

The Impact of Upper Limb Training with Breathing Maneuver in Lung Function, Functional Capacity, Dyspnea Scale, and Quality of Life in Patient with Stable Chronic Obstructive of Lung Disease

Amira Permatasari Tarigan^{1*}, Fannie Rizki Ananda², Pandiaman Pandia¹, Bintang YM Sinaga¹, Maryaningsih Maryaningsih³, Anggriani Anggriani

¹Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; ²Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; ³Faculty of Physiotheraphy, STIKES Siti Hajar, Medan, Indonesia

Abstract

Citation: Tarigan AP, Ananda FR, Pandia P, Sinaga BYM, Maryaningsih M, Anggriani A. The Impact of Upper Limb Training with Breathing Maneuver in Lung Function, Functional Capacity, Dyspnea Scale, and Quality of Life in Patient with Stable Chronic Obstructive of Lung Disease Open Access Maced J Med Sci. 2019 Feb 28; 7(4):567-572. https://doi.org/10.3889/oamjms.2019.113

Keywords: COPD: Upper limb training: Breathing manoeuvre; Lung functions; Functional capacity; Dyspnea scale; Quality of life

*Correspondence: Amira Permatasari Tarigan Department of Pulmonology and Respiratory Medicine Faculty of Medicine, Universitas Sumatera Utara, Medan Indonesia. E-mail: amira@usu.ac.id

Received: 21-Dec-2018; Revised: 25-Jan Accepted: 26-Jan-2019; Online first: 25-Feb-2019

Copyright: © 2019 Amira Permatasari Tarigan, Fannie Rizki Ananda, Pandiaman Pandia, Bintang YM Sinaga, Maryaningsih Maryaningsih, Anggriani Anggriani. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

Funding: This research did not receive any financial suppor

Competing Interests: The authors have declared that no competing i

BACKGROUND: Exercise tolerance is one of the main impacts of COPD. COPD patients often experience dyspnea and fatigue after doing daily activities using their limb parts, even in simple thing such as lifting or grooming. Nowadays, many pulmonologists concerned in pulmonary rehabilitation to modify some limb training with breathing manoeuvre to get positive impact in stable COPD patient.

AIM: The purpose of this study is to examine the impact of this modified upper limb training in lung function, functional capacity, dyspnea scale, and quality of life in patients with stable COPD.

METHOD: This was a quasi-experimental study held in 2017 on 22 stable COPD patients (based on GOLD 2018 criteria). Patients were given modified upper limb training with breathing manoeuvre that leads and monitored by a physiotherapist and physician in 10-20 minutes twice a week for 8 weeks. Before and after completed all sessions of training, we measured pulmonary functions test include FEV1 and FVC, functional capacity by 6 MWT, dyspnea scale by mMRC, and quality of life by CAT assessment. Statistical analysis was performed by Wilcoxon and paired t-test

RESULTS: There was an improvement of lung function, both FEV1 (40.7 ± 13.8 to 47.3 ± 14.2; p-value 0.001) and FVC (50.7 ± 14.1 to 54.1 ± 14.7; p-value: 0.207) after training. There was a significant change of functional capacity in 6 MWT mean (277.3 ± 80.8 to 319.1 ± 78.3; p-value: 0.001). There was an improved quality of life after training, measured by decreasing in CAT score (23.9 ± 5.5 to 18.3 ± 5.2; p-value: 0.000). There was no significant change in the mMRC scale (p-value: 0.429)

CONCLUSION: There was an improvement of lung function, functional capacity, and quality of life in stable COPD after upper limb training with breathing manoeuvre in stable COPD patients.

Introduction

COPD (Chronic Obstructive of Lung Disease) is a common disease characterised by persistent respiratory symptoms and airflow limitations caused by airway and alveolar abnormalities due to significant exposure of noxious gases [1]. COPD is a preventable and treatable disease that challenge physicians to find new cases and treat patients with early respiratory

symptoms.

Exercise tolerance is one of the main impacts of COPD. Many patients report the limitation of exercise that further impacts their quality of life. Some studies stated that COPD patients often experience dyspnea and fatigue after doing daily activities using lower and upper limb parts, even in simple things such as lifting or grooming [2], [3]. In people with COPD, there is an increase in metabolic and ventilatory, particularly in unsupported arm work. During arm

Open Access Maced J Med Sci. 2019 Feb 28; 7(4):567-572.

exercise, the accessory muscles of respiration will prioritise the arm task than breathing, and it leads to thoracoabdominal dyssynchrony then aggravate dyspnea. It also limits the tidal volume in results of increasing chest wall impedance to maintain the trunk and move the arms during arm activities [3], [4].

Many studies just concerned on lower body training to decrease impact in COPD patient, and there are just little studies that concerned mainly to upper limb training. However, upper limb training can improve lung function and functional capacity, then reduce symptoms and improve quality of life in patients with COPD [5], [6]. Supported and unsupported arm training increased have the endurance capacity and result in reduced breathlessness in daily life with a patient with COPD [7]. Upper limb training considered to decrease respiratory dyspnea scale. improve muscle coordination, and beneficial adaptations to the exercise [8]. During exercise, some patients often felt dyspnea or chest discomfort, particularly at the beginning of the training session. So, it is needed a few combinations of training include breathing pattern such as pursed lips breathing to minimalise the impact of training in patients symptom during a training session.

Exercise technique in this study is adopted in some pulmonary rehabilitation programs. However, there was no definite pattern of upper limb training with breathing manoeuvre pattern has been conducted. It gives a challenge to pulmonologist concerned in pulmonary rehabilitation to modify some upper limb training to get positive impact in stable COPD patient.

The purpose of this paper is to examine the impact of this modified upper limb training in lung function, functional capacity, dyspnea scale, and quality of life in patients with stable COPD.

Methods

This research was a quasi-experimental study held in the Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara in 2017. This study protocol was approved by the Ethics Committee of Faculty of Medicine in Universitas Sumatera Utara.

Participants

Twenty-two participants enrolled in this study from a patient who came to the Department of Pulmonology and Respiratory Medicine in General Hospital of H. Adam Malik, Medan. Sampling was carried out by consecutive sampling with 22 patients who matched inclusion criteria and had no exclusion criteria. The inclusion criteria were stable COPD patients age 40-80 years and had not been involved in any exercise program for these two months. The diagnosis of COPD was established by history, physical examination, then confirmed by spirometry examination with GOLD 2017 criteria (FEV₁/FVC < 70). The exclusion criteria were patients in exacerbation state, did not want to follow or had an irregular exercise program, and had malignancy.

Protocol

After all, the participants had understood the contents of the study and filling the informed consent; they were scheduled for a training program. Before training, they had been given short-acting beta agonist (Salbutamol 2,5 mg) with a nebuliser, and they were confirmed in a clinically stable state when they came to the training program by a physician. First, they underwent warm up and muscle stretching for avoiding muscle injury for 10-15 minutes. Then, upper limb training for 10 minutes leads by physiotherapist and video prepared before. Upper limb training with breathing exercises consists of few manoeuvres such as:

1. Pursed lip breathing with exhaling while tilting your head towards your shoulder.

2. Bird-like pattern with inhaling while body straightening, exhale while bending forward to the bottom.

3. No-way pattern with pursed-lip breathing, seeing a movement to left and right alternately.

4. Shoulder shrug with pursed lip breathing.

5. Fan-like movement with pursed-lip breathing, hands are bent together, then turn right and left.

6. Chicken cuckoo like movements with rotating the shoulder with hands bent at the shoulder.

7. Vampire-like movement, hands straight forward while inhaling, then rotating the body to the right, left, and forwards while exhaling.

8. Calling movement, the hand is lifted, then touched it downwards, in the opposite direction.

9. Butterfly-like pattern, hands stretched straight forward then hands stretch.

10. It is cooling down.

This upper limb training held twice a week for 8 weeks. Before and after every session of training, vital sign measured and there were few physicians for leading and monitoring patients in the training program.

The followings were measured before and

after the training:

1. Lung function was measured by Forced Expiratory Volume in 1 second (FEV₁) and Forced Volume Capacity (FVC). The GOLD grade was made based on FEV₁ that divided into four categories. GOLD 1 for FEV₁ > 80%, GOLD 2 for FEV₁ 50-79%, GOLD 3 for FEV₁ 30-49%, and GOLD 4 for FEV₁ < 30%.

2. Oxygen saturation was measured by pulse oximetry. Oxygen saturation below 88 indicated hypoxia in stable COPD patient and needed for oxygen therapy while training session.

3. Functional capacity was measured by six minutes walking test (6 MWT). Patients were instructed to walk as fast as they can for 6 minutes on the hospital corridor. The patient may take a rest or decrease their speed if they experienced dyspnea or chest discomfort, but the timer was not stopped.

4. Dyspnea scale was measured by the modified Medical Research Council (mMRC) which score ≥ 2 indicates patients have more symptoms.

5. Quality of life measured by the COPD Assessment Test (CAT) questionnaire. The result \geq 10 from CAT indicates patients' quality of life were impaired.

Statistical Analysis

All the collected data was entered and analysed by using SPSS (Statistical Package for the Social Science) for Windows version 16.0. Data was described in the distribution of frequencies then analysed using paired T-Test or Wilcoxon Test for bivariate analysis to know whether there is a significant change of lung function, functional capacity, dyspnea scale, and quality of life mean before and after the upper limb training program.

Results

Total twenty-two patients enrolled in this study consisted of women and men, age 40-80 years old, with a diagnosis of stable COPD and adequate adherence of completed all session of upper limb training rehabilitation program.

From Table 1, we can see that the majority of the subject was male in 60-69 years old with severe index Brinkmann (IB \geq 600). Based on airway obstruction, most participants were in grade III with FEV₁ 30-49%. All participants had more symptoms of COPD with low quality of life, based on CAT score \geq 10. Most participants had high dyspnea scale from mMRC that interpret most participants had limitations in moderate to daily activities.

Characteristics		N	%	Mean ± SD
Sex				
Female		3	13.6	-
Male		19	86.4	
Age				62.9 ± 8.56
(Years Old)	40-49	1	4.5	
	50-59	6	27.2	
	60-69	1	59.0	
	70-79	2	9.0	
Brinkman Index				1236 ± 954
	Mild (< 200)	3	13.6	
	Moderate (200-599)	3	13.6	
	Severe(≥ 600)	16	72.7	
GOLD severity (FEV ₁)				40.7 ± 13.8
%	I (≥ 80)	0	0	
	II (50-79)	6	27.2	
	III (30-49)	1	45.4	
	IV (< 30)	6	27.2	
CAT score	. ,			23.9 ± 5.5
	< 10	0	0	
	≥10	22	100	
mMRC				
	0-1	6	27.3	
	≥ 2	16	72.7	

There was an increase of FEV₁ mean after 8 weeks of upper limb training compared to before training (40.7 ± 13.8 to 47.3 ± 14.2). It was in line with the statistical analysis using the Wilcoxon test that showed p < 0.05, interpret as there was a significant change of FEV₁ after 8 weeks of upper limb training. The same results also happen in FVC that showed an increased of mean after 8 weeks of training (50.7 ± 14.1 to 54.1 ± 14.7), but it was not significant in statistical analysis using paired T-test with p-value > 0.05.

Table 2: Mean and standard deviation of lung function, functional capacity, dyspnea scale, and quality of life before and after upper limb training

Characteristics	Mean ± SD Before	Mean ± SD	P value
	training	After Training	
FEV1	40.7 ± 13.8	47.3 ± 14.2	0.001**
FVC	50.7 ± 14.1	54.1 ± 14.7	0.207*
6MWT	277.3 ± 80.8	319.1 ± 78.3	0.001*
mMRC	2.36 ± 1.2	2.1 ± 0.9	0.429**
CAT	23.9 ± 5.5	18.3 ± 5.2	0.000*

*p-value from paired T-test, considered significant if p < 0.05; **p-value from Wilcoxon Test, considered significant if p < 0.05.

Functional capacity was measured by six meters walking test (6MWT) that showed significantly increased of mean after 8 weeks of training (277.3 \pm 80.8 to 319.1 \pm 78.3), and when analysed in statistical analysis using paired T-test, there was a significant change of functional capacity with p-value < 0.05.

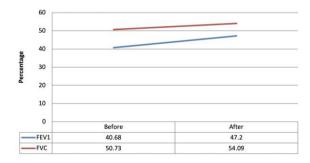


Figure 1: Comparison of lung functions between before and after training

Dyspnea scale could be measured by a few variables. In this study, we used the mMRC scale that

showed slight improvement after 8 weeks of training although it was not significantly changed in statistical analysis using the Wilcoxon test with p-value > 0.05.

Quality of life was measured by CAT questionnaire, a higher point in the CAT questionnaire showed the lower quality of life in a patient with COPD. In this study, there was a decreased mean of CAT after 8 weeks of training that interprets the increased quality of life in stable COPD patient.

Discussion

Some studies stated that COPD is a respiratory disease not only affecting the lungs, but also giving non-respiratory manifestations, including skeletal muscle dysfunction with atrophy and weakness, systemic inflammation, nutritional depletion and malnutrition, which can contribute to exercise limitation and affect patients' function and mobility [5], [9], [10], [11], [12]. Papaioannou et al. observed that higher systemic levels of oxidative stress in COPD patients may contribute to a reduction in the body mass and fat-free mass indexes, thereby contributing to impaired exercise capacity [13].

Muscles of the superior part of the thorax and scapular girdle, which serve for respiratory and postural functions, have thoracic and extrathoracic attachment points, such as the inferior/superior trapezius. latissimus dorsi. serratus anterior. subclavius and pectoralis major and minor. In COPD with pulmonary hyperinflation, which patients frequently occurs, the diaphragm lowers and loses its capacity to generate force, so that the ribcage muscles become more important to generate the inspiratory pressures [14].

Strategies have been used in COPD patients aiming to improve exercise performance. Pursed lip breathing is an intuitive technique that frequently COPD patients adapt to reduce dyspnea during exertion as a breathing retraining form. This strategy relieves the dyspnea sensation immediately after beginning to use the technique and encourages expiration time during the concentric phase of upper limb movements. Therefore it seems to be a form of physical exercise that could minimise the action of the accessory muscles [15].

COPD is a chronic disease that manifests in late age, after more than 10 years old insignificant noxious gases exposure. Long-term inflammation in airway and lung parenchyma due to free radical and oxidant in tobacco smoke and other environmental pollutions lead to subsequent airway and lung parenchyma damage [16]. Further, there was lung ageing theory that state lung function will decline along to increasing age because of structural and functional change. In elderly, there will be few changes in alveolar structure that sometimes called senile emphysema, changes in the chest wall caused by osteoporosis, stiffness in ribs, and reduced thickness in intervertebral discus [17], [18]. All these data related to our study that showed the majority of participants are in 60-69 years old.

Smoking is the main risk factor for COPD. The longer and the more of cigarette consumption, the longer and the greater inflammation will occur in airway and lung parenchyma. Cigarette smoke and nicotine can decrease the function of macrophages in lung, and specific enzymes that serve as energy for phagocytosis can be suppressed. It also inhibits mucociliary transport that made the most vulnerable to infection. Further, the materials in cigarette smoke can defect the alpha-1 antitrypsin that leads to the breakdown of elastin, component maintaining the elasticity of the lung, by neutrophil elastase [19], [20]. In this study the most Brinkman Index Values were severe (72.7%). This is similar to Ignatius et al., reported that COPD patients tend to have a Brinkman index medium to severe caused by high consumption of cigarette on patients [21].

From our study, we can see that there was an improved lung function, including FEV_1 and FVC, although FVC was not a significant change. This is line with Elmorsy study that stated improvement of FEV_1 and FVC after 8 weeks of upper limb training, but not significant in statistical analysis [22] (Elmorsy, 2013). Ries et al. found that there was a significant improvement of lung function include FVC, Residual Volume (RV), Functional Residual Capacity (FRC), Total Lung Capacity (TLC), but there was no significant change of FEV_1 after 6 weeks of upper limb training [23]. These inconsistent results caused by different type of upper limb training manoeuvre and clinical condition in every participant enrolled in each study.

In this data, there was no significant change in the dyspnea scale using the mMRC questionnaire. This is in line with McKeough study that stated there was no significant decrease in dyspnea in patients with stable COPD after upper limb training [6]. The same results also stated in Zanchet study that showed that there was no significant dyspnea improvement after pulmonary rehabilitation with upper limb endurance training after 6 weeks of training b session [24]. Sciriha study in South Europa also found there was no significant difference after 8 weeks of training program [25]. In contrast, Lacasse et al. showed a significant decrease in dyspnea means after 8 weeks of upper limb training [26]. In meta-analysis study in China, there was an improvement of dyspnea after more than 8 weeks of upper limb training, but it was not a significant change in statistical analysis. However, when upper limb training is given in shorter period, 3-8 weeks, there was a significant decrease of dyspnea, which suggest that short duration of upper

limb training can reduce dyspnea symptom in stable COPD patient [27].

Functional capacity is the ability to perform activities of daily life. An objective assessment of the functional capacity in this study was the 6 minutes walking test. There was a significant change of 6 minutes walking test mean after 8 weeks of intervention in this study (p = 0.001). There is an increase about of 41.81 ± 48.07 meters at the end of the training session. This is in line with few studies that showed improvement of functional capacity after limb training. Finnerty et al. reported an increase of about 59 meters after receiving 6 weeks of pulmonary rehabilitation compared to controls [28]. Bendstrup et al. reported an increase of 6 minutes walking distance of about 79.8 meters in the treatment group and 21.6 m in the control group (p < 0.001) [29]. Lacasse et al. conducted a meta-analysis of patients with COPD who received pulmonary rehabilitation and found the mean difference in the 6 minutes walking test is an increase of 55.7 meters and concluded that the minimum increased is 50 meters [30]. British Thoracic Society (BTS) recommends a minimum increase of 6 minutes walking test which considered clinically significant is 54 m [31].

Regular and intensive exercise in COPD will give effect in cardiopulmonary physiology, hormonal balance, and biochemical part in tissue. In general, regular exercise can induce oxidative capacity, decrease ventilation in submaximal workloads, and decreased oxygen consumption in submaximal workloads [32]. Exercise can increase the myoglobin amount in type 1 skeletal muscle fibre that helps the diffusion of oxygen from the cell membrane into the mitochondria [33]. All these processes impact the significant improvement of functional capacity in stable COPD patient.

Assessment of the quality of life in these patients also showed significant differences after the intervention. Participants had a decreased mean in CAT Questionnaire from 23.9 ± 5.5 to 18.3 ± 5.2 that interpret they had decreased symptoms in daily life. A multicenter study conducted by James W Dodd in 2011 correlate the CAT assessment before after 8 weeks of training in pulmonary rehabilitation and showed significant differences in which 162 patients feel better after pulmonary rehabilitation programs [31]. Lacasse et al. reported from a meta-analysis that pulmonary rehabilitation would reduce the symptoms of breathlessness and improve the activity of patients with COPD so that the functional capacity and quality of life also increase [30]. Subin et al., also conclude in their study that upper limb training can improve quality of life, although they used a different method to measure the quality of life, by using CRQ (Chronic Respiratory Questionnaire) [34]. Elmorsy et al., also stated that there is an improvement of the quality of life in patients who received upper limb training, and or without combination with lower limb training [22]. explained Berry et al., also that pulmonary

rehabilitation would increase the maximum oxygen consumption and maximum work capacity thus increasing the functional capacity and quality life of patients with COPD [35]. Aerobic exercise can pulmonary symptoms increasing improve bv maximum heart rate and anaerobic threshold in metabolic level, decreasing airway inflammation and increasing the usage of the ventilatory reserve [36]. [37]. Besides, regular exercise has social, emotional and mental effect improvement. Patients can have more self-confident to control their symptoms in daily life [38] contribute to an improvement in the quality of life in patients with stable COPD after the upper limb training program.

There are some limitations of this study, include the number of participants and the methodological used. A small group of participants can make it was difficult to rule out the personal factor that could interfere with the result of this study. In the method, this study did not have a control group so we could not make the comparison between intervention study and control group. Dyspnea scale could be measured in some questionnaire, such as CRQ, mMRC, and SGRQ (St George Respiratory Questionnaire), but in this study, we use mMRC to measure the severity of dyspnea. Besides, we suggest measuring further parameters of lung function such as total lung capacity (TLC), residual volume (RV), maximal Peak Inspiratory Pressure (PImax), vital capacity (VC), and PEFR (Peak Expiratory Flow Rate).

From this study, we can conclude that upper limb training gives a positive impact on stable COPD. Improvement of lung function, functional capacity, and quality of life of stable COPD patient after 8 weeks of training showed significant change. So, upper limb training must be a part of a pulmonary rehabilitation program in the comprehensive treatment of COPD.

Acknowledgement

This study was funded by the Directorate of Research and Development Ministry of Research, Technology, and Higher Education, the Republic of Indonesia, Budget Year of 2018.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, And Prevention of Chronic Obstructive Pulmonary Disease 2018 Report, 2018.

2. Criner GJ, Celli BR. Effect of unsupported arm exercise on ventilatory muscle recruitment in patients with severe chronic airflow obstruction. Am Rev Respir Dis. 1988; (138):856–61.

https://doi.org/10.1164/ajrccm/138.4.856 PMid:3202459

3. Celli BR, Rassulo J, Make BJ. Dyssynchronous breathing duringarm but not leg exercise in patients with chronic airflow obstruction. N Engl J Med. 1986; 314:1485–90.

https://doi.org/10.1056/NEJM198606053142305 PMid:3702963

4. Celli BR. The clinical use of upper extremity exercise. Clin Chest Med. 1994; 15:339–49. PMid:8088097

5. Dourado, V. Z., et al. Effect of three exercise programs on patients with chronic obstructive pulmonary disease. Brazilian Journal of Medical and Biological Research. 2009; (42):263-271. https://doi.org/10.1590/S0100-879X2009000300007 PMid:19287905

6. McKeough ZJ, Velloso M, Lima VP, et al. Upper limb exercise training for COPD (Review). Cochrane Database of Systematic Reviews. 2016; 11. https://doi.org/10.1002/14651858.CD011434.pub2

7. Kathiresan G, Jeyaraman SK, Jaganathan J. Effect of upper extremity exercise in people with COPD. Journal of Thoracic Disease. 2010; (2): 223-236. PMid:22263051 PMCid:PMC3256474

8. Costa D, Cancelliero KM, IKE D, et al. Strategy for respiratory exercise pattern associated with upper limb movements in COPD patients. Clinics. 2011; 66(2):299–305. <u>https://doi.org/10.1590/S1807-5932201100020020</u> PMid:21484050 PMCid:PMC3059857

9. Wouters EF, Creutzberg EC, Schols AM. Systemic effects in COPD. Chest. 2002; 121(5 Suppl):127S-30S.

https://doi.org/10.1378/chest.121.5_suppl.127S PMid:12010840

10. Agusti AGN. Systemic effects of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2005; 2:367-70.

https://doi.org/10.1513/pats.200504-026SR PMid:16267364

11. Roig M, Reid WD. Electrical stimulation and peripheral muscle function in COPD: a systematic review. Respir Med. 2009; 103:485-95. https://doi.org/10.1016/j.rmed.2008.11.008 PMid:19091537

12. Roig M, Eng JJ, Road JD, Reid WD. Falls in patients with chronic obstructive pulmonary disease: a call for further research. Respir Med. 2009; 103:1257-69. <u>https://doi.org/10.1016/j.rmed.2009.03.022</u> PMid:19419852 PMCid:PMC3326069

13. Papaioannou AI, Mazioti A, Kiropoulos T, et al. Systemic and airway inflammation and the presence of emphysema in patients with COPD. Respir Med. 2010; 104:275-82.

https://doi.org/10.1016/j.rmed.2009.09.016 PMid:19854037

14. Martinez F, Couser J, Celli B. Factors influencing ventilatory muscle recruitment in patients with chronic airflow obstruction. Am Rev Respir Dis. 1990; 142:276-82. <u>https://doi.org/10.1164/ajrccm/142.2.276</u> PMid:2382890

15. Spahija J, de Marchie M, Grassino A. Effects of imposed pursedlips breathing on respiratory mechanics and dyspnea at rest and during exercise in COPD. Chest. 2005; 128(2):640-50. https://doi.org/10.1378/chest.128.2.640 PMid:16100149

16. Khan S, Fell P, James P. Smoking-related chronic obstructive pulmonary disease (COPD). Journal of Diversity and Equality in Health and Care. 2014; 11:267-71. <u>https://doi.org/10.21767/2049-5471.100020</u>

17. Miller MR. Structural and physiological age-associated changes in aging lungs. Semin Respir Crit Care Med. 2010; 31:521–527. https://doi.org/10.1055/s-0030-1265893 PMid:20941653

18. Brandsma CA, de Vries M, Costa R, Woldhuis RR, Königshoff M, Timens W. Lung ageing and COPD: is there a role for ageing in abnormal tissue repair? European Respiratory Review. 2017; 26(146):170073. <u>https://doi.org/10.1183/16000617.0073-2017</u> PMid:29212834

19. Evans MD, Pryor WA. Cigarette smoking, emphysema, and damage to alpha 1-proteinase inhibitor. American Journal of Physiology. 1994; 266(1):593-611

20. Nowak MD, Ruta U. Nicotine inhibits alpha-1-proteinase inhibitor inactivation by oxidants derived from human polymorphonuclear leukocytes. Exp Pathol. 1990; 38(4):249-55. https://doi.org/10.1016/S0232-1513(11)80236-7

21. Ikalius, Yunus F, Suradi, et al. Difference in quality of life and functional capacity of patients with chronic obstructive pulmonary disease after pulmonary rehabilitation Majalah Kedokt. Indonesia,

2007:57.

22. Elmorsy, AS, Okasha, AE. Effect of Upper Limb, Lower Limb, and combined Training on Exercise Performance, Quality of Life, and Survival in COPD. Egyptian Journal of Chest Disease and Tuberculosis. 2012; 61(3):89-93. https://doi.org/10.1016/j.ejcdt.2012.10.008

23. Ries AL, Ellis B, Hawkins, RW. Upper Extremity Exercise Training in Chronic Obstructive Pulmonary Disease. Chest. 1988. https://doi.org/10.1378/chest.93.4.688

24. Zanchet RC, Viegas CA, Lima T. Efficacy of pulmonary rehabilitation: exercise capacity, respiratory muscle strength and quality of life in patients with chronic obstructive pulmonary disease. Jornal Brasileiro de Pneumologia. 2005; 31(2):118-24. https://doi.org/10.1590/S1806-37132005000200006

25. Sciriha A, Moore K, Montefort S. Combining inspiratory muscle training and upper limb exercises. Does it improve outcomes in COPD patients? Journal of Association of Chartered Physiotherapist in Respiratory Care. 2009.

26. Lacasse Y, Goldstein R, Lasserson TJ, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006;CD003793. https://doi.org/10.1002/14651858.CD003793.pub2

27. Pan L, Guo YZ, Yan JH, Zhang WX, Sun J, Li BW. Does upper extremity exercise improve dyspnea in patients with COPD? A metaanalysis. Respiratory medicine. 2012; 106(11):1517-25. https://doi.org/10.1016/j.rmed.2012.08.002 PMid:22902265

28. Finnerty JP, Keeping I, Bullough I, et al. The effectiveness of outpatient pulmonary rehabilitation in chronic lung disease. Chest. 2001; 110:1705-10. <u>https://doi.org/10.1378/chest.119.6.1705</u>

29. Benstrup KE, Jensen JI, Holm S, et al. Out-patient rehabilitation improves activities of daily living, quality of life and exercise tolerance in COPD. Eur Respir J. 1997; 10:2801-6. https://doi.org/10.1183/09031936.97.10122801

30. Lacasse Y, Wong E, Guyyat GH, et al. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. Lancet. 1996; 348:1115-19. <u>https://doi.org/10.1016/S0140-6736(96)04201-8</u>

31. Dodd JW, Hogg L, Nolan J, et al. The COPD Assessment Test (CAT): response to pulmonary rehabilitation. A multicentre, prospective study. Thorax. 2011; 66(15):425-9. https://doi.org/10.1136/thx.2010.156372 PMid:21398686

32. Crystal GR, West JB, Weibel ER. The Lung: Scientific Foundation (2nd ed). Philadelphia, New York. Lippincott-Raven, 1997.

33. Burhan E, Yunus F. Changes in lung physiology in the elderly. J Respir Indonesia. 2001; 21:160-165.

34. Subin, Vaishali R., V.Prem, Sahoo. Effect of upper limb, lower limb, and combined training on health-related quality of life in COPD. Wolters Kluwer-Medknow Publications Lung India. 2010; 27(1):4-7

35. Berry MJ, Rejeski WJ, Adair NE, et al. Exercise rehabilitation and chronic obstructive pulmonary disease stage. Am J Respir Crit Care Med 1999; 160:1248-1253.

https://doi.org/10.1164/ajrccm.160.4.9901014 PMid:10508815

36. Stendardi L, Binazzi B, Scano G. Exercise dyspnea in patients with COPD. International journal of chronic obstructive pulmonary disease. 2007; 2(4):429. PMid:18268917 PMCid:PMC2699965

37. Bernard S, Whittom F, LeBLANC PI, Jobin J, Belleau R, BÉrubÉ C, Carrier G, Maltais F. Aerobic and strength training in patients with chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 1999; 159(3):896-901. https://doi.org/10.1164/ajrccm.159.3.9807034 PMid:10051269

38. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, Pitta F. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. American journal of respiratory and critical care medicine. 2013; 188(8):e13-64. https://doi.org/10.1164/rccm.201309-1634ST PMid:24127811