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PhD THESIS

**RESPIRATORY REHABILITATION IN PATIENTS
WITH SEVERE COPD IN THE CONTEXT OF THE
COVID-19 PANDEMIC**

A B S T R A C T

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a serious and progressive respiratory disease, caused in most cases by the consumption of tobacco, especially in the form of cigarettes.

Smoking is actually chronic intoxication with about 4000 harmful substances, including nicotine, tar, carbon monoxide and benzopyrene, all of which are present in tobacco leaves. Thus, there is clear evidence that emphasizes the fact that smoking is a significant risk factor for 24 diseases, including some very serious ones, such as malignant diseases with different locations, cardiovascular diseases and chronic respiratory diseases.

Despite the measures to discourage tobacco consumption, the number of smokers and implicitly those suffering from COPD is constantly increasing. For this reason, I believe that the prevention and management of COPD are current topics, useful for the general population but especially for medical professionals and essential to improve the health of the population and increase the quality of life of COPD patients.

COPD management consists of two main strategies: controlling symptoms and reducing future risk, aiming to prevent disease progression and decrease mortality. Thus, by reducing the symptoms, the patient's quality of life increases, and by reducing the risk, the rate of progression of the disease, the frequency and severity of exacerbations decreases, and implicitly the reduction of mortality. Therapeutic intervention for patients diagnosed with COPD includes both pharmacological and non-pharmacological means, both of which are essential for a net superior outcome of therapy than considering them separately.

The means of non-pharmacological treatment include a series of general measures, such as smoking cessation, regular physical activity adapted to the patient's tolerability, appropriate nutrition, pulmonary rehabilitation, vaccination, surgical treatment, oxygen therapy and ventilator support.

Pharmacological treatment of patients with COPD is generally based on long-acting bronchodilators, with additional combinations determined according to the risk group in which the patient is, while assessing the presence of complications and comorbidities. Possible additional therapies for bronchodilators are inhaled corticosteroids (always used in combination with a longacting bronchodilator),

theophylline, mucolytics, antioxidants, and in some selected cases, prophylactic antibiotics. Although oral medication is associated with a higher adherence rate, inhaled therapy is preferred in the treatment of COPD due to its topical action and reduced systemic side effects.

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea syndrome (OSAS) are two pathologies frequently encountered in current practice, especially among pneumophthologists, which have relatively similar pathophysiological and molecular consequences. These consequences are: hypoxia and inflammation that contribute to the appearance of associated conditions such as cardiovascular and pulmonary hypertension. Some epidemiological studies indicate that 10% of the population over the age of 40 have COPD, and a large part of patients remain undiagnosed and even untreated because they either do not see a specialist or reach advanced stages.

Another finding of the studies was that mortality from COPD is higher at night, especially between 00 and 08 a.m., and a high prevalence is also found in patients with obese overlap syndrome. Looking at the current data, the prevalence of SASO is 14% among men and only 5% among women.

Frequent desaturations during the night in those with apnea are much more frequent than those with COPD, and hypoxemia, hypercapnia and pulmonary hypertension are much more pronounced. The role of diurnal hypoxemia due to bronchial obstruction is paramount in the determination of permanent hypertension and is also correlated with the severity of obesity.

The medical literature also mentions more severe alterations in cardiac function in those with overlap than those with COPD due to nocturnal hypoxemia. The paraclinical diagnosis is established following paraclinical investigations that correlate with the signs and symptoms presented or not by the patient.

Pulmonary rehabilitation is an important branch of medical rehabilitation that is increasingly visible these days given the impact of Covid-19 on lung function and all the changes we left with the patient's negative. The purpose of rehabilitation is to improve and restore the functional capacity and quality of life of people with physical disabilities/disabling conditions and/or handicap, the objective being the restoration of optimal function in the context of the presence of various physical, tissue and/or functional injuries (Order of the Minister of Public Health no. 1509/2008, with subsequent amendments and additions). Pulmonary rehabilitation is a

comprehensive intervention based on a detailed patient assessment followed by tailored therapies, including but not limited to exercise, education and lifestyle changes, designed to improve the physical and mental status of people with respiratory disease comorbidities and to promote long-term adherence to health-enhancing behavior.

The basic role of respiratory rehabilitation is to reduce the symptoms, to improve the functional status, to reintroduce the patient to society and of course to try to reduce the costs for medical assistance, so every program must have three characteristics in mind:

- The presence of the multidisciplinary team
- Program focused on the individual to be made according to his needs
- Corroboration of the elements of physical, mental, emotional and social disability

Pulmonary rehabilitation indications

But every respiratory rehabilitation program must begin with an objective assessment of respiratory function – oximetry, spirometry and establishing the degree of respiratory dysfunction by evaluating exercise tolerance with the help of specific tests:

- the 6-minute walk test
- incremental cardiorespiratory exercise test
- the sit to stand test (STST)
- chair test performed in 60 seconds

The main objective proposed in respiratory rehabilitation is exercise retraining, achieved through physical exercise. This is achieved through ventilatory muscle training and skeletal muscle training.

Standardized scales are applied and quality of life questionnaires are used at the beginning of therapy but also at the end of therapy to record progress (BORG, Visual Analogue Scale, CAT, STOP BANG, Chronic Respiratory Disease Questionnaire (CRQ) and Saint George's Respiratory Questionnaire-SGRQ). The applied questionnaires are standard and subjective, they are interpreted by the specialist doctor and indicate the degree of impairment of mental status and daily

activities. The 6-minute walk test is the cheapest screening method, it measures the distance traveled by the patient on a linear route in 6 minutes.

Blood pressure, peripheral oxygen saturation, body mass index and distance covered are recorded. Using standard formulas, the predicted distance is calculated for the patient's age, gender and height.

The goal of pulmonary rehabilitation is to relieve symptoms, modify long-term health behavior and also improve exercise capacity, participation in daily activities, autonomy and increase quality of life.

Contraindications of pulmonary rehabilitation

- non-adherence to the rehabilitation program
- severe neurological diseases that affect compliance or memory
- severe pulmonary, cardiac, renal or hepatic failure, metastases
- the acute phase of lung diseases
- recent cerebrovascular accidents
- advanced arthritis with the impossibility of mobilizing the joints

Another concept that I insisted on when starting my doctoral thesis was cognition, which is a collective term for high-order neural processes that are the basis of information manipulation. In practice, cognitive abilities are mainly inferred from behavior, which itself is determined by a wide variety of neurological, psychological, and emotional factors. The relationships between the many processes involved in an everyday cognitive task are complex, but cognitive ability is usually divided into discrete domains, although it is rarely possible to study individual domains in isolation.

A key proposed mechanism for cognitive dysfunction in COPD is hypoxia-mediated neuronal damage, but it has also been suggested that oxygen-dependent enzymes that are important in the synthesis of neurotransmitters such as acetylcholine may be affected. A magnetic resonance spectroscopy study in patients with severe non-hypoxic COPD showed that cerebral metabolism was significantly altered and that the pattern of disturbance was different from that observed in heart failure and diabetes.

Inflammation may play an important role, as there is evidence that C-reactive protein may be associated with cognitive decline, either through a direct neurotoxic effect or through an effect on cerebral atherosclerosis. Other inflammatory mediators

have also been linked to cognitive dysfunction, including interleukin (IL)-6, IL-1b, tumor necrosis factor- α , and α 1-antichymotrypsin. However, these studies suggest an association rather than a causal link.

Age and education are demographic variables believed to be strongly related to neuropsychological performance in all populations. This shows that although many factors are shared by both groups, many cluster more commonly in COPD. The association between lung function and cognitive function has been assessed in a number of studies in large healthy populations, particularly in elderly groups, but correlations have often been weak and confounding factors have not always been adjusted. It has been suggested that lung function is actually a marker of physical activity, which itself may explain any association with cognitive status. Studies investigating the relationship between lung function and cognition in COPD populations have shown even less consistent results, suggesting that lung function is not a reliable predictor of cognitive function in this group.

Although most studies evaluated hypoxemic patients, deficits were also found in nonhypoxemic patients. It is difficult to draw clear conclusions by comparing these studies because of differences in disease severity and testing methodologies used. The definition of hypoxemic COPD also varied between studies. However, attention deficits and problems with executive and motor functions of memory appear to be common. Perceptual and language difficulties appear to be less frequently reported.

The correlation between cognitive function and arterial oxygen tension (PaO₂) is weak ($r \sim 0.2$) and oxygen saturation contributed only 5% of the predicted variance in clinician-rated global cognitive performance. These observations from the NOTT and Intermittent Positive Pressure Breathing (IPPB) studies contrast with those from a previous small study in which PaO₂ correlated with attention, motor function and processing speed ($r^2 = 0.63$) [25]. Another study reported that memory was correlated with PaO₂, but language and perception were not. Nocturnal PaO₂ has been shown to correlate with attention, but it is unclear whether coexisting obstructive sleep apnea (OSA) has been excluded.

Thus, the exact relationship between cognitive impairment and hypoxemia remains unclear. While a number of studies have shown a clear association between hypoxemia and poor cognitive performance, these have been inconsistent and correlations have been weak. There are also inconsistencies as to whether patients with early disease and mild hypoxemia have significant cognitive impairment.

Current evidence would suggest that hypoxemia alone is not sufficient to fully explain the cognitive deficits seen in COPD.

Studies have reported a variable correlation between blood carbon dioxide (PaCO_2) and cognitive function. In patients with hypercapnic respiratory failure, PaCO_2 correlated with memory, complex attention, and speed of information processing, but not with language, motor function, and simple attention. Heat et al. suggested that PaCO_2 was correlated with verbal memory and achievement, and in a study of patients awaiting lung transplantation, lower PaCO_2 was significantly correlated with better ratings of executive function, attention, and verbal memory. In contrast, there was no correlation between cognitive function and hypercapnia in the NOTT and IPPB studies or in the studies by Grant et al. and Fix et al. In general, the relationship between PaCO_2 and cognitive impairment is even less clear than that for PaO_2 .

A number of studies have shown that physical activity is associated with both maintaining and improving cognitive function in COPD. A case-control study of pulmonary rehabilitation showed that while visual attention, verbal memory, and visuospatial functions were impaired at baseline, they improved after 3 weeks of treatment. However, practice effects were not addressed and this may also have been due to regression to the mean effect. In addition, the control group had lower exercise capacity, higher oxygen consumption, and took COPD medication less regularly than the treatment group. Verbal fluency improved significantly with exercise in a randomized control trial of non-hypoxemic COPD patients comparing exercise training plus education versus education alone. Another study showed an improvement in verbal fluency after just 20 minutes of exercise. In a group of patients with mild COPD, 6-minute walking distance and aerobic fitness predicted 83% of improvement in "fluid intelligence" (reasoning and problem solving) among COPD patients undergoing exercise programs short and long term. Overall, there appears to be a link between exercise and cognitive function.

In the general population, hypertension was associated with faster decline in logical reasoning and problem solving, and diabetes was associated with accelerated decline in executive function tasks. In addition, the combined vascular risk factors explained a significant proportion of the variance in information processing ability and speed, as well as general cognitive status. Given that more than 50% of hospitalized patients with COPD have coexisting vascular disease, this

is likely to influence cognitive function. However, the pattern of cognitive dysfunction in COPD was found to be different from that found in multi-infarct dementia, and memory was found to be worse in subjects with chronic cerebrovascular disease than in those with COPD. Therefore, it is unlikely that cognitive dysfunction in COPD is due to vascular comorbidity alone.

In addition to the increased risk of cerebral atherosclerosis, certain particles in cigarette smoke are thought to have a direct neurotoxic effect, with heavy metal constituents of smoke linked to an increased risk of Alzheimer's disease. Smoking may also influence cognitive function by exacerbating cerebral hypoxia due to chronic elevation of carbon monoxide causing a leftward shift of the oxyhemoglobin dissociation curve. A multicenter European cohort showed that annual decline in MMSE was associated with smoking status, after adjustment for baseline MMSE, education, and vascular events. Smoking is a risk factor for preclinical changes detected on brain computed tomography, and longitudinal studies have found associations with midlife smoking and cognitive dysfunction in men over a 20-year period. Cognitive deficits associated with smoking include reduced processing speed, verbal memory, and MMSE. However, while smoking appears to be an independent factor in cognitive dysfunction, studies have found associations between impaired lung function and cognition that are independent of current and lifetime smoking status.

Sleep is thought to be important in memory, learning, attention and tracking. COPD patients show excessive daytime sleepiness and over 50% report long sleep latency. OSA occurs in 20% of individuals with COPD, and the conditions have a similar comorbidity profile. Moderate to severe OSA may be associated with impaired cognitive performance, primarily alertness and executive function, with a lesser effect on intellectual and verbal abilities. However, the increase in cognitive deficit appears to be less than the increase in sleepiness. While the degree of cognitive impairment has been reported to be similar in COPD and OSA, with common deficits in complex reasoning, learning and memory, cognitive domains thought to be sleep-dependent, such as attention, were more impaired in OSA, while those thought to be affected by hypoxemia, such as motor skills, were more degraded in COPD. This observation is supported by another small study that showed that patients with severe OSA had a distinctive cognitive profile, that is, a

group-specific pattern of cognitive dysfunction compared with COPD, Alzheimer's disease, and multi-infarct dementia.

The prevalence of depression in COPD patients ranges from 10% to 79%. Depressive symptoms are present in older people with cognitive impairment or dementia, but although it is associated with impairment in executive function, memory and processing speed, it may account for only 1–2% of the cognitive variance in COPD. In the NOTT trial, the modest improvement in cognitive function was not associated with improvement in emotional or depressive symptoms.

Complete neuropsychological testing requires time and specialized training to perform and interpret. A simple and brief clinical assessment would be useful to screen individuals who may need more comprehensive neuropsychological testing. Recent work suggests that the combination of an MMSE score of 24 and dependence on at least one IADL may fulfill this role.

Further work is needed to determine whether all patients with COPD require screening or whether it should be limited to those who report cognitive difficulties or who have risk factors for cognitive impairment, such as hypoxemia, airflow obstruction, and vascular comorbidities.

Sleep and cognitive function appear to be correlated in late life; however, the exact nature of this relationship has yet to be elucidated. Future investigations should continue to evaluate the range of sleep-cognition relationships. Important questions remain regarding: the role of normal sleep changes in normal cognitive aging; the role of pathological changes in sleep on the development of dementias and the usefulness of treating sleep disorders to improve cognitive functioning, protect unwanted cognitive decline and slow down the course of neurodegenerative diseases.

An intriguing prospect for future studies is to examine the additive impact of treating sleep disturbances in combination with focused cognitive interventions. Perhaps the combination of interventions that focus on different pathways of change may have a synergistic effect and lead to more pronounced cognitive improvements. Increasing our knowledge of the ways in which sleep may affect cognitive functioning in COPD patients in late life could have far-reaching benefits.

The COVID-19 pandemic has led to dramatic change in our community and the loss of many lives. Although pulmonary rehabilitation has traditionally been centered in the hospital or clinic, the pandemic has caused discussions and debates

about the merits of pulmonary rehabilitation at home, as well as telerehabilitation. There is now a pressing need for high-quality studies of these health care modalities to enable successful implementation of rehabilitation, both supervised and unsupervised at home and via teleconferencing technologies.

For the unification of pulmonary telerehabilitation, a joint effort of the scientific and professional society is needed for international organizations. This effort should be developed in collaboration with the most important international societies in the field of pulmonology, the European Respiratory Society (ERS) and the American Thoracic Society (ATS).

Priority will be given to the protection of personal rights, the regulation of access to health data and the prevention of manipulation, as well as the security of the transmission, conversion and storage of health data, i.e. cyber security. The conclusion of our study is that the use of digital devices can force the respiratory muscles of patients with chronic respiratory diseases. Thanks to the use of algorithms and real-time data analysis, it is possible to detect symptoms in the early phase of exacerbation and by changing the therapy in time, we can prevent deterioration. Given the accuracy, predictability, and customization that characterize digital remote monitoring devices, it is imperative that current and future technologies be incorporated into the treatment of patients with chronic respiratory disease.

Respiratory muscle training supplemented by a mobile phone app can improve respiratory muscle strength and diaphragmatic mobility. Furthermore, ultrasound assessment could be used as an additional tool to quantify the clinical effects of pulmonary rehabilitation in COPD patients.

Although it is a disease of the lungs, the extrapulmonary features of COPD are increasingly recognized as important contributors to morbidity and mortality. Skeletal muscle dysfunction is of particular interest because it directly influences exercise performance, is associated with poor health, and is an independent predictor of healthcare utilization and mortality. In addition, respiratory muscle function plays a key role in the pathogenesis of dyspnea and peak inspiratory pressure is an independent predictor of survival in severe disease.

The most commonly studied skeletal muscles are the quadriceps and the diaphragm. Crosssectional studies, with careful matching of patients to controls, have revealed the complexity of muscle dysfunction in COPD.

Although the ability of the diaphragm to generate transdiaphragmatic pressure is reduced in COPD, this is largely the product of hyperinflation, which places the muscle at a mechanical disadvantage. Indeed, when corrected for lung volume, diaphragm contractile strength in COPD is not reduced compared to healthy individuals and may even be enhanced in some cases.

The maintenance of strength in this muscle is probably due to persistent involuntary training secondary to the increased work of breathing. As a result, the diaphragm adapts by remodelling its fiber type profile toward a fatigue-resistant phenotype with a relative increase in the proportion of type I fibers. Relative to healthy individuals, samples reveal 20%–50% increases in total fiber proportion of type I, correlated with reductions of type IIX fibers.

There is little information related to changes in diaphragm fibers, and there is debate as to whether their cross-sectional area or force-generating capacity changes. Some studies report no change in fiber size, while others note selective atrophy of type I fibers. Similarly, lower isometric force-generating capacity (normalized for cross-sectional area) has been reported among the fibers of the patients tested in vitro, while others have found no difference between patient and control fibers. More established is the intrinsic resistance to fatigue that occurs through the increased concentration of mitochondria, capillary density and the ability to generate adenosine-5'-triphosphate through oxidative pathways, marked by an increase in succinate dehydrogenase activity.

In patients with COPD, diaphragmatic fatigue is not observed with maximal voluntary ventilation or exhaustive treadmill exercise. Diaphragm fibers from patients are also more efficient than controls, with a lower cost of adenosine-5'-triphosphate to maintain a similar level of isometric force. The reduced energy cost may be explained by the number of cross-bridge formations in each fiber, with diaphragm muscle fibers in COPD patients having fewer active cross-bridges and each exerting a greater force than in the muscle of healthy individuals.

Where other accessory respiratory muscles have been studied, they appear to adapt in the same way in response to increased work of breathing. The fiber type shift from II to I seen in the diaphragm is also seen in the parasternal intercostal muscles of patients with severe disease.

A contrasting change in fiber type expression was observed in the external intercostals muscles, which may reflect their postural role in this group. Functionally,

pectoralis major and latissimus dorsi strength are preserved relative to the quadriceps, as is abdominal strength, probably due to additional expiratory muscle activity in COPD patients.

The changes seen in the respiratory muscles are in stark contrast to those of the quadriceps muscles in COPD. While the quadriceps muscle is characterized by reduced mass and loss of fatigue-resistant type I fibers and oxidative capacity, which affects strength and endurance, the diaphragm remodels to a fatigue-resistant profile with a relative increase in type I fibers and the resulting increase in oxidative capacity, a pattern mirrored in other accessory muscles of respiration. These observations support that muscle disuse is a major etiologic factor for the differential adaptation of peripheral and respiratory muscles in COPD.