.2±0.2	0.2±0.07
LF/HF	15.9±15.3	9.2±11.1	11.3±7.5

Values are means±SD. DG=COPD group; FG=CHF group; CG=control group; E/I ratio=inspiratory/expiratory ratio; ΔIE=inspiratory-expiratory differences in beats per min; root mean square of successive differences between adjacent RRI; SDNN= standard deviation of normal to normal RRI; LFab=low frequency in absolutes values; HFab= high frequency in absolutes values; LFnu=low frequency in normalized units; HFnu=high frequency in normalized units; * p<0.05=DG vs CG; † p<0.05=FG vs. CG (one-way ANOVA with Tukey's post-hoc test).

Discussion

The main findings of the present study showed that both participants with COPD and participants with CHF showed changes in autonomic modulation of HR at rest and during the M-RSA when compared to apparently healthy individuals matched for age.

Impact of the cardiorespiratory diseases on HRV at rest

In the present study, the COPD participants showed reduced sympathetic activity when compared to the controls. Some authors^{8,30} have observed that both sympathetic and parasympathetic activity are reduced in individuals with COPD. In contrast, Volterrani et al.⁷ observed that patients with COPD showed higher values of the HF band (nu), reflecting an increase in parasympathetic activity over the control of HR. These authors consider that these findings can be related to bronchoconstriction and, consequently, to the reduction in FEV₁ showed by these patients. However, in the study by Volterrani et al.⁷, some methodological features that differ from the present study may have influenced the results. In the study by these authors⁷, the COPD group had a wide age-range (31 to 68 years), with a large number of young individuals diagnosed with asthma who may have already had an exacerbated vagal response. Our results are similar to those reported by Chen, Chen and Kuo⁹, who showed a reduction in sympathetic activity in patients with COPD.

In the present study, the participants with CHF also experienced a significant reduction in HRV when compared to the control group, with reduced sympathetic and parasympathetic activity. These findings corroborate those of other authors who also observed a reduction in time domain indices in patients with CHF³¹. In accordance with our findings, Saul et al.³² observed that patients with congestive CHF had a reduction in all frequency bands compared to the healthy group with similar anthropometric characteristics and age. Guzzetti et al.³¹ observed that patients with CHF showed a reduction in the time domain indices and lower values of LF band when compared to healthy participants, resulting in lower sympathetic activity.

In contrast, other authors¹⁵⁻¹⁷ reported reduced HRV in CHF patients with a predominance of sympathetic activity. These authors suggest that sympathetic hyperactivity in HR control is a reflection of compensatory changes in the autonomic system caused by the evolution of the disease and aimed at ensuring homeostasis with an appropriate increase in cardiac output. In the present study, we found a reduction in both sympathetic and parasympathetic action on the sinus node, possibly due to regulatory changes in the autonomic centers¹², sensitivity of chemoreceptors¹³ or the respiratory pattern marked by periodic oscillations in these patients¹⁴.

However, it is important to note that our findings were observed in the absolute values of the LF band, which is influenced by the VLF bands, combined with the systems of long-term autonomic control. Additionally, the CHF patients involved in the present study continued the drug treatment. The action of beta-blockers³³ on the sinus node receptors, the action of digitalis drugs³⁴ on the sodium and potassium pumps of the myocardial and on the angiotensin-converting enzyme inhibitors promote the autonomic regulation of the heart, attenuating sympathetic hyperactivity and possibly influencing the present results.

Impact of cardiorespiratory diseases on HRV indices during the M-RSA

Regarding the indices of HR and RRI obtained with the M-RSA, it was observed that both the COPD and CHF participants showed reduced parasympathetic response compared to the control participants. The results corroborate other findings in the literature that reported a significant reduction in RSA in patients with DPOC^{35,36} and CHF³² compared to healthy participants. However, no previous study has compared the HRV indices and RSA in both pathologies.

The variables related to HRV analysed in the time domain (RMSSD and SDNN) and the frequency domain (LFab and HFab) showed that the DG and FG showed lower HRV than the

participants in the CG. RSA, a product of the interaction between the respiratory and cardiovascular systems, is influenced by respiratory frequency and tidal volume³⁷. In the present study, in which the respiratory frequency was controlled during the M-RSA, it can be assumed that the lower values of the RSA indices are related to reduced tidal volume, further strengthening our speculation that the reduction in HRV observed in patients of both groups may be related to changes in lung compliance and the response of pulmonary stretch receptors.

Methodological considerations

The present study has some limitations. Regarding the participants, groups with more participants would have been ideal; however, the strict exclusion criteria did not allow a larger sample because both diseases can be associated with respiratory and cardiovascular changes. Additionally, we considered that an echocardiogram of the participants with COPD would be important to exclude the coexistence of cor pulmonale or right ventricular failure, and we considered that arterial blood gas analysis was needed to classify the patients with COPD as hypoxemic or hypercapnic. Similarly, the measurement and control of tidal volume during controlled respiration, which were not performed in the present study, could contribute to the consolidation and interpretation of the results. Finally, the evaluation of complete lung function (static volumes) would be of particular relevance in the evaluation of patients, but such measurements involve expensive equipment.

Clinical relevance

Autonomic control is a major means of adjustment in response to postural, physical changes under stress or during physical exercise in conditions of health or coexisting pathologies. In this sense, the knowledge of autonomic variations in HR in patients with cardiopulmonary diseases contributes to a more appropriate physical therapy evaluation and prescription of rehabilitation programs and to a better understanding of the effects of different physical therapy interventions.

Conclusion

The results of the present study suggest that patients with COPD or CHF show modification of the autonomic control of HR, with reduced sympathetic and/or parasympathetic activities, when compared to healthy participants due to the integration of both cardiorespiratory diseases. Moreover, both COPD and CHF showed attenuated responses to enhanced parasympathetic activity during the M-RSA.

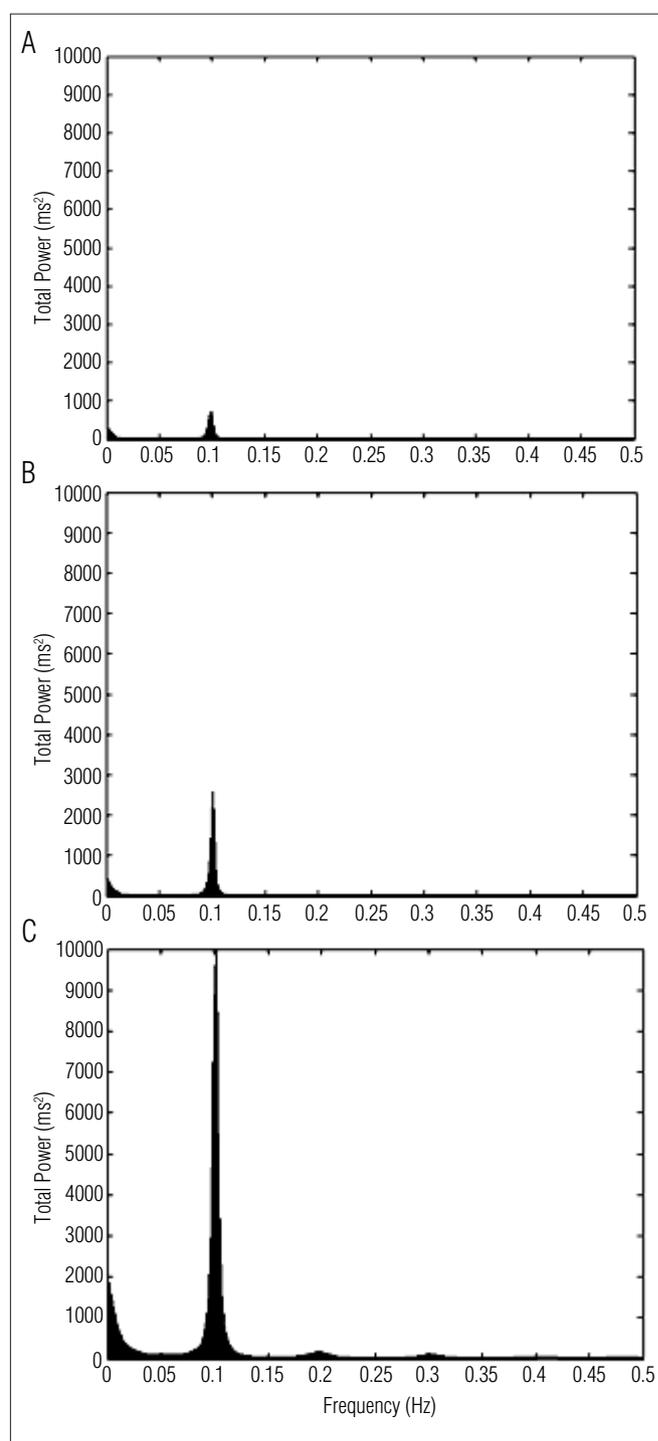


Figure 1. Decomposition of the spectrum into single spectral components - very low frequency (VLF), low frequency (LF), and high frequency (HF) - during respiratory sinus arrhythmia maneuver. (A) COPD patient, (B) CHF patient, and (C) control.

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