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Effectiveness of a Pulmonary Rehabilitation Program on Changes in Heart Rate Variability and Physical Performance in Chronic Obstructive Pulmonary Disease

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Abstract

Changes in autonomic regulation are evaluated in COPD patients by using heart rate variability (HRV) in rehabilitation. Our aim was to evaluate the presence of autonomic dysfunction and to assess the effect of a rehabilitation program.

R-R intervals were measured for 6 minutes in 36 patients (16 female; 20 male) before and after an inpatient pulmonary rehabilitation program that included 30 minutes of respiratory training, chest wall mobilization, learning controlled breathing techniques, inhalation, expectoration and personalized training. Ectopic beats were eliminated. Parameters used: minimal pulse (p.min), average pulse (p.avg), maximal pulse (p.max), maximum-minimum pulse difference (p.max-p.min). Long-term continuous RR intervals (stda), standard deviation of instantaneous beat-to-beat variability (stdb), the number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals (pNN50). Spectral analysis provided the low-frequency/high-frequency ratio (LF/HF).

HRV showed decreased p.max-p.min (15.78 ± 9.2 bpm), depressed dynamics (stda: 39.63 ± 33.5; stdb: 22.72 ± 35.84) with sympathetic overload (pNN50:3.17 ± 5.24, LF/HF: 169.52 ± 208.83), heavy parasympathetic modulation (pNN50:5.51 ± 5.59, LF/HF: 27.28 ± 13.12) in severe COPD patients. Rehabilitation resulted in lowered p.min-p.max (12.5 ± 9.01 bpm), overdepressed dynamics (stda: 34.56 ± 35.97; stdb: 20.88 ± 41.5) strong sympathetic overload (pNN50:3.33 ± 6.76, LF/HF: 252.01 ± 351.16).

Patients showed abnormal physiological response in resting autonomic regulation. The rehabilitation resulted in improvement in overall status, autonomic balance.

Keywords: Chronic obstructive pulmonary disease; Heart rate variability; Pulmonary rehabilitation; Cardiovascular function; Sympathetic and parasympathetic nervous system

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous clinical syndrome found in 6-8% of the population [1]. COPD patients experience functional and structural changes of the respiratory system that deeply influence cardiovascular function [2]. Several factors, including abnormal autonomic control of cardiopulmonary function, may contribute to the development of arrhythmias in these patients [3-7]. Determination of autonomic balance may be important in understanding the pathophysiology of COPD and might be useful clinically in the treatment of patients with COPD [8].

The application of heart rate variability (HRV) to assess the risk of sudden cardiac death and diabetic neuropathy is well known [9,10]. The sympathetic and parasympathetic (autonomic) nervous systems innervate the heart and regulate the heart rate (HR). As illustrated in Figure 1 the HRV represents a physiological phenomenon that may be monitored and analyzed to determine the state of the nervous system that controls the heart [11]. HRV data can be collected in relatively simple devices such as modern wrist computers [12-14]. although autonomic control of the cardiovascular system is also affected by baroreceptors, chemoreceptors, muscle afferents, local tissue metabolism, and circulating hormones (Figure 2) [15]. Critical adjustments are continually made to the cardiovascular system to meet the diverse demands of the musculature and heart [16,17]. These dynamic adjustments in cardiac and peripheral vascular control, including their regulation by the autonomic nervous system (ANS), occur in part as a response to rapid changes in heart rate and blood pressure. Though there are some reports on changes in time-domain and frequency-domain heart rate variability in COPD patients, the information on HRV in patients with COPD has so far been conflicting [18-21].

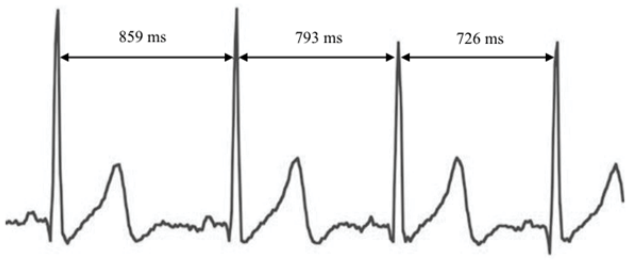

Figure 1: R-R variants of R-R distance for calculation of heart rate variability (HRV).

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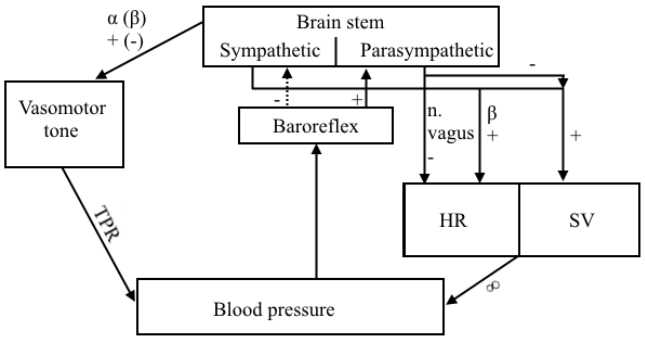

Figure 2: This model of HRV control illustrates independent actions of the vagal, α- and β- sympathetic system. The actions of these systems can be assessed by measuring heart rate variability, blood pressure variability, and the baroreflex mechanism. The parasympathetic nervous system is responsible for the bradycardia accompanying baroreceptor stimulation, and for the tachycardia accompanying baroreceptor deactivation, with the sympathetic nervous system also playing a minor role.

Exercise training reduces the possibility of sudden cardiac death and decreases cardiovascular mortality [22]. Regular training and exercise play an important role in COPD rehabilitation. The effectiveness of pulmonary rehabilitation can be monitored by measuring HRV and cardiac function because exercise training is capable of modifying the autonomic balance. Since the complex mechanism of HRV changes are not totally clear, experimental studies are still needed to explain specific changes in HRV [23].

The aim of this study was to evaluate the presence of autonomic dysfunction in patients with COPD by HRV and to assess the effect of a four-week rehabilitation program.

Materials and Methods

Study subjects

36 patients with COPD (age: 65.4 ± 7.4 years (51-78); BMI: 26 ± 5 kg/m^2, male:female: 20:16) participated in this study. All of the patients provided written consent for the study in the Department of Pulmonary Rehabilitation. The study protocol was approved by the Ethical Committee of the National Koranyi Institute for Pulmonology with 25/2017 registration number. It was an observational study using the general management of the patient; it was a non-interventional study. Patients` characteristics are presented in Table 1.

Pulmonary function

According to ATS/ERS guidelines all patients underwent a post-bronchodilator pulmonary function testing (Vmax 229 and Autobox 6200, Sensormedics), including spirometry measurements [24]. COPD patients inhaled 400 μg salbutamol 20 minutes before testing.

Characteristics (n=36)	
Age (years)	65.47 ± 7.39
Male: female	20:16
BMI (kg/m^2)	27.99 ± 6.98
FEV_1 (%pred)	45.43 ± 20.2
Hypertension	32:36
Diabetes	11:30
Atherosclerosis	27:36
Pulmonary hypertension	9:36
BMI: body mass index; FEV_1: forced expiratory volume in the first second	

Table 1: Patients' characteristics.

Measurements

6 minutes walking distance: The 6MWD was measured at the corridor of our department. Before, during and after walking, oxygen saturation and heart rate were measured, and a modified Borg-scale was evaluated. The speed of walking was as fast as possible [25]. The 6MWD was made according to the international guideline [26].

Chest wall expansion: Chest wall expansion (CWE) means the difference of chest circumferences between deep inspiration and expiration. It is measured at the level of processus xypho ideus [27].

Maximal inspiratory pressure: To evaluate MIP we used a special digital instrument. Power Breathe K1 (POWERbreathe International Limited). The calculation of diaphragmatic force was based on the patient's height, weight,age and sex (very poor, poor, average, fair, good, very good). Patients were asked to inhale suddenly with maximal force after a maximal exhalation [28].

Breath holding time: Breath holding time (BHT) displays the severity of COPD. After a maximal inhalation the subjects were asked to hold the breath as long as possible with closed nose and mouth without inhalation [29].

Grip strength measurement: Kern handgrip dynamometer (2016 Kern & Sohn GmbH-Germany) was used to identify the peripheral muscles force [30].

Protocol of resting HRV evaluation

During our measurements R-R intervals for autonomic regulation tendencies were measured for 6 minutes in a supine position by Polar H1 sensors and Polar Precision Performance 2.0 software (Polar Electro. Finland). The software enabled the visualization of HR and the extraction of a cardiac period (R-R interval) file in "txt" format. Following digital filtering complemented with manual filtering for the elimination of premature ectopic beats and artifacts, at least 256 R-R intervals were used for the data analysis, and all arrhythmic beats were excluded from data evaluation. Simple HR data was complemented with an HRV and one lead ECG measurement device iQRS (IQRS Hungary). Measurement frequency was 1 kHz. A standardized protocol was used; the measurements were noninvasive and performed at the same time period of the day at the National Koranyi Institute for Pulmonology. We performed our resting evaluations on the first and last day of the rehabilitation. Patients were asked not to do any physical activity on days of measurements, the assessing room was separated. quiet and temperature-controlled (maintained around 24°C). The subjects had rested quietly in a supine position during the measurements.

Parameters of HRV measurements

The most commonly used HRV parameters in ANS evaluation are the frequency-domain, time-domain, and Poincaré plot parameters. While the nomenclature of the different measurements is complex, they represent different ways to look at the variability and distribution of the heart rate over time.

The following time domain parameters were used: minimal pulse (p.min), average pulse (p.avg), maximal pulse (p.max) of the 6 minutes resting measurements, and maximum minimum pulse difference (p.max-p.min).

For HRV analysis in the frequency domain; we used standard deviation of the long-term continuous RR intervals (stda), standard deviation of instantaneous beat-to-beat variability (stdb), the number

of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals (pNN50) [15,23]. Spectral analysis provided the low-frequency/high-frequency ratio (LF/HF).

The Poincaré plot is a map of points in Cartesian coordinates that is constructed from the values of the RR intervals. Each point is represented on the x-axis by the previous normal RR interval and on the y-axis by the following RR interval [31].

Personalized training program

Our pulmonary rehabilitation program was an inpatient program; included 30 minutes of respiratory training in the morning, chest wall mobilization, learning-controlled breathing techniques, inhalation, expectoration, improving the overall psychological condition. smoking cessation and personalized training. Patients participated in an individualized continuous or interval type of cycle and/or treadmill training for 10-30 minutes, 2-3 times a day for the whole duration of their hospitalization. The duration of the rehabilitation program was 4 weeks. The intensity of the training was progressive from 60-80% of peak work rate based on maintaining Borg dyspnea scale breathlessness and leg fatigue both on grade No. 7. The training method was very effective and demanding for the patients; it is equivalent of 6-8 weeks of regular training [32,33].

Statistical analysis

Patient characteristics, lung function, HRV analysis, resting and exercise functional variables were compared by a paired *t*-test, a non-parametric sign test and a Wilcoxon test. Significance was accepted at the $p<0.05$ level. The distribution around the mean was expressed as ± SD in tables. Scatterplot distribution was observed in figures. Distributions were tested for normality by the Kolmogorov-Smirnov test.

Results

Functional and quality of life parameters are presented before and after the rehabilitation program in Table 2. Pulmonary function did not show improvement after the rehabilitation period (Table 2). Significant changes were detected in MIP, CWE, BHT, GS, 6MWD, CAT, mMRC (Table 2). The clinically significant difference was accepted at $p<0.05$ level (Table 2).

Eleven patients had severe arrhythmias (8 males. 3 females). and the ectopic beats were left out of the analysis. After the four-week rehabilitation, the ectopic beats ceased in all but 4 patients (3 males. 1 female).

Minimal, average and maximal pulse decreased, as did maximum minimum pulse difference. These changes showed only a marginal improvement. but significant increment was shown in min-max pulse difference (Table 3).

Parameter	Before Treatment	After Treatment	p-value
FEV_1 (l)	44.00 ± 17.00	45.48 ± 17.05	n.s.
FVC (l)	73.59 ± 17.04	76.00 ± 13.84	n.s.
mMRC	1.97 ± 0.61	1.55 ± 0.56	<0.01
MIP (cm H_2O)	60.38 ± 16.74	69.17 ± 15.34	<0.001
CWE (cm)	3.31 ± 1.72	4.86 ± 2.17	<0.001
BHT (sec)	28.45 ± 9.94	35.69 ± 12.85	<0.001
GS (kg)	26.60 ± 9.92	28.89 ± 10.01	<0.001
6MWD (m)	347.45 ± 89.96	403.62 ± 112.07	<0.001
CAT	15.86 ± 8.07	10.24 ± 6.16	<0.001

FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; mMRC: modified Medical Research Council Dyspnoea Scale; MIP: maximal inspiratory pressure; CWE: chest wall expansion; BHT: breath holding time; GS: grip strength; 6MWD: 6-minute walking distance; CAT: COPD assessment test

Table 2: Functional and quality of life marker parameters.

Parameter	Before Treatment	After Treatment	p-value
p. min (bpm)	68.86 ± 15.53	66.53 ± 13.52	n.s.
p. avg (bpm)	76.11 ± 14.26	73.06 ± 13.04	n.s.
p. max (bpm)	84.5 ± 14.22	79.31 ± 13.46	n.s.
p. max- p. min (bpm)	15.78 ± 9.2	12.5 ± 9.01	<0.05
Stda	39.63 ± 33.5	34.56 ± 35.97	<0.05
Stdb	22.72 ± 35.84	20.88 ± 41.5	n.s.
pNN50 (%)	3.17 ± 5.24	3.33 ± 6.76	n.s.
LF/HF	169.52 ± 208.83	252.01 ± 351.16	n.s.

p. min: minimal pulse; p. avg: average pulse; p. max: maximal pulse; p. max- p. min: maximal-minimal pulse difference; stda: standard deviation of the long-term continuous RR intervals; stdb: standard deviation of instantaneous beat-to-beat variability; pNN50: the number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals; LF/HF: spectral analysis of the low-frequency/high-frequency ratio

Table 3: HRV results.

The standard deviation of the long-term continuous RR intervals and the standard deviation of instantaneous beat-to-beat variability has not shown a clear, significant improvement. Considering changes on an individual level, these parameters show a narrowing tendency (Table 3). The decreasing trend in HRV was confirmed with the data found in our research on COPD patients (Table 3). We would like to underline that 12 patients were in a very severe parasympathetic overload. On average the four-week treatment resulted in no significant improvement in stda and stdb, but the ratio shifted into a sympathetic autonomic modulation.

As a result of the four-week rehabilitation program, the number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals and the spectral analysis of the low-frequency/high-frequency ratio showed improvement. although these changes did not achieve clinical significance (Table 3). These results show that four weeks of rehabilitation had a favorable impact on autonomic function and overall wellbeing.

Discussion

Pulmonary rehabilitation program resulted in a clear decrease in HRV data. with a shift into sympathetic autonomic modulation. As a result of the rehabilitation program in our research, we did not find any correlation between HRV and functional markers. Although decreasing HRV is related to increased morbidity and mortality, we believe that the changes in HRV were caused by higher sympathetic stimulation, contributing to improved health-related quality of life, autonomic function and overall wellbeing.

Beat-to-beat variability in heart rate is a well-known phenomenon. Breathing, digestion, thermoregulation, but even breathing aritmia, extrusion, applying cold to the face, changes in body position and stress all lead to changes in the length of time between heartbeats; the heart rate variability (HRV) analysis measures these changes [34-36]. HRV has been used as a tool to analyze the behavior of the autonomic nervous system on the heart and to compare possible differences between healthy and unhealthy people. Decrease in HRV is related to increased morbidity and mortality [22,31]. Other studies indicate that there are changes in HRV in a list of cardiorespiratory disorders. COPD is associated with vascular remodeling that modifies the pulmonary circulation; this pathological mechanism is usually caused by hypoxia generated by the disease [35].

Reis, et al. [37] aimed to evaluate the influence of respiratory

muscle strength on the magnitude of respiratory sinus arrhythmia. They assumed that respiratory muscle weakness negatively influences HRV during respiratory maneuvers in COPD. This study had a very similar protocol to ours: ECG signal and the instantaneous HR were obtained at rest in the supine position for 15 minutes while volunteers went through a respiratory sinus arrhythmia maneuver in the same position in the following order: For one minute at rest with spontaneous breathing; for four minutes while performing the respiratory sinus arrhythmia maneuver; and for one minute at rest with spontaneous breathing. As in our study, COPD patients showed evidence of impaired autonomic modulation of heart rate at rest and during respiratory sinus arrhythmia maneuver.

Both COPD and congestive heart failure (CHF) patients show alterations in autonomic modulation of heart rate at rest and during respiratory sinusal arrhythmia maneuver (RSA-M) compared with apparently healthy individuals, according to a study by Reis, et al. [37]. COPD patients showed a reduction in sympathetic activity compared to the control group at rest. In our study we found similar results at the start of the four-week rehabilitation program: Lower min-max pulse difference, depressed Poincaré plot proportion and LF/HF ratio. The patients demonstrated reduced sympathetic activity; in 12 patients we found heavy parasympathetic overload. These findings indicate a possible relationship between regulatory changes of the autonomic centers and the sensitivity of chemoreceptors or respiratory pattern characterized by periodic oscillations in COPD patients.

In a recent review Mohamed, et al. [38] found that aerobic exercise training causes a significant increase in time domain HRV, but frequency domain HRV analyses were not significantly affected by aerobic exercise training. Also, baroreceptor sensitivity seems to be very low in COPD patients. causing a limited beneficial effect on autonomic function. This can be one reason for the HRV data not reaching clinical significance in our study.

In a clinical study, de Carvalho, et al. [39] found decreased stda (SD1) and stdb (SD2) in COPD patients group while the stda/stdb ratio were similar between healthy and COPD patient groups. These findings are in line with ours and also suggest a reduced HRV in patients with COPD. The reduced stda index indicates a reduction in the activity of these individuals. Compared with healthy subjects he found a collapse in the values of stdb too in patients with COPD. This indicates an overall reduction in the autonomic modulation of these individuals, which suggests global autonomic damage in COPD. Our findings show similar tendencies; both stda and stdb show loss of variability, reduced vagal control and autonomic modulation. These effects are chronic as pulmonary rehabilitation program has not resulted in clinically significant changes in stda and stdb.

De Carvalho, et al. [39] also found greater dispersion of data through the analysis of the Poincaré plot in COPD, which, again, suggests the same reduction in HRV. Van Gestel came to a similar conclusion in a study [40]. The aim was to evaluate the association between cardiac autonomic dysfunction and health-related quality of life in COPD patients. A six-minute walk test was performed by patients in a 30 m indoor track. Resting parasympathetic tone was independently associated with health-related quality of life. The importance of supervised exercise in subjects with COPD was highlighted since the literature shows beneficial effects on cardiac autonomic modulation. As a result of rehabilitation, concentrating mainly on physical rehabilitation through exercise, we found a strong sympathetic activity in autonomic modulation and a clear, significant improvement in most functional and quality of life markers.

Camillo, et al. [41] analyzed HRV after two exercise programs in 40 COPD patients. Two groups were created: A high-intensity, endurance exercise group and low-intensity calisthenics, breathing exercise group. The three months of high-intensity exercise training proved to have an important role in post-training cardiac autonomic function improvement in patients with COPD. This underlines the importance of further investigation of the sustained long-term effects of our four-week rehabilitation program.

HRV is an important tool for assessing the autonomic nervous system (ANS), which has an important role in maintaining homeostasis. It is a clear predictor of the internal functions of the body, whether they are normal or pathological conditions. The correct usage can lead to characterization, evaluation and identification of problems in human development, growth and health [42].

Our study has limitations. One of them is that we focused only on patients with COPD and not other chronic respiratory diseases. Our pulmonary rehabilitation program was somewhat shorter than an eight-week program. but the total amount of work was comparable; our patients performed training two to three times per day with high intensity of load. Further research is needed to better understand the effects of training load and rehabilitation program on autonomic control of COPD patients.

Conclusion

The data collected in this study show the importance of HRV as a low-cost method for early diagnosis of cardiovascular diseases, deranged autonomic modulation, and loss of HRV concomitant with lung diseases since these diseases tend to coexist, influencing the morbidity and mortality of these patients. It is well-known that COPD patients tend to have a reduced HRV and, consequently, a deterioration of symptoms. Our study attempted to show the importance and complexity of the pulmonary rehabilitation program, as it helps to minimize the effects that COPD may have in patients.

Acknowledgement

The study protocol was approved by the Ethical Committee of the National Koranyi Institute for Pulmonology with 25/2017 registration number. The study was financed by the sources available at Deparment of Pulmonary Rehabilitation. National Koranyi Institute for Pulmonology, Budapest, Hungary.

Conflict of Interest

None of the authors reported conflict of interest.

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