Applicability of non-invasive physiology testing methods in chronic obstructive pulmonary disease status assessment and rehabilitation

PhD Thesis

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a complex and heterogenous clinical syndrome. This disease is progressive leads to the worsening of respiratory function and decrease of pulmonary parenchyma; these changes also affect cardiovascular function. The associated multisystemic inflammations and other respiratory comorbidities like weakness of respiratory muscles, autonomous nervous system problems strongly contribute to high mortality rates.

The changed pulmonary milieu (hypoxia, vasoconstriction, damages in extracellular matrix) cause changes in the endothelium that lead to cardiovascular diseases, right ventricular dysfunction, pulmonary hypertension, coronary diseases and atherosclerosis.

Research on endothelium of COPD patients is important because the endothelium of the respiratory system is a new therapeutic area for glucocorticosteriods, because these compounds can partly or wholly regenerate the endothelium dependent vasodilatation.

In terminal state COPD patient's pulmonary hypertension (PAH) is a well known and common phenomenon and is caused by the arteries endothelial dysfunction. PAH occurs in 50% of

COPD patients during physical activity, and is caused by the hypoxia related constriction of pulmonary arteries.

Seriousness of PAH is directly proportional to the seriousness of hypoxia. The lack of oxygen causes pulmonary artery vasoconstriction inducing ventilation perfusion disproportion.

Cigarette smoke, high cholesterol level and high blood pressure is key in formation of atherosclerosis but the bad eating habits and sedentary lifestyle caused by COPD is also playing a role in it.

The role of smoking must be highlighted even at the start of the disease, because it causes oxidative stress, induces inflammation. Chronic low-grade inflammation is common in cardiovascular diseases and COPD. Oxidative stress contributes to the progression of these diseases. It is important to note that among COPD patient's hypoxia can have multiple causes besides smoking: diminished pulmonary function, clogging of small blood vessels, PAH, left ventricular hypertrophy and dysfunction.

Chronic inflammation, coronary diseases, high blood pressure are the most common comorbidities in COPD apart from PAH. These problems usually overlap and have a strong impact on the quality of life and survival rates of COPD patients.

These causes are responsible for 20-30% of deaths among mild and moderately serious cases of COPD.

Physical activity plays a great role in handling the comorbidities. COPD patients usually are obese, this leads to forming habits which influence vagal function in a harmful way. Regular physical activity plays a very favorable role in systemic inflammation, pulmonary function and loss of muscle mass. Peripheral muscle function, glucose homeostasis is in connection with physical and pulmonary rehabilitation. Increased load-ability is strongly correlated to quality of life. Treatment of COPD patients is a complex process and physical rehabilitation plays a highlighted role in it. Personal adjusted pulmonary rehabilitation (PR) causes increased load-ability, breathing mechanics (BM), chest kinematics (CK). These changes cause an increase in oxygenation of the inner organs, contractile ability of the diaphragm, peripheral circulation and metabolism and a decrease in dynamic hyperinflation.

Apart from detection and treatment of cardiovascular problems, the understanding and management of autonomic nervous system disbalance can also have an impact on understanding and treatment of the pathophysiology of COPD in a large scale.

Measurement of heart rate variability (HRV) can help in understanding connections in diabetic neuropathy, sudden cardiac death and other diseases and the autonomic nervous system imbalance.

The peripheral nervous system has a complex role on the R-R interval of the heart. Regulation of the cardiovascular system is very complex chemoreceptors, pressure receptors, muscle afferents and hormonal impacts play a combined role in it.

The economic and society impact of the chronically sick cohort cannot be underestimated. It is a clear and very unanimous effort that those patients who are able to work should maintain their ability to work as long and as stable as possible.

2. Objectives

The aim of our study was to assess the availability and usability of physiological measuring methods used in the Institute of Exercise Physiology and Sport Medicine at the University of Physical Education in the assessment and pulmonary rehabilitation of COPD patients.

During the clinical research we worked together with the Department of Pulmonary Rehabilitation, National Koranyi Institute for Pulmonology. We also used the results of classic clinical monitoring methods.

We measured reflective attributes of the peripheral vasculature, declined aortic elasticity combined with the heart rate variability results that show peripheral nervous system status. Changes in peripheral muscle oxygen consumption was also measured, the goal was to objectively measure changes caused by the rehabilitation program.

Our goal was to create the most complex assessment of the patients in the rehabilitation program, to see correlation of results regarding cardiovascular, breathing mechanics load-ability, quality of life and changes of these.

We analyzed the results of the resting and functional tests before and after the 3-week rehabilitation program.

3. Methods

3.1. Patients data

Data of patients who attended the rehabilitation program between 2016-2018 were used in this thesis.

The demographic data of the patients can be seen in the 1. table. Hypertonia was the most common comorbidity (89%), 25% had PAH and 75% had aortic stenosis. Patients with overlap syndrome combined with asthma could not be a part of the study. We also left out patients with serious cardiac status and unstable COPD.

N=40	
Age (years)	65,47±7,39év
Male/Female	24:16
BMI (kg/m^2)	27,99±6,98
FEV_1 (ref%)	45,43±20,2
Hypertension	36/40 (90%)
Diabetes	12/40 (30%)
Pulmonary hypertension	10/40 (25%)
Atherosclerosis	30/40 (75%)

Table 1: Demographic data of the patients involved in the study

We used a standardized protocol; all methods were noninvasive and performed 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 ^{o}C).

To eliminate the differences in circadian rhythm and physical activity, we did the measurements in the same time window between 8:00-10:00 AM on every occasion.

The subjects had rested quietly in supine position for 5 minutes before the measurements.

The measurement itself took 6-8 minutes, during which the patients had no task, they had to stay fully relaxed in a supine position.

3.2.1. Cardiovascular system, arterial stiffness

Arteriograph (Tensiomed Ltd., Hungary) was used to collect information on the overall cardiovascular status, endothelial function, central blood pressure and large arterial characteristics of the patients.

The Arteriograph is a patented, invasively validated sociometric tool, which collects information by analyzing the pulse pressure curve registered in the upper arm with a simple upper arm cuff. We used a special stop-flow method, (occlusion of the brachial artery) eliminates the distortion of the pressure curve. The determination of the position and the amplitude of the reflective wave enables the simultaneous and simple determination of pulse wave velocity (PWV), augmentation index (AIX) and diastolic area index (DAI). The traditional blood pressure measurement data (systolic and diastolic blood pressure, heart rate) were also collected.

PWV represents the speed of the pressure wave on the aorta generated by the heart's contraction, which is crucially affected by the elasticity of the aorta. PWVao is a solid, independent, proven predictor of death associated with cardiovascular risks. The threshold limits of PWV are the following: optimal: PWV<7 m/s; normal: 7 m/s ≤ PWV ≤ 9,7 m/s; elevated: 9,7 m/s ≤ PWV ≤ 12 m/s; pathological: 12 ms < PWV.

AIX traces the degree of pulse wave reflection; it basically depicts the state of peripheral circulation. AIX and the peripheral circulation are related with cardiovascular mortality. Physiologically a negative AIX is optimal, a positive AIX means a continuous extra load on the heart. AIX is divided into four quartiles: 1. optimal: AIX < -30%; 2. normal: -30% ≤ AIX ≤ -10%; 3. elevated: -10% ≤ AIX ≤ 10%; 4. pathological 10% < AIX. AIX has prognostic value over classic risk factors, what is the reason we used it in our study.

DAI represents the diastolic proportion of the cardiac cycle. With the use of DAI and DRA (diastolic reflection area) we can get more information about the pressure properties of the left coronary artery, and the work of the atrea, the isovolumetric relaxation, the rapid inflow and the diastasis. In healthy individuals the DAI is between 50 and 60%

3.2.2. Assessment of the peripheral nervous system, heart rate variability

The application of heart rate variability (HRV) to assess risk the sympathetic and parasympathetic (autonomic) nervous systems. During our measurements R-R intervals for autonomic regulation tendencies with millisecond accuracy. To ensure maximal accuracy we used two measurement system. Polar H1 sensors and Polar Precision Performance 2.0 software (Polar Electro, Finland) enabled the visualization of HR and the extraction of a cardiac period (R-R interval). These data were also analyzed with a one lead ECG measurement device iQRS (IQRS Hungary) with a measurement accuracy of 1 kHz.

The most commonly used HRV parameters in ANS evaluation are the frequency-domain, time-domain, and Poincaré plot parameters.

The following time domain parameters were used: minimal pulse (p.min), average pulse (p.avg), maximal pulse (p.max), maximum minimum pulse difference (p.max-p.min).

For HRV analysis in the frequency domain we used spectral analysis provided the low-frequency/high-frequency ratio (LF/HF).

The Poincaré-plot parameters: 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).

3.2.3. Measurement of tissue oxygenation using near infrared spectroscopy (NIRS):

The muscle- and tissue oxygenation using NIRS technology can be measured in a non-invasive way and can provide information about the hemodynamics and changes in oxygenization in the muscle. The NIRS device used in our measurement was the clinically validated Moxy Monitor (Fortiori Design LLC). The measured NIRS parameters were the following: tHB: total hemoglobin index; SmO2 avg: average muscle oxygenization; SmO2 min: minimal muscle oxygenization; SmO2 max: maximal muscle oxygenization.

3.2.4. Functional parameters:

The functional parameters help to characterize COPD patients load-ability, quality of life, breathing and peripheral muscle function, chest kinematics, breathing mechanics. The functional parameters were also measured at the start and at the end of the rehabilitation. The changes help to clarify the success of pulmonology rehabilitation.

Chest wall expansion-CWE
Maximal inspiratory pressure-MIP
FEV_1(ref%)
FVC (ref%)
6-minute walking distance (6MWD)
Grip strength-GS
Breath-holding time-BHT
Modified Medical Research Council dispone questionnaire
COPD Assessment Test (CAT)

Table 2: Functional parameters

3.3. Physical rehabilitation

During the creation of the structure of our program we were very conscious of it being complex and well thought out. We have registered the patients individual needs and comorbidities.

Physical training was a key part of the pulmonary rehabilitation. The 30-minute breathing training in the morning was based on controlled patterns. Patients participating in the study of this thesis had personalized endurance training. This training was mostly done on treadmill, exercise bike and hand ergometer. The resistance was set in a way that allowed dynamic work. Static exercise should be avoided with COPD patients because these cause a raise in chest pressure. We asked for a feedback on a BORG scale at the start and finish of every training session, we also used pulse monitors to observe the intensity. If the performance increased on the exercise bike they could start training on the treadmill.

3.4. Processing of data

We collected data in an excel sheet, every row represented one patient. Mathematical-statistical analysis was based on the data from the excel sheet. Significance level was set at $p<0,05$, using Wilcoxon Signed test. Scatterplot distribution was analyzed. Descriptive statistics was created (average, SD±), normal distribution was tested by Kolgomorov-Smirnov test.

4. Results

4.1. Functional and quality of life parameters.

Significance level was set at $p<0,05$. Pulmonary function (FEV_1, FVC). did not show significant changes, The Load-ability of the patients increased significantly, besides this CWE, BHT, GS, 6MWD, CAT and mMRC data showed significant increase. 6MWD showed even bigger increase in case of patients, who had lower starting result. MIP results also increased significantly, but remained under the physiological level of the healthy population.

Parameter	**BR**	**AR**	**p**
FEV_1 (l)	45,43±20,2	45,06±18,2	n.s.
FVC (l)	75,81±22,71	74,78±17,37	n.s.
mMRC	1,86±0,71	1,63±0,6	<0,01
MIP (cmH_2O)	57,72±22,69	63,63±18,01	<0,001
CWE (cm)	2,84±1,26	4±1,76	<0,001
BHT (sec)	25,77±10,63	29,21±11,60	<0,001
GS (kg)	24,87±11,88	27,03±11,43	<0,001
6MWD (m)	335,32±110,43	398,32±126,21	<0,001
CAT	17±8,49	11,89±7,31	<0,001

Table 3: functional and quality of life parameters before and after rehabilitation program

4.2. Arteriograph results.

Systolic, diastolic blood pressure, resting heart rate showed slight improvement, these data decreased slightly as a result of rehabilitation. The AIX, PWVao, DAI results did not show significant changes but progressive tendency.

Parameter	**BR**	**AR**	**p**
Sys (Hgmm)	133,38 ± 22,15	126,48 ± 20,22	<0,001
Dias (Hgmm)	76,95 ± 14,37	75,4 ±12,7	<0,001
Pulzus (bpm)	76,95 ± 14,37	72,53 ± 13,65	<0,05
AIX (%)	3,54±35,59	2,93±30,79	n.s
PWVao (m/s)	11,74±2,13	11,4±2,73	n.s
DAI (%)	46,32±6,81	47,1±70,2	n.s

Table 4: Arteriograph results before and after treatment

4.3. Heart rate variability results:

Pulmonary rehabilitation had a positive affect on the function of the peripheral nervous system. Minimum, average, maximum pulse decreased as did max-min pulse difference. These changes only reached the level of clinical significance in the case of min-max pulse difference. Stda and stdb results, pNN50 and LF/HF results showed progressive tendencies but changes remained unsignificant.

Parameter	BR	AR	p
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.

Table 5: HRV results

4.4. NIRS parameter results:

As a result of pulmonary rehabilitation neither the tHB nor SmO_2 did not show significant changes. On individual levels all measured SmO_2 level shows progressive trend. The maximal muscle oxygenization levels decreased the minimal muscle oxygenization levels increased, both reached the level of clinical significance. These results clearly show the effect of the rehabilitation program on the normalizing peripheral oxygen consumption.

Parameter	**RE**	**RU**	**p**
tHB (%)	12.76±1.3	12.82±1.4	n.s.
SmO_2 avg (%)	67.47±14.39	65.21±20.39	n.s.
SmO_2 min (%)	42.6±12.60	54.8±14.32	<0.01
SmO_2 max (%)	98±20.51	90.1±14.33	<0.01

Table 6: NIRS results

5. Conclusions

Higher arterial stiffness is associated with COPD patients even without the usual comorbidities, like diabetes mellitus or other cardiovascular diseases. The increasing arterial stiffness can cause other not atherosclerotic diseases like several heart-, renal diseases and other cardiovascular diseases. At the start of the rehabilitation several patients had increased pathological result regarding several parameters. As a result of physical rehabilitation AIX increased in more half of the patients, blood pressure showed similar results. In functional markers the rehabilitation program resulted in significant increase, these results correlated with the arteriography results. The lack of change in PWVao results is either a product of some of the patient’s inability to maintain the appropriate intensity during physical activity or medications targeting lipid metabolism and high blood pressure do not cause changes in PWVao. The 6MWD results positively correlated with the severity of arterial diseases and negatively with PWVao results. Not only smoking habits bit the severity of COPD is the main influencing factor of the efficiency of pulmonary rehabilitation.

As a result of the rehabilitation program chest kinematics, function of breathing muscles and breathing mechanics improved

COPD patients have an extremely decreased R-R interval difference, this might be in connection with the extreme overload on the peripheral nervous system of these patients. The comorbidities superimpose the difficulty of measurement and interpretation of heart rate variability.

One of the fundamental assumptions of our study was to be able to use physiological testing methods used in exercise physiology during the pulmonary rehabilitation of COPD patients. In healthy subject a raise in LF/HF ratio is caused by an increase in autonomous activation, sympatho-vagal balance can change to training in different intensity and length. In recreational bikers with the increased load LF/HF results also increase showing a degrade in parasymphatic tone and an increase in symphatic tone. Our results showed similar cumulative symphatic changes in COPD patients. Unfortunately, we did not find clear correlation between HRV parameters and classical functional parameters. The higher symphatic activation has a clear impact on the COPD patients' autonomous function and load-ability.

SmO_2 levels were elevated, this can be caused by the elevated cardiac output or the elevated hemoglobin levels caused by the rehabilitation program. These results are even more significant on an individual level, out of 40 patients 16 showed significant changes in NIRS results, the SmO_2 levels showing strong hypoxia (40-57% SmO_2) normalized to normoxic levels (74-78% SmO_2) as a result of the rehabilitation. To understand

NIRS results mora validly and profoundly more robust prospective research is needed.

In the future we would like to increase the sample number, using the GOLD classification system. Our sample number did not make it possible in this work.

Aerobic training causes significant improvement in heart rate variability time domain parameters but not int frequency domain parameters. The reason for this might be baroreceptor sensitivity, which is very low in case of COPD patients, causing a diminished autonomous function.

Long term training causes changes in HRV which are good indicators of adaptation. The measurement of HRV can be a good method for planning daily training loads.

Individual training monitoring of COPD patients with the use of GOLD classification of these patients could be a good method for further training individualization. In further studies we would like to use these and the classic functional parameters to better understand connections of HRV and pulmonary rehabilitation in COPD.

6. Bibliography of the candidate's publications

6.1. Publications related to the PhD thesis

Szűcs B, Petrekanits M., Fekete M., Varga J.T. The use of near-infrared spectroscopy for the evaluation of a 4-week rehabilitation program in patients with COPD Physiology International 2021; 13, DOI: 10.1556/2060.2021.00185,
IF: 2,090

Szűcs, B.; Szűcs, C.; Petrekanits, M.; Varga, J.T. Molecular Characteristics and Treatment of Endothelial Dysfunction in Patients with COPD: A Review Article. International Journal of Molecular Science 2019; 20:4329. Special Issue Endothelial Dysfunction: Pathophysiology and Molecular Mechanisms
IF:4,556

Szűcs B, Petrekanits M, Varga J (2018) Effectiveness of a 4-week rehabilitation program on endothelial function, blood vessel elasticity in patients with chronic obstructive pulmonary disease. Journal of Thoracic Disease 2018; 10(12), DOI: 10.21037/jtd.2018.10.104
IF:2,027

Szűcs B, Petrekanits M, Varga J (2018) Effectiveness of a Pulmonary Rehabilitation Program on Changes in Heart Rate Variability and Physical Performance in Chronic Obstructive

Pulmonary Disease. Journal of Pulmonary Respiratory Medicine 2018; 8(5); DOI:10.4172/2161-105X.1000474