UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
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PhD THESIS
ABSTRACT

RESPIRATORY REHABILITATION IN CHRONIC OBSTRUCTIVE BRONCHOPNEUMONIA

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Abstract

COPD is a disease characterised by the **partially reversible obstruction** of the airways, according to the GOLD Guide. The obstruction is usually progressive, with an abnormal inflammatory response to the noxious particles and gases, associated with systemic manifestations. COPD represents a group of irreversible chronic diseases determining dyspnoea by bronchial obstruction (chronic bronchitis or emphysema). The mechanism of obstruction is different for each entity. **Chronic bronchitis:** presence of cough with expectoration, for at least three months a year, for two years. The **emphysema** involves the destruction of the alveoli with dyspnoea predominance and the clinical symptomatology. Currently, COPD is considered to be: the disease with increasing prevalence worldwide, much under-diagnosed and reported, major cause of death and disability. [1],[2]

According to WHO: COPD currently affects 210 million people worldwide. Roughly, 4-6% of the adult populations worldwide have clinically relevant COPD. 3 million deaths are recorded every year, caused by COPD (5% of all deaths). It is estimated that by 2020, it shall become the third cause of mortality in the world and the fifth cause of disability by 2020.[3],[4],[5]

The main cause of COPD is tobacco. **One in seven smokers may suffer from COPD during their lifetime** [6]. Other causes include the deficiency of alpha 1-antitrypsin, prolonged exposure to powders and gases, genetic predisposition, low birth weight and repeated lung infections. WHO assesses that there are currently 1.1 billion smokers worldwide, and this number could reach 1.6 billion by 2025.[4][7] According to the statistics provided by WHO, Romania is on the top of European countries concerning the prevalence of lung diseases.

The lung diseases with increased incidence in Romania are: chronic obstructive pulmonary diseases (COPD), asthma, lung cancer, bronchiectasis, tuberculosis. It is assessed that the number of individuals suffering from COPD in Romania is of 1 million, but of these, only 100000 are diagnosed and treated. Smoking kills approximately 33,000 Romanians/year. In our country, there are over 80,000 hospitalisations a year for the COPD exacerbations, in 2006 representing 1, 76% of the all hospitalisations (DRG). On average, 2.3 exacerbations/case occur in one year, and two thirds of these need hospitalisation. [8]. The COPD patients’ adherence to treatment is deficient in Romania. In this respect, we quote the results of a questionnaire for the COPD patients published in Pneumologia 2006 by Strambu I and collaborators: “Most patients with COPD averagey undergo chronic treatment only 6 months a year, only 25% of them constantly undergoing a (correct) treatment.

According to Global Strategy for the Diagnosis Management and Prevention of COPD (Dec. 2011), it is forecasted that COPD, which was in 1990 the sixth cause of death worldwide, [9],[10] it shall become by 2020 the third cause of death in the world. “Current pharmacotherapy of COPD is used only to decrease the symptoms and/or complications (Evidence A)”. “The exacerbations
and comorbidities are factors influencing the severity of the disease”. “Preventing the exacerbations is a major goal recognised as key element in the COPD pharmacotherapy”.

According to the same guide, reviewed in 2001, COPD assessment is based on: intensity of symptoms, risk of future exacerbations, severity of spirometry values and identification of comorbidities.[11], [12], [13]. The emphasis is on the following aspect: “The exacerbations and comorbidities are factors influencing the severity of the disease”. The GOLD Guide highlights that the VEMS (FEV1) is an insufficient parameter to complexly stage the disease and it also defines the notion of frequent exacerbations like at least two exacerbations a year.

Many authors, including Soler-Cataluna JJ at al warn about the increase of mortality in COPD, proportionally to the frequency of exacerbations. [25]

“The comorbidities are risk factors for the frequent exacerbations, which could influence the mortality and hospitalisations. COPD common comorbidities are: cardiovascular diseases, lung cancer, osteoporosis, depression and anxiety, dysfunctions of the skeletal muscles, metabolic syndrome. [24]

For these reasons, the increased interest for the study of respiratory rehabilitation therapies, as well as for new perspectives in this field is fully justified.

Nowadays, the medical treatment is not enough for the respiratory disability patient. Such patient needs a set of complementary and progressive measures, which would aim at improving the clinical condition and global physical condition.

We planned to lead the research activity into two main directions:

- **innovative attempt to increase the efficiency of complex respiratory rehabilitation therapies to maintain the patient’s best effort capacity and to study some new rehabilitation methods.**
- **preventing the occurrence of exacerbations or improving the symptomatology, to improve the quality of life and maintain the patient in daily activities for a longer period of time.**

Throughout this context of COPD, respiratory rehabilitation is required with all its components: kinesiotherapy program, education, psychological, behavioural and nutritional support.

**The respiratory rehabilitation** is a multidisciplinary program of treating patients with chronic respiratory diseases, which aims at increasing the quality of patient’s life, by increasing the physical activity, reintegration into the society and regaining the autonomy. The rehabilitation programs can be used from the patients with COPD risk to those with severe COPD.

The roots of respiratory rehabilitation therapy originate in distant history. In the writings of ancient peoples: the Assyrians, Egyptians, Hebrews, Greeks and Romans found evidence about using the natural physical agents for therapeutic purposes: **air, water, heat, light.** Among the ancient medicine pioneers, we mention Hippocrates (460 – 377 BC), who showed great concern in deepening the rehabilitation therapies in various pathologies, including the respiratory ones.

The concept of rehabilitation also arrives in our country in 1969, the statistics of the Ministry of Health assessed that 3% of the active labour force lost its ability of work and recovery and reintegration measures were imposed. In 1974, at the fifth session of the Romanian Academy of Medical Sciences, the first guidelines to respiratory rehabilitation were drawn. In recent years,
we witness an explosion of the respiratory rehabilitation services, of various techniques and devices used in the recovery of bronchopathies. [15],[16],[17]. According to the World Health Organisation (WHO), rehabilitation (recovery) represents: “the use of all means to reduce the impact of the conditions generating disabilities and handicap and to allow them to succeed to optimally integrate into the society” [18].

The respiratory rehabilitation has three main components:

Multidisciplinary – Any rehabilitation program includes the experience of several medical disciplines adapted to the patient’s individual needs;

Customised – based on the uniqueness of each patient by establishing the realistic targets.

Psychosocial approach – with physical, psychosocial, emotional and social involvement.

The goals of respiratory rehabilitation are:
- Decrease of the symptomatology
- Encouragement of the participation in physical and social activities
- Quitting active and passive smoking
- Change in the lifestyle by long term beneficial changes
- Prevention of respiratory disability
- Increase of the quality of life

The respiratory rehabilitation requires a multidisciplinary approach, by using the diagnosis and therapy information and techniques within several medical disciplines. It falls under the concept of “integrated care” defined by WHO as a concept which brings together the beginning, distribution, management and organisation of the services related to: diagnosis, treatment, care, rehabilitation and health promotion [19] [21],[22].

Type of the study: the observational, prospective study of witness batch type, performed between 01.01.2010-31.12.2011. The assessment of the clinical and paraclinical factors for each patient before the respiratory rehabilitation program, as well as after completing the respiratory rehabilitation program.

Creation of batches:

Exposed batch: we have included 100 patients into the study, suspected to have COPD within the “Victor Babes” Clinical Hospital of Craiova, of which 87 were spirometrically confirmed. For various reasons, the study batch was eventually formed of spirometrically confirmed 71 patients with COPD within the “Victor Babes” Clinical Hospital of Craiova. The patients were grouped according to their gender, age, background.

During the initial assessment, the following were done: patients’ anamnesis, paraclinical evaluation: the oxygen saturation by means of pulse oximetry; spirometry; St. George questionnaire; CAT questionnaire; LINQ questionnaire; measurement of: body weights (kg), waist (cm), thighs (cm), the BMI was calculated; the BODE index was calculated; blood pressure; heart rate; assessment of dyspnoea was done by the BORG and MRC scale; the six minute test was done; it was established whether the patient was a smoker or ex-smoker; the presence or absence of other comorbidities was established; it was established whether the patient correctly
undergoes the treatment in the ambulatory; it was established whether the patient is vaccinated against pneumococcal and against Hemophilus Influenz; the average number of exacerbations for last year was established; the patient’s status was established (pensioner or active).

The patients within the study group were then subject to a complex program of pulmonary rehabilitation consisting of 16 sessions of physical exercises and 16 sessions of education, 2 sessions a week, for 8 weeks. Each session of physical exercises was of approximately 40 minutes and the session of education of approximately 30 minutes. Each patient has their own schedule of exercises, customised according to the COPD study and initial assessment.

After the confirmation of the diagnosis by spirometry, the group of patients in the study, formed of 71 patients – Type I COPD 17 cases, type II COPD 17 cases, type III COPD 23 cases, and 14 type IV COPD 14 cases. Of these, 61 cases suffered from chronic bronchitis and 10 cases from emphysema.

The witness group consisted of 65 patients.

The research activity within this PhD thesis proved that the respiratory rehabilitation programs for the patients with a chronic obstructive pulmonary disease (COPD) can bring various benefits to patients. In particular, it can increase the individual’s quality of life and can fit them with appropriate knowledge to control their dyspnoea and increase their tolerance to practice.

By prospectively studying the demographic data, the following results were obtained:

**SEX**

![Figure 1 - The structure of the group by gender](image)

In the studied group, men predominated with a percentage of 63.4%. (p=0.0327).

**Area of origin**

![Figure 2 - The structure of the group by area of origin](image)
Of the total of 71 cases included into the studied group, 25 cases (35.2%) were from the rural areas. (p=0.0176).

![Activity environment](image)

*Figure 3 - The structure of the group by the activity environment*

By analysing the structure of the group in terms of the work environment, one may notice a significant preponderance of pensioners, in a percentage of 70.4% (50 cases), (p=0.0009). The average age of the cases in the group we studied was of 63.36 ± 10.2 years (IC 95% 60.9516 - 65.7808; Limits 40 -92 years).

![Age ranges](image)

*Figure 4 - The structure by age ranges*

Figure 4 shows the structure of the group by age ranges: the maximum incidence of COPD was recorded at the age range 60-69 in a percentage of 38% (27 cases). The age range of 40-49 is represented in percentage of 8.5% (6 cases) – the most weakly represented one, the age range of 50-59 in a percentage of 28.2% (20 cases), and 25.4% of the patients were over 70 (p=0.0049). We observe that the age group of 40-49 is the most weakly represented.

In developing countries, as in Romania, smoking (the main risk factor of COPD) becomes increasingly more common, especially in the urban environment, particularly in men. From this point of view, the analysis of the studied group has emphasised the connection of all patients with the habit of smoking, 44 smokers (62%) and 27 ex-smokers (38%) who have quit smoking for a variable period of time (between 2 and 8 years) when the study was done. The prevalence of smokers certified the direct involvement of the most important risk factor in the onset of COPD: tobacco (p=0.0576).
In the group of patients we studied, those with the COPD bronchitis type were predominant, in a percentage of 85.9% (61 cases). (p=0.0001). The male gender is present in a high percentage both in the bronchitis type by 62.3% (38 cases of 61) and in the emphysema one of COPD by 70% (7 cases of 10). (p=0.9087).

The above graph highlights the presence of tobacco consumption in 60.7% (37 cases) with bronchitis component. Taking into account the low number of cases with pulmonary emphysema (10 cases) compared to the bronchitis ones (61 cases), an appropriate comparison cannot be done between the two types of COPD, from this point of view. The predominance of the tobacco consumers was certainly observed in both the bronchitis component and the emphysema one. (p=0.8315).
1.2.2 Staging the COPD

Figure 10. – Staging the COPD according to GOLD 2011

Analysing the group according to the COPD stage and gender highlights the prevalence of men regardless of stage. (p=0.0430).

Figure 11 – Percentage distribution of cases according to the stage of the COPD and gender

By analysing the structure of the group according to the COPD stage and area of origin, we may observe the predominance of the rural environment in all stages. (p=0.7969).
Figure 13 – Distribution of cases according to the stage of COPD and smokers’ status.

A higher frequency of smoking at the initial stages II and III may be observed.

**Assessing the adherence to treatment within the studied group**

Figure 14 – Distribution of cases according to the therapeutic adherence and stage of COPD

The absence of adherence to treatment was associated with a higher frequency of exacerbations. The therapeutically incompliant cases showed a risk to be affected by more than 2 exacerbations a year, by 1.69 times higher compared to those therapeutically compliant. (RR=1.69; IC95% 1.2 - 2.35; P=0.002).

**Assessing the dyspnoea by means of the dyspnoea scales BORG**

Figure no. 15. – The average value of the BORG scale was of 7.06±1.34 (IC95% 6.74 - 7.37; Limits 4-10).
The average values of the BORG dyspnoea scale for the patients of the study were between 6 and 8. Grading the dyspnoea by means of the BORG scale correlates with the variation of the inspiratory ability for COPD patients, thus suggesting the role of hyperinflation in causing the dyspnoea.

![Figure 16 – Average value of the Borg Scale for women and men](image)

No significant differences of the BORG scale were identified for women and men, or according to the area of origin, or for smokers and non-smokers (p=0.79).

**The six-minute test before and after the respiratory rehabilitation**

![Figure 17 – Average values of the six-minute test before and after the rehabilitation](image)

According to the clinical studies, an improvement of the six minute test by 54m is clinically significant when patients do not show other comorbidities. In the post-rehabilitation studied group, in the presence of comorbidities, an improvement of the six-minute test of 8.29% was recorded. The initial value of the test-281.24±82.17 m, post-rehabilitation-259.7±78.163 m, the difference between the two averages being statistically valid (p=0.0379).
The drop of the values of the BORG scale after the rehabilitation sessions was of 30.47%. The initial value - 7.056±1.34, the final value 5.41±1.1, the difference being statistically significant (p<0.001).

As it may be observed in the figure, the decreasing trend of the number of cases shows a tendency of decrease in the dyspnoea severity after rehabilitation.

An impressive decrease, of more than 12 times, was observed 4 MRC (25 cases, 35.2%). The post-rehabilitation ones were no longer in the 4th degree of MRC, except for 2 cases (2.8%). The risk for a patient to be in the class 4 MRC of pre-rehabilitation was 4.17 times higher compared to the possibility of post-rehabilitation classification (RR=4.167; 2.3874 - 7.2721; p<0.001)

The average value of the initial CAT, before the rehabilitation, was of 23.85±4.44, the value being 12.86% higher than the average value of CAT recorded after the rehabilitation, of 21.13±4.17, the difference between the two averages being highly significant (IC 95% -4.146 to -1.294; p=0.0002).
The Saint George questionnaire was one of the tests used to assess the health state for the COPD patients. Measuring the average score after the rehabilitation showed a value of 72.35±11.9, post-rehabilitation - 62.84±9.61. The positive effects of the rehabilitation were validated by the decrease of the Saint George score by almost 15% compared to the initial value (14.99%; IC95% 5.94 – 12.82), a difference validated with a very high statistical significance (p<0.001).

The Initial and Final LINQ

The improvement of the post-rehabilitation doctor-patient communication was observed by the decrease of the score of LINQ upon the final assessment; from the initial 10.69 to 6.72 final average value.
The BODE index before and after the respiratory rehabilitation

Figure 24 – Percentage distribution of the classification into the classes of BODE index before and after the rehabilitation

The BODE index of respiratory pre-rehabilitation is predominant in class 2 (44 cases – 61.97%). Class 1 is predominant for women in a percentage of 65.4%, and for men in a percentage of 60.0%. The respiratory rehabilitation proved to be an important way of treatment, by increasing the patient’s tolerance to effort and independence degree. The kinesiotherapy program, performed in groups, was designed to optimise the physical, social performance and functional independence.

CONCLUSIONS

1. Preparing an optimal and customised respiratory rehabilitation program is done only after completing a well established protocol. It includes clear information provided by actually and correctly applying all clinical and paraclinical anamnestic methods used in assessing the patient’s respiratory pre-rehabilitation.

2. Studying the elements used in the assessment before and after the respiratory rehabilitation of the COPD patient highlights the inestimable value of the gathered information, which led to preparing a customised rehabilitation program, with direct impact in increasing the patient’s quality of life.

3. Because COPD is a slowly progressing and lately diagnosed disease, due to the specific absence of the symptomatology, the early identification of the cases and guidance to a respiratory rehabilitation program are required, accompanied by efficient methods to combat smoking.

4. The COPD patient’s initial assessment protocol, in order to classify them into a respiratory rehabilitation program is based on: anamnestic data, demographic data, body weight index, BORG and MRC dyspnoea scales, the six-minute test, CAT, St GEORGE and LINQ questionnaires, as well as the BODE index.

5. The relevant risk factors for COPD are: male gender, the age range between 50-70, urban environment and smoking.
6. The predominance of pensioners and advanced stages of the disease, III and IV, highlight a late diagnosis of the disease. Patients have 3 and more than 3 exacerbations a year without a correct administration of the treatment, which requires an implementation of the respiratory rehabilitation programs, with physical exercises and education sessions, both preventively and along the medical treatment.

7. The increase of the number of smokers and overweight and obese patients implies that the bronchitis patient’s rehabilitation work would begin by avoiding all external factors that may trigger, maintain or negatively influence the disease, namely: allergens, smoking, polluting environment, viroes, nutrition and lifestyle, as well as cessation of smoking by specialised programs or encouraging them to keep their final decision to quit smoking.

8. Spirometry represents "the gold standard" that proves the limitation of the air flow, confirms the diagnosis and monitors the respiratory function, emphasising significant drops of the respiratory post-rehabilitation obstructive syndrome.

9. Education is an important component in each respiratory rehabilitation program, which is necessary, but insufficient by itself. It proved its efficiency in combination with an appropriate program of physical exercises for the individuals with chronic obstructive pulmonary disorders (COPD), which together significantly reduce the hospitalisation rate, number of exacerbations, they increase the adherence to treatment, lower dyspnoea and improve the quality of life.

10. Physical exercises increase the effort capacity, the oxygen intake, improve the muscle coordination by increasing the muscle mass and losing the fat tissue and the obstructive syndrome is improved, by increasing the survival.

11. The respiratory rehabilitation programs lead to an improvement of the BMI by decreasing the body fat.

12. The BORG dyspnoea scale was one of the first tools which showed the improvement of effort dyspnoea after a respiratory rehabilitation program. A stronger correlation was noticed when comparing between the six-minute test and BORG scale classes measured after the rehabilitation (by a significant drop of the frequency of severe dyspnoea cases by almost 5 times after the respiratory rehabilitation).

13. The MRC dyspnoea scale is considered to be a tool able to classify COPD patients according to their respiratory disability degree and to assess the severity degree of the disease. An impressive decrease, of more than 12 times, was observed at those cases which were classified in class 4 MRC when included into the study, and at the final assessment, they passed into lower
degrees. The risk for a patient to be in the degree 4 of the MRC scale of pre-rehabilitation was 4.17 times higher compared to the possibility of classification into the same degree after the rehabilitation.

14. The six-minute test is a simple test, widely applicable in respiratory rehabilitation. In the presence of comorbidities, after the rehabilitation, an improvement of the six-minute test of 8.29% was recorded.

15. The CAT questionnaire is a simple test to quantify the COPD impact on the patient and communication between doctor and patient; it is a complex yet sensitive questionnaire, easy to perform, in order to assess the impact of the disease on the lung state. The average value of the initial CAT was by 12.86% higher than the average CAT value registered after the rehabilitation. Women register an improvement of the CAT questionnaire, that is slightly higher than that of men. The respiratory rehabilitation program has a favourable impact on the CAT score, regardless of the patient’s weight state.

16. The St George questionnaire measures the health state in COPD patients. The positive effects of the rehabilitation were validated by the decrease of the Saint George score by almost 15% compared to the initial value, a difference validated with a very high statistical significance (p<0.001). For the cases with ages between 60-69, a significant improvement of the health state after the rehabilitation is noticed, according to the St. George questionnaire, by lowering its score by 18.67%.

17. The LINQ questionnaire is an assessment method from the patient’s perspective. The LINQ questionnaire is able to measure the informational change received and understood by the patient before and after the respiratory rehabilitation program, as well as the ability to exercise and quality of life. The improvement of the doctor-patient communication after the rehabilitation was observed by the decrease in the score of LINQ on the final assessment; The patients with an increased need to be informed were almost twice as many on the initial assessment of knowledge about the disease and doctor-patient communication.

18. The number of cases at the BODE index after the respiratory rehabilitation is predominant in class 2, compared to the one before the rehabilitation, where class 3 was predominant, by a percentage of 46.48%. Class 1 respiratory post-rehabilitation is predominant in women. It is thus associated with the increase of the quality of life and survival.

19. The benefit of respiratory rehabilitation consisted in an improvement of the respiratory performances measured by means of the six-minute test, by 10%. This leads to the improvement of dyspnoea, by reducing the values on the BORG scale, both for normal weight, overweight and obese individuals, compared to the witness group.
20. By appreciating the benefits of the COPD rehabilitation complex therapy, we consider it appropriate to establish *the respiratory rehabilitation centres* for those patients with respiratory dysfunctions, the equipment of which is not expensive. The collaboration between pulmonologist, physical and rehabilitation medicine doctor, kynetotherapist, nurses and nutritionists shall lead to decreasing the symptomatology, reducing the number of exacerbations and implicitly to increasing the survival of COPD patients in Romania.
BIBLIOGRAPHY


3. Wilson Pk, William Ma, Humphrey R, Hodkin Je, Lui K et al – Contemporary cardiovascular and pulmonary rehabilitation AACVPR-the first 20 years, American Association of Cardiovascular and Pulmonary Rehabilitation, 2005, Tampa, Faircount;

4. WORLD HEALTH ORGANIZATION (WHO);

5. Cartea Albă a Specialităţii de Medicină Fizică şi de Reabilitare în Europa – Uniunea Europeană a Medicilor Specialişti (UEMS) - Secţiunea de Medicină Fizică şi de Reabilitare, Ed. Universitară „Carol Davila“, Bucureşti, 2006;


8. Rupert Jones – Optimal respiratory health, General Practice airways group, august 2008;

9. AMERICAN THORACIC SOCIETY, EUROPEAN RESPIRATORY SOCIETY ATS / ERS STAMENT ON PULMONARY REHABILITATION.AM J RESPIR CRIT CARE MED 2006, 1390-1413;


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Duță – FUMATUL ȘI SĂNĂTATEA PUBLICĂ ÎN ROMÂNIA CUNOȘTINȚE, ATITUDINI ȘI
PRACTICI LEGATE DE CONSUMUL DE PRODUSE DIN TUTUN ÎN RĂNDUL POPULAȚIEI
GENERALE DIN ROMÂNIA – Centrul pentru Politici și servicii de Sănătate, 2004, introducere;

raport publicat de către Organizația Mondială a Sănătății, Institute for Global Tobacco Control,
Johns Hopkins School of Public Health, 2001;

15. Ștefani Constantin – Estimarea prevalenței consumului de tutun în unitățile sanitare din
Ministerul Apărării Naționale - Elaborarea unui program de prevenire și abandon a fumatului în
mediul militar – teza doctorat 2011;
Celli Br, Cote Cg, Marin Jm et al – The body mass index, airflow obstruction, dyspnea and
exercise capacity index in chronic obstructive pulmonary disease“, N Engl J Med 350 1005-
1012, 2004;

16. Cote Cg, Celli Br – Pulmonary rehabilitation and the BODE Index in COPD, Eur Respir J
26: 630-636, 2005;

17. Nishimura K, Izumi T, Tsukino M et al – Dyspnea is a better predictor of 5 year survival
than airway obstruction in patients with COPD, Chest 121 : 1434-1440, 2002;

18. Pinto-Plata Vm, Cote C, Cabral H et al – The six minute walk distance: change over time
and value as a predictor of survival in severe COPD, Eur Respir J 23 :28-33, 2004;

surgery correlates with survival, Chest 129 : 873-878, 2006;

21. Stolk J Ng Wh, Bakker Me, Reiber Jhc, Rabe Kf, Putter H Stoel Be – CORRELATION BETWEEN ANNUAL CHANGE IN HEALTH STATUS AND COMPUTERS TOMOGRAPHY DERIVED LUNG DENSITY IN SUBJECTS WITH ALPHA-ANTITRYSIN DEFICIENCY, TORAX 2003 , 58: 1027-30;


