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DEPARTMENT OF PHYSIOTHERAPY

The Effect of Airway Clearance Techniques on Patients with Chronic Obstructive Pulmonary Disease: A Literature Review

Master Thesis

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Abstrakt

Název

Vliv metody uvolňování dýchacích cest u pacientů s chronickou obstrukční plicní nemocí.

Cíl

Hlavním cílem této studie je popsat a zhodnotit účinnost metod uvolňování dýchacích cest (airway clearance techniques) u pacientů s chronickou obstrukční plicní nemocí na základě plicních funkcí a měření kvality života podle publikovaných prací.

Metodika

Tato práce je literární rešerší. Vybrané studie vycházejí ze zařazovacích a vyřazovacích kritérií. Jedná se o práce v anglickém jazyce publikované v rozmezí let 2000–2017. K prohledávání publikací v zájmové oblasti byly využity tyto vědecké databáze: PubMed, MEDLINE, Embase, Cochrane, PEDro a CINAHL. Výsledky parametrů z článků byly také vybrány hodnocením statistických rozdílů na základě hodnot P.

Výsledky

Za použití zařazovacích a vyřazovacích kritérií a měřitelných výsledků bylo ze 117 publikací vybráno 23 článků. Jednalo se o tyto metody: metoda aktivního cyklu dýchací techniky (ACBT), pozitivního výdechového přetlaku (PEP), temporárního pozitivního výdechového přetlaku (T-PEP), oscilujícího pozitivního výdechového přetlaku (O-PEP), vysokofrekvenční oscilace hrudní stěny (HFCWO), pomalého výdechu s glottis otevřenou v laterální poloze (ELTGOL), polohové drenáže a autogenní drenáže. Věk pacientů se pohyboval v rozmezí od 30 do 91 let. Mezi články byly zjištěny rozdíly u těchto parametrů plicních funkcí: FEV_1, FVC, poměr FEV_1/FVC, PEF, FEF, ERV, TLC a RV. Mezi statistickými rozdíly byl zjištěn rozptyl, přestože byla často používána metoda PEP a její úpravy.

Závěr

Metody uvolňování dýchacích cest u pacientů s chronickou obstrukční plicní nemocí hodnocením plicních funkcí a měření kvality života nejsou dosud dostatečné, i když některé studie poukazují na zlepšení.

Klíčová slova

chronická obstrukční plicní nemoc, metody uvolňování dýchacích cest, hrudní fyzioterapie, nefarmakologická léčba, respirační péče, zkoušky plicních funkcí, měření kvality života, odstraňování hlenu, plicní rehabilitace

Abstract

Title

The effect of airway clearance techniques on patients with Chronic Obstructive Pulmonary Disease.

Objective

The main purpose of this study is to expose and evaluate the efficacy of airway clearance techniques on patients with Chronic Obstructive Pulmonary Disease by using pulmonary functions and Quality of Life measurements from recent studies.

Methodology

This thesis is literature review. The selected studies were according to inclusion and exclusion criteria. The selections of recent studies were published from the year of 2000 until 2017 in English language. The following research databases were selected to identify the relevant topic: PubMed, MEDLINE, Embase, Cochrane, PEDro, and CINAHL. The parameters' results from the articles have been also selected by evaluation the statistical differences according to the P-values.

Results

Twenty-three articles out of 117 have been found according to inclusion criteria, exclusion criteria, and outcome measures. The techniques were active cycle of breathing technique (ACBT), positive expiratory pressure (PEP), temporary of positive expiratory pressure (T-PEP), Oscillating positive expiratory pressure (O-PEP), high-frequency chest wall oscillation (HFCWO), slow expiration with glottis opened in lateral posture (ELTGOL), postural drainage, and autogenic drainage. The patients age was ranged between 30 to 91 years old. The parameters of pulmonary functions that were found in differences between articles are: FEV_1, FVC, FEV_1/FVC ratio, PEF, FEF, ERV, TLC, and RV. There were variations in statistical differences although there were frequent using of PEP and its modifications.

Conclusion

The evidence of airway clearance techniques on patients with Chronic Obstructive Pulmonary Disease by evaluation of pulmonary functions and quality of life measurements are still poor although there were mentioning of improvements in some studies.

Key words

Chronic Obstructive Pulmonary Disease, airway clearance techniques, chest physiotherapy, nonpharmacological management, respiratory care, pulmonary function tests, Quality of Life measurement, mucus clearance, pulmonary rehabilitation.

Declarations

I, Hussam Ali Milibari, hereby declare that the work on which this thesis is based in my original work (except where acknowledgements indicate otherwise) under supervision of Doc. Paed Dr. Dagmar Pavlů, CSc. I declare that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce this thesis for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Acknowledgements

I would like to express my appreciation and deep gratitude to my supervisor Doc. Paed Dr. Dagmar Pavlů, CSc for her patient guidance and enthusiastic encouragement for this thesis project.

I would also like to extend my grateful thanks to all my teachers for allowing me to pursue the Master's Degree of Physiotherapy at Charles University in Prague.

Dedications

I would like to dedicate this thesis to my mother who has given me the greatest influence with encouragement and support for my all endeavors.

I also wish to dedicate it to my late father who prepared me to confront and incur the challenges with faith and humility.

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List of Abbreviations

AARC: American Association of Respiratory Care

ACBT: Active cycle of breathing techniques

ACT: Airway clearance technique

AD: Autogenic drainage

ANCOVA: Analysis of covariance

ANOVA: Analysis of variance

ATS: American Thoracic Society

BD: Bronchodilator

BTPS: Body temperature (37 C^{o}), ambient pressure, saturated with water vapor

BTS: British Thoracic Society

CCPT: Conventional chest physiotherapy

CI: Confidence interval

CMH: Chronic mucus hypersecretion

CPT: Chest Physiotherapy

CTWPR: Conventional treatment without pulmonary rehabilitation

DF: Degree of freedom

ELTGOL: Slow Expiration with Glottis Opened in lateral posture

ERS: European Respiratory Society

ERV: Expiratory reserved volume

FEF: Forced expiratory flow

FET: Forced expiratory technique

FEV_1: Forced expiratory volume in 1 second

FVC: Forced vital capacity

G: Group number

GOLD: Global Initiative for Chronic Obstructive Lung Disease

HFCWO: High frequency chest wall oscillation

IMT: Inspiratory muscle training

IPV: Intrapulmonary percussive ventilation

ITT: Intention-to-treat

MCD: Mucus clearance device (flutter)

MEF: Medium expiatory flow

MLG: Music listening group

MT: Mechanical percussion

NICE: National Institute for Health and Clinical Excellence

NS: No significance difference

OPEP: Oscillating positive expiratory pressure

P-value: Probability value

PD: Postural drainage

PEF: Peak expiratory flow

PEFR: Peak expiratory flow rate

PEP: Positive expiratory pressure

PEPR: Post-exacerbation pulmonary rehabilitation

RCT: Randomized controlled trial

SSG: Sitting Still Group

T1: Before Treatment (baseline)

T2: Immediately after treatment

T3: 90 minutes after treatment

T-PEP: Temporary positive expiratory pressur

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an incapacitating of respiratory condition with a growing the prevalence worldwide. It is defined by obstruction of airway that is not fully volatile. It is typified by chronic and progressive shortness of breath, chronic cough and production of sputum. The chronic cough and sputum are independent hazards of early COPD-related demise, and they are closely correlated with exacerbations frequently. Acute exacerbations of COPD (AECOPD) are clinically important conditions known to negative influence on health-related quality of life, lung functions, utilization of healthcare provided, and mortality rate. (Osadnik, McDonald, and Holland, 2013) Smoking is the major cause of chronic obstructive pulmonary disease, with many of its chemical substances that can provoke inflammatory, carcinogenic, and cytotoxic effects. (Watchie, 2010) Kolar et al. (2013) depicts that some studies showed the wide spreading of smoking has been decided as a risk factor among men and women. In 2020, it is estimated to be the third leading cause of global mortality and the fifth major source of morbidity and healthcare burden. In 2013, it resulted in 2.9 million deaths that is higher than 2.4 million deaths in 1990. (Vos et al., 2015; Vestbo et al., 2013)

Early treatment can result in recovery quality of life enhancement, and practices to evict airways sputum (airway clearance techniques) that could be important. Airway clearance techniques (ACTs) act by manipulation of lung volumes, flowing of gases, pulmonary pressures, and forces of compression for sputum shearing through the airway cavity across the mouth. This procedure is primary for effectiveness secretion clearance in cases when mucociliary dysfunction is existing as in chronic obstructive pulmonary disease. (Osadnik, McDonald, and Holland, 2013) There are variations of available airway clearance techniques. These include postural drainage, manual methods as percussion, active cycle of breathing technique, autogenic drainage, using of positive expiratory pressure device and its modifications, and others. (Wong, Sullivan, and Jayaram, 2018)

2. Theoretical Background

2.1. What is Chronic Obstructive Pulmonary Disease (COPD)?

The bronchial Obstructive Lung Diseases (OLD) generally includes asthma, chronic bronchitis, emphysema, bronchiectasis, and cystic fibrosis which are featured by airflow limitation that is particularly noticeable during forced expiration. Airflow limitation can result from some obstacles inside the airways such as excessive secretions, edema fluid, or foreign material. In addition, it is possible the presence of airway narrowing such as bronchoconstriction, mucous gland hypertrophy, or inflammation. The another possible is peri-bronchial abnormalities such as destruction of lung parenchyma, as in emphysema, or compression by enlarged lymph nodes or tumors. This debilitating condition is resulting in significant increasing of morbidity and mortality rate. It is the fifth leading cause of death in the UK and estimated to be the third by 2020. World Health Organization expressed that around 250 thousand people had died in Europe because of COPD in 2008. In 2001 and depending on the European White Book, the yearly cost of chronic obstructive pulmonary disease was approximated to be 38.7 billion euros, 73% of costs being related to work incapability, 12% to care ambulation, 7.5% were hospitalized, and 7.5% with medication. (Achilleos and Powrie, 2011; Watchie, 2010; Raherison and Girodet, 2009; Vestbo et al., 2013; Gibson, Loddenkemper, Sibille, Lundbäck, and Fletcher, 2013)

Due to the significant deal of interfere the peculiarities clinically and in pathophysiologic in respect of asthma, chronic bronchitis, and emphysema and many patients have features of more than one of these diseases, the generic diagnosis of chronic obstructive pulmonary disease (COPD) is frequently used, sometimes called Chronic Obstructive Lung Disease or Chronic Obstructive Airway Disease (COLD, COAD respectively). Common to all obstructive pathologies is chronic inflammation of the airways and parenchymal and vascular destruction which occur in highly variable combinations. In

most cases of COPD is a slowly in progressiveness and partially reversibility with treatment. (Watchie, 2010)

Smoking is the principal cause of COPD, with many of its chemical substances that can provoke inflammatory, carcinogenic, and cytotoxic effects. Also, restraint of ciliary function is correlated with reoccurrence the presence of bronchitis and lower respiratory tract infections. However, only a few of people who have smoking can cultivate to COPD; more frequently they can have such a serious peripheral vascular, cerebrovascular, and cardiovascular diseases. (Watchie, 2010)

Chronic obstructive pulmonary disease (COPD) is an airflow obstruction that cannot be fully reversed and is featured by symptoms of dyspnea, chronic cough and secretion production. However, the acute exacerbation of COPD is an increasing of breathlessness with raising of expectoration, and changing in the sputum color from familiar to green or yellow, or raising the rate of coughing in patients with COPD. In the systematic analysis for the Global Burden of Disease Study of patients across 72 countries from 1990 to 2013, they found that is one of the basis leading cause of global mortality and a major source of morbidity and healthcare burden. In 2013, it resulted in 2.9 million deaths up from 2.4 million deaths in 1990 and increased by mean 20%. (Vos et al., 2015) In a study of CT scan analysis of the chest, it depicts that at least 30 percent of COPD patients have bronchiectasis. The existing of bronchiectasis in COPD is correlated with increasing the severity of airflow obstruction, the existing of bronchial colonization by possibility of microorganism pathologies, and with prior hospitalization admission due to exacerbations. In another study, the most frequent in COPD patients have reported with lower lobe of bronchiectasis, and was also correlated with frequent raised of bacterial colonization in lower part of airways, more severe COPD exacerbations and raised markers of inflammation in sputum. The chronic productive cough is the major projecting symptom of patients with bronchiectasis that occur in more than 90 percent of patients. (Miravitlles, 2011)

2.1.1. Chronic bronchitis

Bronchitis causes a cough that produces sputum or phlegm, difficulty of breathing and a rigid sensation in the chest area. The chronic condition is that last preserved a long time. Therefore, the chronic bronchitis is that inflammation that lasts more than three-month period. (Heath and Mongia, 1998)

As Heath and Mongia (1998) showed that the chronic bronchitis is one of the major demonstration of chronic obstructive pulmonary disease which is the fourth essential cause of death in the United States of America by around 10 million people are influenced by some degrees of COPD and by around 40 thousand deaths yearly.

2.1.2. Emphysema

Emphysema is an abnormal constant increasing the size of the air space that is located in the terminal area of bronchioles with walls destruction of air sacs, but there is no fibrosis. Emphysema is recruited mutually with COPD. The theory has been formed since the 1950s, with a notion of irreversibility and/or constant destruction of acinar cells. On the other hand, the new information posit that raised of sediment collagen causes active fibrosis, which inevitably is correlated with damages of the lung's elastic framework. The combination of fibrosis and emphysema has been depicted to present subset of patients with emphysema. (Cottin et al., 2005) There are three kinds of emphysema: Centrilobular emphysema that impact the upper airways that result in destruction in bronchioles, panlobular emphysema can affect the lower part of airways that result in dispersing the diffusion within the alveoli, and paraseptal (or paracinar) emphysema which is a destruction of lower lobe alveoli of lung that lead to isolation of blebs over the peripheral part of the lung. (Goodman and Snyder, 2013)

Emphysema and chronic bronchitis are the same in limitation of airflow and clarified that in inclusion within chronic obstructive pulmonary disease. Just as asthma is no longer joined within COPD. The actual COPD has been defined by the Global Initiative for Chronic

Obstructive Lung Disease (GOLD) and no more differentiation between emphysema and chronic bronchitis. (Agusti et al., 2017; Rabe et al., 2007)

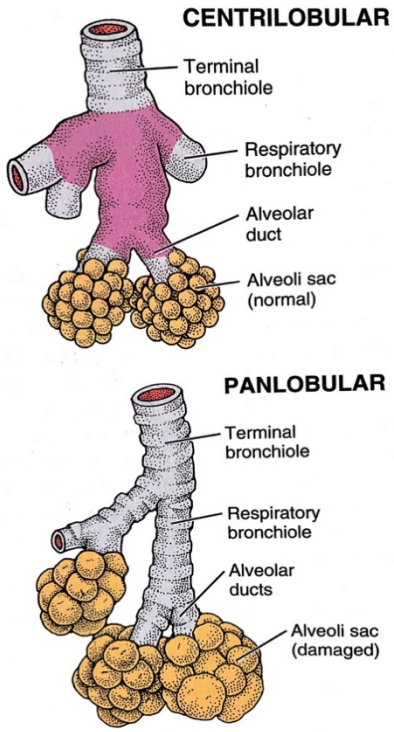

Figure 1. Centrilobular emphysema and panlobular emphysema (Goodman and Snyder, 2013)

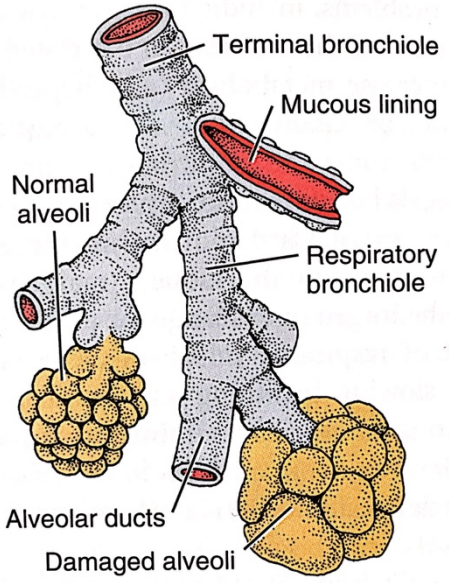

Figure 2. Chronic bronchitis (Goodman and Snyder, 2013)

2.2. Pathophysiology

Mucosal edema is the result of chronic inflammation of the airways with raising production of amount of mucus with ciliary dysfunction, and sometimes constriction of bronchi. The aforementioned can lead to increasing of airway resistance that resulting in limitation of expiratory flow. At the beginning, the disease is without symptoms, but when the forced expiratory volume in 1 second (FEV_1) falls around 50% of predicted normal value, symptoms usually become visible. (Watchie, 2010)

Small airways become obstructed during progression of chronic obstructive pulmonary disease due to the thickness of airway, because of remodeling procedure and collection of inflammatory that stimulated by mucociliary dysfunction. Therefore, in moderate or severe conditions, early happening of airway closing without emptying alveoli totally, so it will increase residual volume gradually, air trapping, and lung hyperinflation that are usually removed by exercise or what known as dynamic hyperinflation that lead to a barrel-shaped chest, which changes the breathing mechanics. The diaphragm begins to be flattened as a primary of respiratory muscle, so pulling of muscle changed to be more horizontal and prevent chest expansion; therefore, the accessory muscles of respiration are worked for breathing. (Hogg, Chu, and Utokaparch, 2004; O'Donnell and Parker, 2006)

The subsequent aggravation of the mismatching with abnormal work of breathing raise the possibility of ventilatory failure or right ventricular failure with cor pulmonale. During training, cardiovascular will be limited in connection with increasing of pulmonary dysfunction. Inability to perform physical exercises is one of the chief complaint and due to several factors complex interdependent fans limitation expands because of expiratory flow limitation, irregular breathing mechanics and dynamic hyperinflation, impaired gas exchange, and increasing of breath, dramatic raised of pulmonary vascular pressures during less workloads, also in people who have normal pressures with slight or without hypoxemia during rest. Sometimes, it leads to pulmonary hypertension even if there is no exercise-

induced hypoxemia. RV pump dysfunction stimulated by pulmonary hypertension results in decreased stroke volume and increased sub-maximal heart rates. (Watchie, 2010)

Kolar et al. (2013) demonstrated that the disease can happen in different stages of severity. The following are categorized: Stage 1: mild that depicts a mild airflow limitation ($FEV_1/FVC<70\%$, but FEV_1 80% predicted). Stage 2: moderate with 50 percent to 80 percent as predicted of FEV_1 with breathlessness after exertion. Stage 3: severe that featured by more severe obstruction of bronchi with 30% to 50% FEV_1. Stage 4: is very severe condition with 30% of the predicted FEV_1. Chronic respiratory failure can lead to respiratory or circulatory right-sided failure that happens by reducing in oxygen partial pressure dramatically with lesser than 60 mm/Hg and raising of CO_2 over 50 mm/Hg.

The main mechanisms witch responsible for hypersecretion of sputum patients with COPD are the increasing the secretions by goblet cells, and the declining removing of mucus with excessive growth of the submucosal glands in thickness. In addition, there is increasing in thickness among the epithelium and cartilage that overlays the bronchi. The girth of the submucosal glands is associated with the inflammatory degree in airways. (Ramos, Krahnke, and Kim, 2014)

The risk factors of COPD, that will be described later, lead to the overproduction of mucus and from raised degranulation and by mainly neutrophil elastase that lead to awkwardness in removing secretions due to the weakness of ciliary function, distal airway obstruction, and no effect of coughing which is associated with respiratory muscle weakness and decreased PEF. After raised the inflammation of airway, the epithelium of airway remodels and goes through metaplasia, suggested changes in phenotype that happens through cell type adults, and even the presence of hyperplasia, indicating an increasing the number of total cells through a given type of tissue. The hypertrophied goblet cell with hyperplasia happened in large airways during smoking or any other noxious agents, and hypertrophied goblet cell lead to epithelial mucin stores that are more than normal. (Ramos et al, 2014; Innes et al., 2006)

The pathogenesis of mucus hypersecretion in chronic bronchitis as a cellular and molecular mechanisms include gained dysfunction of cystic fibrosis transmembrane conductance regulator (CFTR) and activate epidermal growth factor receptor (EGFR). Smoking cigarette can even rise the synthesis mucin MUC5AC through receptor of epidermal growth factor activation in the epithelial cells of airways. Essential of the fibroblast growth factor is upregulated and transformed growth factor-β. Also, the higher frequency of the tumor necrosis factor-α polymorphism have been involved in the pathogenesis of chronic bronchitis. There are several factors and proteases catalyze hypersecretion of mucus and many of them do their impacts within the activation of epidermal growth factor receptor (EGFR) (Ramos et al., 2014; Agusti et al., 2017)

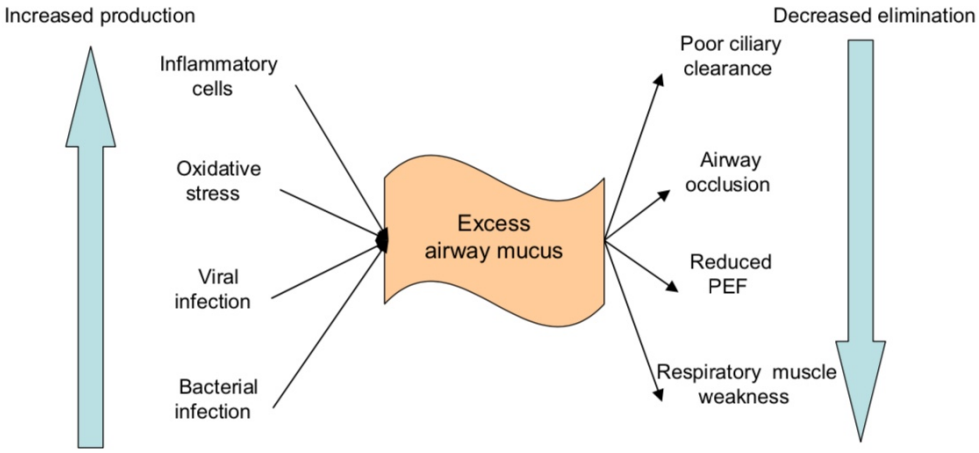

Figure 3. Causes of mucus secretion in COPD patients (Ramos et al., 2014)

2.3. Risk Factors for COPD

Risk factors are in connection with the presence of influencing environmental factors with genetic predisposition that can lead to present the signs and symptoms and even depends on the existence of associated comorbidities.

2.3.1. Smoking

One of the major risk factor of COPD is being smoking actively. The risk likely to have been caused by active smoking in patients with COPD is ranged between 40% to 70% depend on each country. (Raherison and Girodet, 2009; Rodriguez-Roisin, Rabe, Vestbo, Vogelmeier, and Agustí, 2017)

Active smoking among women during pregnancy can even modify lung development of fetus and lead to asthma in predisposed children. Also, the result of passive smoking can delay in fetal lung development. There are several mechanisms of action on lung tissues and parenchyma by smoking. Many controversies increasing between in vitro and ex vivo experiments are in favor of airway inflammation. The cell and molecular agents unlike from those who have asthma. Histological analysis of bronchial biopsies from patients who have mild and moderate chronic obstructive pulmonary disease depict the infiltration of CD8+ lymphocytes in proximal airways are present. The presence of neutrophils in large concentrations in the sputum of patients with COPD. In addition, direct smoking of cigarette influences different kinds of cells, specially macrophages and epithelial cells of airways, so the contribution for rising production of mediators and cytokines that contribute in preserving of the inflammatory reaction. The smooth muscle cells of bronchi will play an important role in the remodeling of the airways of patients with COPD in connection with reaction of epithelium and extracellular matrix. (Raherison and Girodet, 2009) Turato et al. (2002) also expressed that the patients with severe COPD and still smoking had a raised number of leukocytes in the small airways.

In respect of (Raherison and Girodet, 2009), they showed that the other theories have been established to try and explain the irreversible histological lesions caused by the component of tobacco. For instance, an imbalance in proteases/anti-proteases is thought to result in destruction of assemblage of extracellular matrix, specially elastin. This concept still controversial and is based on an original study showing around 40% changes in the function of an anti-protease, antitrypsin, in smoker people, in comparison with non-smoker.

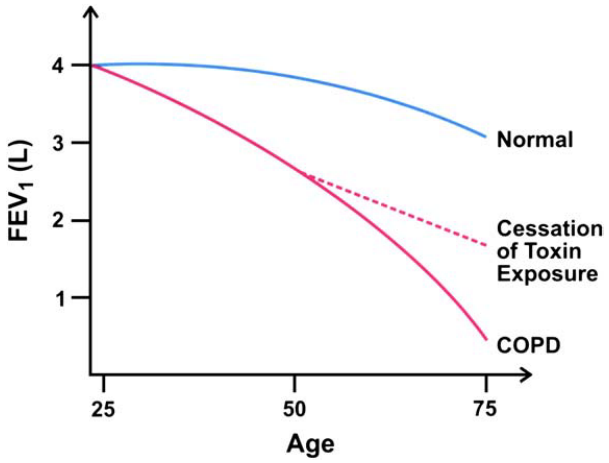

Figure 4. The normal lung function capacity falls overtime (in a 25-year-old adult) according to FEV_1, but this fall can be dramatically if the adult exposed to toxins as in smoking cigarette. However, this quickened fall can be deliberated when stopped the toxin exposure. (Daheshia, 2005)

2.3.2. Genetic factors

Not all people who smoke would develop chronic obstructive pulmonary disease in their life although the using cigarettes is a significant factor, but the genetic factor can be even associated impliedly. In general, the children respiratory function has assigned seemingly by their parents of respiratory function. Therefore, among their parents who already have a low respiratory function (last one-fifth), 37% will have a relatively low respiratory function. In contrast, the parents with normal or high respiratory function, 41% will have a normal respiratory function. (Raherison and Girodet, 2009)

Nowadays, one of approved genetic factor is severe deficiency of alpha 1-antitrypsin (A1AT) which is responsible for PiZZ phenotype. 1-3% of COPD patients who had this related to aforementioned deficiency and in particular emphysema. The responsible of alpha 1-antitrypsin synthesis is single-nucleotide polymorphisms (SNP) which has been considered in six haplotypes of SERPINA 1 gen, so the aforementioned gen is recognized as crucial factor for chronic obstructive pulmonary disease. (Raherison and Girodet, 2009)

In addition, there were several studies on other gens, specifically the genes coding of metalloproteinase of the extracellular matrix (MMP). The MMP-9 which is included in the destroyed contents of the extracellular matrix in gelatin, collagens (IV, V, XI and XVII) or elastin as some examples. It showed that a polymorphism of MMP-9 (C-1562T) is correlated with upper lung as an emphysema. Also, in severe cases of COPD, there was illustration of genetic decay in proteolysis of elastin that is in association with the different expression of the terminal exons in elastin. It showed that the gene coding for phospholipase A2 which is a protein in fatty acids metabolism is in association with higher condensation of plasma of the enzyme in several inflammatory diseases. Losing weight has been shown in some patients with COPD and it is thought to be relevance with different expression of the subgroup of phospholipase A2 belonging to group 2. Finally, it is important to be considered the connection between COPD and different genetic polymorphisms: icrosomal epoxide hydrolase, glutathione S-transferase, haemoxygenase-1 and tumor necrosis factor. Systematic accumulation for genetic measures in blood samples could be useful in future studies of COPD prevalence. (Raherison and Girodet, 2009) In addition, (Gibson, Loddenkemper, Lundbäck, and Sibille, 2013) expressed that there is a suggestions of genetic risk factor that can play a role with 20 percent of smoker COPD patients.

2.3.3. Occupational exposure

The risk attributable of being exposed in occupational environment in COPD has been appraised at around 19%, and for did not smoke by 31%. The exposure of major areas of nonsmokers have been found in rural environment, where people can be exposed to a crucial level of organic particles such as vegetable dust, and bacterial or fungal toxins. In addition, in industry of texture where people can be exposed with great level of plant dust such as cotton dust, or in the industrial environment such as mining, fusing plants, iron and steel industry, and wood manufacture. The participation of occupational exposures to COPD and, in specific, their potential interplay with smoking the cigarette remains misunderstood. Connection the exposure of smoking with occupational factors has a tremendous elevation the risk of COPD. (Raherison and Girodet, 2009). Also, there is prediction from 15 to 20 percent of COPD patients were work-related. (Gibson et al. 2013)

2.3.4. Air pollution

Pollution exposing at home, specifically in developing countries, is a crucial risk for chronic obstructive pulmonary disease and estimated by 35% of conditions by smoking during cooking or to the method of heating in without appropriate ventilation at home, females are the most focused. In China, the dominance of COPD conditions in non-smoker females is thought to be three times greater in rural environments in comparison with females who are dwelling in urban environments and not vulnerable. The correlation of air pollution as a risk factor is not well understood. Its effect, as an irritating factor, has been depicted in severe conditions of COPD during elevation in air pollution. Lately, a crucial influence after prolonged exposure to particles that carried out by air that lead to the risk of death was found in a large multi-city study of elderly people who were discharged alive after admission with COPD. Validity of environmental measurement is important and rebuild individual exposure with traffic air pollutant dispersion models remains a serious challenge in epidemiology researches. (Raherison and Girodet, 2009; Hu et al., 2010)

2.3.5. Age

The augmented spreading of COPD has a correlation with age. During life, there is a physiological inclination in respiratory function that begins between 30 and 40 years old. Due to of the raising of life anticipation in developed countries, the estimation of older people with COPD is also in redundancy. (Raherison and Girodet, 2009)

2.4. Acute exacerbations of COPD

An exacerbation of COPD is a sustained deterioration of respiratory symptoms which is acute in onset and usually the patient needs medical help or treatment alteration. The deterioration must be more severe than the usual daily variation experienced. Exacerbations are featured by redundancy of breathlessness, coughing, expectoration, wheezing, and chest tightness. Other common characteristics are malaise, decline exercise tolerance, peripheral edema, using of accessory muscle, confusion, and cyanosis. (Currie and Wedzicha, 2006)

The admission in United Kingdom hospital every year with the exacerbation chronic obstructive pulmonary disease had been estimated for up to 10% of all medical conditions, that equal more than 100,000 admissions, with a mean length of stay of more than one week. Therefore, the exacerbations have estimable costs for secondary care and are partially accountable for increasing of recruiting rates of hospital beds. Patients with frequency of exacerbations have a tremendous decreasing in lung functions, impaired quality of life, and restriction of ADL activities, and it can lead to inability to leave the house. In severe COPD cases, the frequency of exacerbations also rises. (Currie and Wedzicha, 2006)

2.4.1. Causes of acute exacerbations COPD

The primary causes of exacerbations are viruses, bacteria, or environmental pollution, but the exact cause still unknown in several cases. Viruses can play a crucial role with rhinoviruses being involved commonly. Number on exacerbations that caused by bacteria in, but the pathogenesis of bacterial action can be grown from the sputum in stable conditions. In contrast, there is a proposal is that the isolation of a new effort can be related with development of an exacerbation. (Currie and Wedzicha, 2006; Daheshia, 2005)

2.4.2. Recurrent Exacerbations

The recurrence of the exacerbation of chronic obstructive pulmonary disease have already done for many patients that lead to frequent returning being admitted in hospital. This is especially so for subjects with hypercapnia respiratory failure who have treated with non-invasive ventilation. In fact, during a year after discharging from the hospital, most of subjects will be returned to the hospital and need more non-invasive ventilation. Other studies are needed to distinguish the causes that lead to recurrent admission to the hospital and to commend strategies to address that problem. (Currie and Wedzicha, 2006)

2.5. Parameterization of pulmonary function tests

Pulmonary function tests compose of a concatenation of maneuvers for inhalation and exhalation that intended to evaluate the integrity and function of the respiration. The data given by pulmonary function tests is useful to the health case provider to create real therapy aims and suitable therapy depending on the patient's condition of lung problems and level of impairment. The available information from pulmonary function tests contain measurements of lung volumes and capacities, ventilation, pulmonary mechanics, and diffusion. (Watchie, 2010)

Lung volumes are linked to size of the body, and the height is the most crucial in relation variability. In children and adolescents, the development of lung reveals to tardiness behind the raise in standing height during the development speed, and there is an alteration in the connexion between the size of lung and height during adolescence. In young male, the height development in between 12.5 and 18 years of age summit around 1 year before the development rate of weight and forced vital capacity, and around 1.5 years before the developmental rate of maximum flow at 50% of forced vital capacity. However, the developmental rates among young females of all lung function parameters decline through the age. Using simple study of the relationships between tallness and lung volumes, the youngest ages have much higher in predicted volume in comparison with oldest adolescent ages that have too lower. (Pellegrino et al., 2005)

In addition, the young males have a higher of the volumes of lung function in comparison with young female by the same tallness, even white individuals have higher values than black individuals. Lung function raises gradually with age until the adolescent developmental spurt at around of the age of ten in females, but by age of twelve in males. The values pulmonary function in relation with height varies with age during adolescence. Thus, a single ratio or the pulmonary function value and height development chart alone couldn’t be completely illustrated the development during the time of adolescence. However, the ethnicity and gender in growth curves of pulmonary function values against

height can make it easier to reveal and evaluate the periodic measures of pulmonary function for an individual child. (Pellegrino et al., 2005)

Furthermore, the pulmonary mechanics (such as flow rates, compliance, and resistance of airway) are dynamic in nature, the measurements of aforementioned can be valid according to the effort of patient with cooperation. The examinations of pulmonary mechanics are usually done before and after the management of bronchodilators to expose the reversibility of limited airflow and to define the effectiveness of usage. Normal values are varied according to the height of person, gender, ethnicity, and age. (Watchie, 2010)

Some of different parameters that can be found on the report in pulmonary function tests include

- Forced vital capacity (FVC): it is the maximal volume of air that has been exhaled with largest forced performance from a maximal inspiration, which is the vital capacity accomplished with a maximally forced expiratory effort, revealed in liters at BTPS. In healthy people, the differences between slow vital capacity (SVC) and FVC (SVC − FVC) is zero in practice, but the difference can be changed if there is and become visible and are particularly associated with the existence of lung hyperinflation. (Miller, Hankinson, Brusasco, Burgos, and Casaburi, 2005; Barros, Pires, and Raposo, 2013)

- Forced expiratory volume in one second (FEV_1): It is the maximal volume of air that been exhaled in the very first second of a forced expiration from a situation of full inspiration, the parameter can be revealed in liters at BTPS.

- FEVt: It is one of lung functions that the maximal volume exhaled by specific time t seconds of a forced expiration from a situation of full inspiration, and it is been shown in liters at BTPS. FEV_1 has been studied to be useful for very young children due to the difficulty to perform prolonged expiration. However, there is enhancement studies for indices that been extracted from blows with forced expiratory times of one second that

might be useful. Currently, there are incomplete data to approve the use of $FEV_{0.5}$ or $FEV_{0.75}$. (Miller et al., 2005)

- FEV_1/FVC ratio: is the forced expiratory volume in one second that demonstrated as a percentage of forced vital capacity. The normal young people can exhale 50-60% of FVC in half of second, 75-85 percent in one second, 94 percent in two seconds, and 97 percent in three seconds. Therefore, the typical ratio of normal healthy adults is ranged between 70-75 percent.

- Forced expiratory flow 25% to 75% ($FEF_{25-75\%}$): it is a forced expiratory flow between 25% and 75% of the forced vital capacity, and it also being known as the maximum mid-expiratory flow. This parameter is taken from the blowing with the biggest accumulation of FEV_1 and FVC. The $FEF_{25–75\%}$ must be evaluated with an accuracy of at least ±5 percent of reading or ±0.200 $L.s^{-1}$ what is higher, over a range of up to 7 L/s^{-1}. It should be noted that it is strongly dependent on the validity of the forced vital capacity measurement and the level of expiratory attempt. (Miller et al., 2005) In addition, the $FEF_{25-75\%}$ has lesser multiplying than FEV_1, and it is hard to explain if the VC (or FVC) is reduced or increased. (Johns and Pierce, 2008)

- Maximum voluntary ventilation (MVV): The MVV is the maximum volume of air an individual can breathe over a specified range of time (normally 12 seconds). This measurement has been strongly replaced by FEV_1, that was illustrated as the index from a single maximum forced expiratory technique that best related with maximum voluntary ventilation (MVV). If FEV_1 is present, so MVV has little additional participation. Nevertheless, it could be useful in some conditions where ventilatory capacity may be failed in mechanism that are varied from FEV_1. (Miller et al., 2005)

- Residual volume (RV): it belongs to the volume of gas that is maintaining in the lung after maximal breathing out with regardless of the lung volumes at which breathing out was started. (Wanger et al., 2005) Residual volume is decreased in restrictive lung problems when interferes with other thoracic expansion. They are raised more than 120

percent of predicted normal in COPD and indicated air trapping. The normal value can be around 20-30% of tidal volume. (Watchie, 2010)

- Peak expiratory flow (PEF): It is the greatest flow attempted from a maximum forced expiration that began with no indecision from a posture of maximal lung inflation. When it is received from flow–volume curve data, it is revealed at BTPS in $L.s^{-1}$. The illustrating features of the flow–time curve are the time received for flow to increase from 10 percent of peak expiratory flow to 90 percent (rise time [RT]), and the period that flow is >90% of PEF (dwell time [DT]). The unit can be described by $L.min^{-1}$ if PEF is received with portable monitoring device. There are different kinds of device that can be utilized to measure PEF such as pneumotachometers, spirometers, turbines and anemometers. (Miller et al., 2005; Quanjer, Lebowitz, Gregg, Miller, and Pedersen, 1997)

- Vital Capacity (VC): it is the variation of lung volume of air between the position of full inspiration and complete breath out, in liters at BTPS. The slow vital capacity can be divided into two types: The expiratory vital capacity (EVC) which is the maximal volume of air being breathed out from the point of maximal inhalation, and inspiratory vital capacity (IVC) which is the maximal volume of breathing in from the period of maximal exhalation, attempted by a slowly breathing out from end-tidal inspiration. These techniques are without forces, besides at the period of attempting residual volume or total lung capacity, where additional force is needed. (Miller et al., 2005)

- Inspiratory capacity (IC): it is volume change recorded at the mouth when the individual takes full inspiration slowly without vacillation from a position of passive end-tidal expiration, which is functional residual capacity, to the maximum breathing in, recorded in liters at BTPS. The inspiratory capacity is an indirect appraise of the degree of lung hyperinflation at rest, and it is used for assessing changes in FRC in combination with pharmacological treatment and physical exercise. (Miller et al., 2005)

- Maximal expiratory flow at 50 percent of the forced vital capacity ($MEF_{50\%}$): is the flowing that the half of FVC maintains to be expired. It is corresponded to $FEF_{50\%}$ and strongly associated with maximum mid-expiratory flow ($FEF_{25-75\%}$). As such, MEF indicates obstruction of small airways and may be utilized as a replacement of early disease of small airways that illustrated by an abnormally low mid-expiratory flow in the existence of normal FEV_1, FVC, and FEV_1/FVC ratio. (Güder et al., 2015)

- Total lung capacity (TLC): is maximum volume of air that the lungs can include following the maximal inspiration = residual volume + expiratory reserved volume + tidal volume + inspiratory reserve volume. It is not measured directly during pulmonary function tests; however, it is collected from other results of parameters. It can be decreased in the processes of disease with place that occupies lesions (for example edema, atelectasis, tumors, and fibrosis), and in pleural effusion, pneumothorax, and deformity of thorax. The TLC can be in normal or increase of patients with obstructive lung disease being increased in hyperinflation. (Watchie, 2010)

- Expiratory reserve volume (ERV): it is the additional amount of air that exhaled forcefully after the end of normal tidal exhalation.
- Tidal volume (TV or V_T): it is the amount of air breathed in or out during normal respiration.
- Inspiratory reserve volume (IRV): it is an additional volume of air inhaled over and above the tidal volume.
- Functional residual capacity (FRC): it is the mount of air that exist in the lungs after a normal tidal expiration = ERV + RV. (Watchie, 2010)

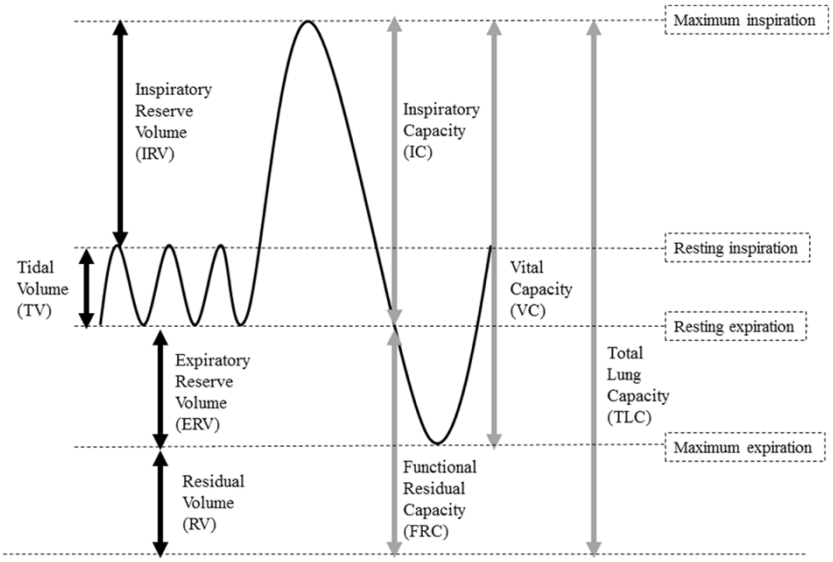

Figure 5. The standard lung volumes and capacities from a spirometer trace. The solid black and gray arrows indicate lung volumes and capacities respectively (Lutfi, 2017)

Table 1. Lung volumes and capacities in healthy adults (Patil and Bhalsing, 2018; Davis, Johanson, Stepanek, and Fogarty, 2008)

Volume	Average value (in Liters)	
	In men	In women
Vital capacity	4.8	3.1 – 3.2
Inspiratory capacity	3.5 – 3.6	2.4
Functional residual capacity	2.3 – 2.4	1.8
Total lung capacity	5.8 – 6.0	4.2
Tidal volume	0.5	0.45
Inspiratory reserve volume	3.1	1.95
Expiratory reserve volume	1.2	0.8
Residual volume	1.2	1.0

2.6. Relationship of COPD with lung functions

There are several studies have confirmed a relation between mucus expectoration and the rate of decreasing in FEV_1 with COPD patients. (Miravitlles, 2011; Miller et al., 2005) Furthermore, Long-term studies of FEV decline have shown the importance of cigarette smoking and exacerbation frequency as some of the factors that affect FEV decline. (Donaldson et al., 2005) There is decreasing in FEV_1 dramatically in respect of age and it has related to the severity of airway inflammation. In addition, the potential of exacerbation and incomplete recovery can result in decreasing of FEV_1. There is also reducing of FVC, and it could be less than VC in COPD if forced exhalation results in collapse or is decreased by mucus plugging and narrowing of bronchioles. (Donaldson, Seemungal, Bhowmik, and Wedzicha, 2002) In conditions of the lung obstruction disease, the TLC and RV points are shifted to the left of flow-volume curve (which is a flow that generated during FVC) due to increasing of volumes, the peak expiratory flow rate is decreased significantly (as the decrease in FEV_1), the FEV_1/FVC ratio can be also decreased lower than 65 percent and the curve is flattened or concave. Some patients have both obstructive and restrictive problems, so they can show mixing of low volumes and decreased expiratory flow rates. (Watchie, 2010) In 2005, the recommendation has been illustrated to demonstrate the airway obstruction by the ATS/ERS guideline to use of lower limit of normal range for FEV_1/VC. (Swanney et al., 2008) On the other hand, the increasing BMI from 20 to 30 kg/m can also decrease the FRC and ERV dramatically in around 3% and 5% respectively. (Jones and Nzekwu, 2006)

2.6.1. Tables of spirometric classification of COPD

Table 2. Spirometric classification of chronic obstructive pulmonary disease (COPD) according to ATS/ERS (Celli et al., 2004):

Severity	Post-bronchodilator FEV_1/FVC	FEV_1 % predicted
At risk	>0.7	≥80
Mild COPD	≤0.7	≥80
Moderate COPD	≤0.7	50-80
Severe COPD	≤0.7	30-50
Very severe COPD	≤0.7	<30

Table 3. Spirometric classification of chronic obstructive pulmonary disease (COPD) based on post-bronchodilator FEV_1 and according to GOLD (Bakke et al., 2011; Vestbo et al., 2013)

Severity	FEV_1/FVC	FEV_1 % Predicted
Stage I: Mild	< 0.70	≥ 80%
Stage II: Moderate	< 0.70	50% ≤ FEV_1 < 80%
Stage III: Severe	< 0.70	30% ≤ FEV_1 < 50%
Stage IV: Very Severe	< 0.70	FEV_1 < 30% or FEV_1 < 50% + chronic respiratory failure

2.7. The St. George's Respiratory Questionnaire (SGRQ)

The most common used respiratory-specific health related quality of life questionnaires are Saint George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ). (Nici et al., 2006; Morishita-Katsu et al., 2016) There are three sections that supply SGRQ scores: symptoms (which concern by effect of pulmonary symptoms, frequency, and severity) by 8 items, activity (that concerns the relationship between activity and shortness of breath) by 16 items, and impacts (to evaluate the potential effect of disease on social function and disturbances of psychology) by 26 items. The total fifty items differ in formation, as polytomous such as Likert-type scale, and dichotomous such as (true/false). The patients are asked to remember the symptoms component over a specific period, as 1 month, 3 months, or 1 year. Other parts are not associated with time. Scores are ranged between 0 which is no impairment and 100 which is the worst. (Meguro, Barley, Spencer, and Jones, 2007; Jones and Forde, 2009; Ferrer et al., 2002)

The SGRQ is designed to assess the effect of chest problems on health-related quality of life and welfare. It can be utilized for COPD and asthmatic patients. The number of options to be respond per question are varied between 2 and 5. Responses are measured and scores are calculated by dividing the collected results by the higher possible result and stating the result in percentage. The results show to be in similarities in although the differences in countries and languages. The lower response clinical significant response to the therapy is determined by improvement for 4 percent on the separate parts and the total score. The validity and reliability of SGRQ was reported in patients with COPD and asthma. (Mölken, Roos, and Van Noord, 1999) However, National Emphysema Treatment Trial Research Group (2003) revealed that the HRQOL can be improved if there is decreasing in the score on the SGRQ more than 8 points (on a 100-point scale) from the level of baseline. The SF-36 has revealed an improvement after pulmonary physiotherapy although generic health related quality of life questionnaires usually are less discriminatory and show less ability to expose the changes occurring voluntarily or with treatment. (Nici et al., 2006).

2.8. Pharmacological management

2.8.1. Bronchodilator

There are three common kinds of bronchodilator as in clinical uses: b-agonists, anticholinergic drugs, and methylxanthines. In spite of essential differences in their place of action through the cell and some proof for non-bronchodilator activity with some trials of remedy, the paramount result of bronchodilator treatment surfaces to be as a relaxation of airway smooth muscle and improvement of exhalation in normal breathing. The consequent rise in FEV_1 could be small; however, it is can be associated by changing dramatically in lung volumes, with decrease in RV and/or a retard of the onset of dynamic hyperinflation through practice. These changes participate in reduction of shortness of breath. Generally, the more burden the COPD, the more crucial the changes in lung volume become akin to those in FEV_1.

Short-acting of BDs lead to raising of exercise tolerance markedly, and long-acting inhalation of b-agonists can progress health status and could be greater range than regular short-acting anticholinergics, decrease symptoms, save medication use and expand the time in exacerbations in comparison with sham. Merging short-acting bronchodilator agents [salbutamol (albuterol)/ipratropium] generates large changes in spirometry measurement than one agent. Combination of long-acting b-agonists and ipratropium decreases exacerbations than one remedy alone. There is no available data to compare between different long-acting b-agonists even though it is probable their effects would similar. Furthermore, a combination of long-acting b-agonists and theophylline occurs to generate improvements in spirometric than either medication alone. The tiotropium can increase of health situation and decreases the exacerbated or hospitalized patients in comparison with whether placebo or regular ipratropium. Theophylline has slight effect as a bronchodilator, that can have anti-inflammatory features. Also, its small therapeutic index and complex pharmacokinetics lead to difficulty in use; however, modern slow-release production have decreased the condition and result in more stability in plasma levels. Ordinarily, the measurement of therapeutic level should be done and patients should be maintained on the

smallest level of effective dose (recommended serum level 8–14 $\mu g.dL^{-1}$). On the other hand, the increasing of mucociliary clearance may needed more than BD as sympathomimetics or anticholinergics. (Celli et al., 2004; Hess, 2007)

2.8.2. Inhaled Corticosteroids

Celli et al. (2004) expressed that there are various of points have been acted by glucocorticoids through the inflammatory cascade although their impacts in COPD are lesser in comparison with bronchial asthma. Ejiofor and Turner (2013) demonstrated that ICS decreases the inflammation of airways, restriction of airflow, treating the symptoms of asthmatic conditions. Nevertheless, the role of ICS is more controversial in patients with COPD generally due to the differences in inflammatory patterns. The domination of neutrophilic infiltration of the inflammation in COPD, with excess in numbers of macrophages and CD8 T lymphocytes; neutrophilic infiltration is not as reacting to steroids as same as in eosinophilic inflammation in asthma. In spite of aforementioned, ICS were utilized in COPD with poor evidence of effect. Their usages in COPD has been lately showed in the Cochrane collaboration. The conclusion was that although the using of inhaled corticosteroids are associated with a decreasing in exacerbation proportion and probability decreased proportion of reducing in FEV_1, these advantages require to be weighed versus high risk of pneumonia and other side effects.

2.9. Non-pharmacological management

Chronic obstructive pulmonary disease (COPD) is a continuing and highly irreversible disorder. The medications alone cannot make certain optimum short and long term results. Therefore, there is raising of interest in the role of non-pharmacological plans and multidisciplinary group input in the overall management of chronic obstructive pulmonary disease. (Currie and Douglas, 2006)

2.9.1. Pulmonary Rehabilitation

The consider referring all COPD patients for pulmonary rehabilitation regardless the age, smoking condition, or functional limitation. An appropriate program is crucial in cut-off the malicious cycle of aggravated breathlessness, decreased physical activity, and reduced many patient's performance, so the pulmonary rehabilitation plays an important role in returning patients to the optimal function condition. For instance, early treatment after an AECOPD can improve the condition greatly in exercise capacity and health. The appropriate program should compose of different components that are exercise training, education, and nutrition.

Physical exercises: pulmonary rehabilitation programs in outpatient consistently applied in two months and by two or three sessions of physical exercises weekly. Clients are advised to do exercises at home and to be considered with attempts and notices the progression. Studies depicts that the physiological changes supported by endurance exercises at the level of skeletal muscle. Physical exercises program leads to exercise tolerance furtherance, even in symptoms, quality of life, peak oxygen uptake, endurance period through bellow the maximal exercises, functional walking distance, and strengthening of respiratory muscles.

Education: This generally consists of different structures of plan directed and systematically relevant conveyance targeted at improving comprehension and inducement. The agenda can be planned with possible issues that involve a breathing control, relaxation, beneficial training, and importance of smoking termination. Group training could be more valuable although the individualization is also beneficial. Contributors can be motivated by taking their responsibility for their own wellbeing, home follow up sessions can even be needed.

Nutritional counselling: Chronic obstructive pulmonary disease involves patients with history of overweight (blue bloaters) or underweight (pink puffers). Regardless the

bigger differences in body constitution and nutritional condition, the pathophysiological assay mark in both manners is related to airflow obstruction. Many patients with COPD are lightweight due to high energy produced linked with the raised effort of respiration with low level of nutritional intake because of restriction by severe shortness of breath. On the other hand, patients can develop into heavier weight due to decreasing activity and eating greedily. The explanations for these phenotypic variations are far from clear, but increased attentiveness of cytokines such as tumor necrosis factor alpha and leptin have been incriminated in losing weight. (Currie and Douglas, 2006; Gibson, Loddenkemper, Sibille, and Lundbäck, 2013)

2.9.2. Airway Clearance Techniques (ACTs)

2.9.2.1. The active cycle of breathing technique

The active cycle of breathing technique (ACBT) is frequently used to assist airway clearance for patients with chronic lung disease and featured by excessive secretions. Unusual secretion production can cause airway obstruction and sputum detention, so predisposing the airways may lead to infection and inflammation. The goal of therapy methods is to clear secretions that can reduce the frequency of infections, then prevent more airway damages and impairment of lung function. Also, there is potential decreasing of progression rate of lung disease. ACBT composed of three major phases: breathing control, deep breathing exercises or thoracic expansion exercises, and forced expiratory technique (FET or huffing). Also, a manual technique (MT) or positive pressure may be joined if needed, to make a more complex cycle to support surpassing airway clearance. (Lewis, Williams, and Olds, 2012)

The FET composed of one or two forced exhalation or huffs, after that breathing control (relaxed breathing). The FET is an essential phase of the ACBT, in connection with thoracic expansion exercises and interspersed durations of breathing control. Hence, the usual ACBT cycle composed of breathing control, three to four thoracic expansion training, breathing control, and the huffing. The number and frequency of each of the parts of the

ACBT may varied; however, all parts of the cycle have to be present, and with presence of breathing control in between. Several maneuvers have been attempted increased airway clearance. The forced expiratory mechanism (low- and high-volume huffing) are thought to enhance sputum movement through alters in thoracic pressures and airway dynamics. Breathing control has been described to avoid bronchospasm and decreasing of oxygen saturation, whereas the thoracic expansion exercises help in secretion removing and the enhancement of collateral ventilation. It is potential that the physiological impact of active cycle of breathing technique can be changed a bit with some patients, according to the amount of secretion, severity of the disease, and even whether in stable conditions or exacerbated. Studies depicts that the ACBT gave significant results in outcomes in people with a different lung diseases that involved non-cystic fibrosis bronchiectasis, cystic fibrosis, and chronic obstructive pulmonary disease. (Lewis et al., 2012)

2.9.2.2. Huffing or Forced expiratory technique (FET)

The beginning of FET explanation was on 1968 by team from New Zealand, the physician Thomson and therapist Thomson were working with asthmatic cases. They illustrated to apply one or two huffs from middle to low lung volumes, and the glottis is opened, and then taking a time for relaxation, controlled diaphragmatic breathing, with slow deep inspiration. Sputum can move from the lower to upper airways to be expectorated, and the task can be redone. (Fink, 2007)

Procedure for Huff Forced Exhalation

1. The patient takes 3–5 slow deep inspiration, breathing in through the nose, exhaling across pursed lips, using diaphragmatic breathing.
2. Take a deep inspiration and hold it for 1–3 seconds.
3. Breath out from mid-to-low lung volume to clear sputum from small airways.

4. Take a normal breath in and then press it out by making contraction the muscles of abdomen and chest and the mouth and glottis are opened, while murmur the word "huff" as sounds like a forced sigh during breathing out. redo few times.
5. As secretions move to the larger airways, breath out from high-to-mid lung volume to clear secretions from more adjacent airways. Repeat technique two to three times.
6. Take few relaxed diaphragmatic breathings before the next cough.
7. Clinician documents teaching attempted, technique performed, and individual's reply in the patient record. (Fink, 2007)

2.9.2.3. Direct cough

Procedure for directed cough:

1. Demonstrate to the patient that the deep inspiration and coughing would assist to maintain the lungs expanded and clear of sputum.
2. Help the patient to be in sitting position, or to a semi-Fowler's position on bed if there is difficulty in sitting.
3. Principle of directed cough technique:
    a. Teach patient to breathe deeply, then hold the breath, the patient utilizes abdominal muscles to compress air against a closed glottis, then cough with a single expiration.
    b. Having few relaxed breaths before and after cough.
    c. Report teaching attempted, techniques accomplished, and patient's reply in the patient's description.
4. Alternate standard "huff" directed cough technique:
    a. Giving a command to the patient to take three to five slow deep inspiration, breath in through the nose, expiring through pursed lips, using diaphragmatic breathing. Command to the patient to take a deep breathing in and hold it for one to three seconds.
    b. Breath out from mid-to-low lung volume to move secretions from small airways. Take a normal breath in and then press it out by making abdominal

and chest wall muscles contraction, then whisper with mouth and glottis opened. redoing few times.

c. As secretions move the bigger airways, expire from high-to-mid lung volume to move and clean secretions from more nearest airways. Repeat the technique two to three times.
d. Take few relaxed diaphragmatic breathing before the after coughing.
e. Report instructing attempt, techniques completed, and patient's response in the patient documentation.

5. Alterations of coughing for:
    a. Patients with history of abdominal or thoracic operation. Give a command by putting hand or a pillow over the section area and make slight pressure during coughing and the therapist can help with section support. Support chest tubes if needed.
    b. In quadriplegic patients, the therapist can put palms on the patient's belly, under the diaphragm, and give a command to the patient by taking three deep inspiration. On expiration of the third breath, therapist press firmly inward and upward during the patient coughs. (Fink, 2007)

2.9.2.4. Postural drainage (PD)

Technique

Timing according to the subject's situation, but the postural drainage in the early morning can assist clear the night's gathered sputum, and PD an hour before sleeping can decrease night coughing. Postural drainage shouldn't be used post-eating. If the patients used bronchodilators, it's better to be taken 15 minutes in advance.

Patients are positioned with the area to be drained uppermost, bearing in mind that these positions may need modification depends on patient comfort or if lung structure has been misshaped by operation, fibrosis, a large abscesses or cysts. The most impacted place is drained first to avoid infected secretions leak into normal lung. Arrhythmias or desaturation should be screened before, during and after postural drainage for patients who

are on monitors.

Drainage durations are different, but preferably each position needs around 10 minutes. If the condition impacts the whole lung, every lobe needs drainage, but a maximum of three positions at a session maintains it bearable. Patients with pointed bronchiectasis or abscess should be positioned and the impacted place upwards. The technique shouldn't be continued if the patient feels of headache, discomfort, dizziness, palpitations, fatigue, or shortness of breath. (Hough, 2001)

2.9.2.5. Autogenic drainage

There is a poor evidence to support or disprove the using of autogenic drainage patients. The beneficial notion is that autogenic drainage could be applied as another airway clearance technique if other techniques have lower effectiveness on patients with non-cystic fibrosis-related bronchiectasis. Researchers recommended for a needed more researches to evaluate the effectiveness of autogenic drainage in patients with non-cystic fibrosis-related bronchiectasis, and further researches to show that the technique is a valid outcome measure for applying in adult patients with bronchiectasis and chronic obstructive pulmonary disease. (Bott et al., 2009)

Before to begin the technique, the secretions should be cleared in the nose and throat by huffing or blowing. The bronchodilator or nebulizers should be taken as described to moist and dilate the airways, and enhance bronchial clearance. The patient should apply the autogenic drainage technique across inhalation therapy. It is recommended to use breath-stimulating position, as in upright sitting or lying on bed. (Agostini and Knowles, 2007)

Inspiration should be performed slowly through the nose, and the breath should be held for two to four seconds. To perform the correct respiration, hold at the end of the required inspiration, the respiration movement should be stopped in its three dimensions with the maintaining of opened glottis. Breathing in is applied diaphragmatically that can be double in size of a normal tidal respiration, according to patient ability, disease and lung

functions. The exhalation should be an active sigh. Exhalation can be through the nose or the mouth. (Schoni, 1989)

2.9.2.6. Manual technique (percussion or vibrations)

Percussion or vibrations can be applied in a position of postural drainage. They target to remove secretions that remained on walls of airways.

The technique

Percussion composed of rhythmic clapping on the area of chest without firm wrist and cupped hand, making as a wave movement that can transferred to the airways. The patient should be covered by sheet but should not be thick because it could decrease the transfer across the chest wall, and correct hand cupping to make that the technique is totally convenient. It's preferably to patients for applying the technique in gentle single-handed, or fast double-handed may lead to holding the respiration and sometimes bronchospasm. The vibrations composed of a fine oscillation by using both hands directed toward against the chest, applied during expiration that following deep inspiration. Shaking is a in roughly fluctuation that can lead to rhythmical compression of chest wall. Vibrations and percussion should be interspersed and with relaxed deep breathing to avoid closing the airways, desaturation, or bronchospasm. (Hough, 2001)

Precautions

Percussion and vibrations can be prevented or altered if there is:

- Ensured of fracture of rib or as suspicion such as metastatic carcinoma or osteoporosis
- Losing of skin benignity such as post-operation, burns or chest drains
- Pain that come from some conditions such as pleurisy or post-herpetic neuralgia
- Recent or excessive coughing up blood from respiratory tract from different causes such as abscess or lung contusion

- Severe clotting disorder as a lesser than 50000 of platelet counts
- Operational emphysema
- Unstable angina or arrhythmias. (Hough, 2001)

2.9.2.7. Positive expiratory pressure (PEP) device

The therapy by using positive expiratory pressure (PEP) was evolved at 1970s, and it has been revealed in the USA as a variation of conventional intervention. The instrument composed of a mask on face or mouthpiece with one-way valve with that of resistance can be done during expiration, and a manometer between the opening and the resistance area, to evaluate the true value of pressure, that can be between 10 and 20 cm H_2O in the period of mid-expiration. The higher PEP technique utilizes high lung volumes and the maneuver of forced expiration against resistances that produce expiratory pressures more than 20 cm H_2O. This device aims to allow more air to get in peripheral airways through collateral channels, to permit the pressure of air to run beyond secretions, moving them through bigger airways where they can easily be expectorated and to avert the collapse in the air sacs of lungs. (Hristara-Papadopoulou, Tsanakas, Diomou, and Papadopoulou 2008; Darbee, Ohtake, Grant, and Cerny, 2004)

Figure 6. Positive expiratory pressure mask fitted with a one-way valve, an expiratory resistor, and a pressure manometer (Darbee, Kanga, and Ohtake, 2005)

Application:

The individual should do this technique in a standing or sitting position. The individual takes a breathing in slowly to vital capacity and then holds the air inside for around 3 seconds. After that, slowly breathing out to the mouthpiece of the device or mask with the fixed the mouth opening resister that is usually set to make the resistance of expiratory pressure into 10 to 20 cm H_2O. This slow deep inspiration technique is redo between 10 and 20 times. Therefore, the forced expiration should follow to empty that have been moved. It is important to take around 1 to 2 minutes for relaxation and breathing control. The individual should prevent any full exhalation. Intervention period and frequency are settled depends on individual necessary. The therapy period is ranged between 15 to 20 minutes with 2 times in stable cases. The device can be given independently to cases of chronic respiratory diseases because it can be portable and with no needs of help and is easy and comfortable in use. Some of studies have documented improved large airway clearance and patient comfort with PEP devices in comparison with standard CPT. The medications that decrease and improve the pulmonary conditions such as bronchodilator is also mentioned. Furthermore, there has been study that there were decreasing in prolonged period of hospitalization. Other studies documented that the intervention of positive expiratory pressure has a positive effect on lung function. (Hristara-Papadopoulou et al., 2008)

2.9.2.8. Oscillatory positive expiratory pressure (O-PEP)

The remedy by utilizing oscillating positive expiratory pressure has been created and exposed as a first time in Switzerland, as a helpful device to traditional airway clearance techniques. O-PEP merges the suggested advantages for positive expiratory pressure with airway vibrations or oscillations. Oscillations reported reduces the viscoelastic characteristics of mucus, by easing the mucus moving up the airways, and produce small bursts of raised expiratory airflow that help in mucus movement the out of airways. Then, the airway clearance is stimulated by deep breathing out into the device or by self-coughing or huffing techniques. There are different devices of O-PEP such as Acapella, Flutter, or RC-Cornet. (Myers, 2007; Cegla and Pneumologie-Zentrum, 2000)

The Flutter

The Flutter is a portable instrument in pipe shape. It consists of ball that is in high-density stainless steel and remains in a circular etcher inside the bowl of the "pipe." The rounded cover upon the ball has holes that allow the expiration of airflow to cross through the instrument. The patient can be in sitting upright position during utilization of flutter or on lying on side. The horizontal position sometimes is more convenient and beneficial for patients. regardless the position of patient, the flutter bowl in pointed upward position to receive the ultimate effect. The primary process of the flutter occurs when expiratory flow across the mouthpiece result in rise and fall of the ball inside the cone space, which produces PEP ranged between 5 cm and 35 cm H_2O. The pulses are in the range 8–26 Hz. The flutter enables in tilting as a tuning slightly upward or downward to modify the shaking frequency. (Myers, 2007)

The directives to the patients to use the flutter

1. The position of patient is in sitting and upright. Straight back and slightly extended head and upward with relaxation of breathing control technique.
2. The patient breaths in twice or thrice and then hold for 2-3 seconds.
3. Put the mouthpiece of flutter in the mouth and the patient breath out at twice the flow of a normal expiration. Keep in expiration till lungs attain FRC.
4. Discourage non-productive cough occurs through the rudimentary secretion-loosening breaths.
5. During expiration within flutter, recommend the patient to set the horizontal tilting of the device to the angulation that can produce the best feeling of oscillation through the lungs.
6. After various loosening breaths, command the patient to take a very deep inspiration, hold for two to three seconds, and then powerfully expire within the flutter till the accomplishment of forced residual capacity.
7. After one or two high-volume, high-expiratory-flow mucus-clearance respiration by huffing or another functional breathing out technique.

8. The extra-treatment sequences which is like the above should be done through the session, until lungs would clear or until the predetermined therapy duration has finished. (Myers, 2007)

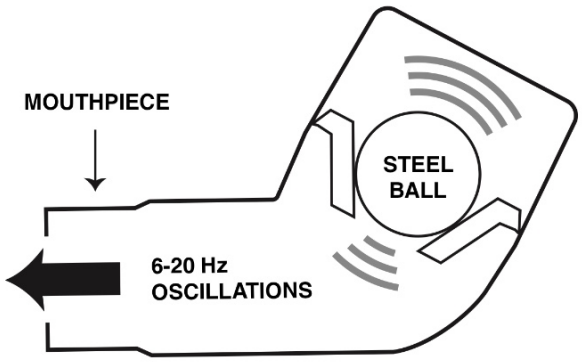

Figure 7. Schematic representation of the mucus clearance device (Flutter; Axcan Scandipharm, USA). For use as a sham mucus clearance device, the steel ball was removed (Wolkove, Baltzan, Kamel, and Rotaple, 2004)

Acapella device

The Acapella device is a combination the rules of high frequency oscillation and PEP by recruiting an equated the lever and magnet. Expired gas passes within a cone, which is sporadically blocked by a plug connected to the lever, resulting in oscillations of air flow. There is a knob which is located at the distal end of the instrument sets the vicinity of the magnet and equated plug, that way setting the frequency, amplitude, and mean pressure. There are two different acapella models: a green device for patients that can incur the expiratory flow for at least 3 seconds of (15 L/min), and a blue device for patients have an expiratory flow 15 liters per minute. Both the Flutter and the Acapella produce positive expiratory pressure and oscillations by the opposition to flow generated by an obturator influencing with metered force. The Flutter utilizes the force of gravity, but the Acapella utilizes the force of magnetic attraction. (Volska, 2003)

Figure 8. Acapella device (Cho et al., 2014)

RC- Cornet

The device consists of a mouthpiece and connected with central marking and internal tube for ventilation. The inner tube is flattened and covered by outer solid tube and muffler. The solid tube connects the ventilation tube particularly. During the blowing into the device, and thus within the ventilatory tube, the air is moving toward of the curve until reaching to crucial level of pressure, that stresses the venting tube briefly up to the solid tube, letting the air to pass within, and then returning to close the airflow. The technique produces oscillation of pressure. The elasticity of ventilation tube and the dimensions can particulate the amplitude and frequency. (Cegla and Pneumologie-Zentrum, 2000)

In the starting position, the complex that is in the ventilation tube of the device is a diameter corresponding of the tube. Rotation of the mouthpiece to that the venting tube is vaulted twists the internal tube. Inside the tube, there is no longer kinking shut the diameter but rather to diagonal. By this procedure, the pressure and capacity can be changed with the

device by mouthpiece rotation. After the mouthpiece is hold the and turned the device bend to one side, the best tube position can be found by the patient. The mouthpiece has gradation points to find the best setting and without delay. (Cegla and Pneumologie-Zentrum, 2000)

The production of pressure in the device is dependent on the gravity, even the elasticity of the tube and the bending in the solid tube set the point the kinking of ventilation tube. Therefore, the RC-cornet can be in different therapeutic positions. (Cegla and Pneumologie-Zentrum, 2000)

2.9.2.9. Temporary positive expiratory pressure (T-PEP)

The temporary expiratory pressure is an instrument that stratifies an expiratory pressure ≤1 cm H_2O only for a part of the exhalation phase. This raise in low pressure is produced within a pulse of flow and the frequency in around 42 Hz. T-PEP is done for clearing the secretions from the peripheral airways, beneficent in pulmonary functions (including decreasing in airflow obstruction). Some researches on COPD patients have approved encouraging benefits in the parameters of pulmonary functions, bronchial burden, breathlessness, and quality of life. (Mascardi, Grecchi, Barlascini, Banfi, and Nicolini, 2016)

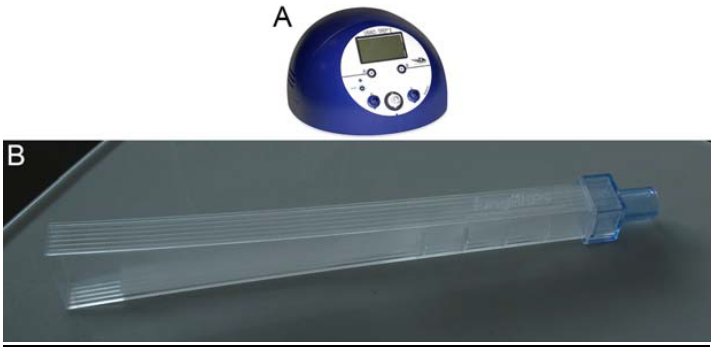

Figure 9. A: T-PEP UNIKO and B: O-PEP lung flutter

(Nicolini et al. 2017)

2.9.2.10. The Slow Expiration with Glottis Opened in lateral posture (ELTGOL)

The slow expiration with glottis opened in lateral posture is less common technique, but it becomes more and more public technique to clear the airways. In this technique, the patient is lying in a position of lateral decubitus and exhales slowly within an open glottis from FRC to RV. The aim of this technique is to control expiratory flow to stop airway obstruction and stimulate mucus clearance. In differences to postural drainage, clearance of secretion is only raised in the dependent and subordinated lung position. (Wong et al., 2018)

The volume of the dependent lung in ELTGOL is decreased by putting the patient in the lateral lying position and by shorten the respiration to ERV. This decreases entire peripheral airways in cross sectional area of the where secretion is originally created. While the extreme airflow speed is reciprocally proportional the diameter of airway, the velocity of airflow in the peripheral airways is raised. Airway clearance is remained by elevation intraluminal pressure by slow breathing out in opened glottis. Therefore, this leads to higher clearance of secretion of peripheral airways (Wong et al., 2018)

2.9.2.11. Intrapulmonary percussive ventilation

The device intrapulmonary percussive ventilation was presented at the beginning by Forrest Bird in 1979. It is a ventilatory technique that transfers of high flow of gas as small bursts inside the lungs and in high rates. This results in to oscillation between 5 and 35 cm H_2O in airway pressures and simultaneous vibration in the airway walls with these oscillations. The phasitron, which is a specific sliding venturi, is powered by compressed gas from 25 to 40 Pisa and produces the oscillations in the range between 80 to 650 cycles/min. During inhalation, the high frequency gas pulsation extends lungs and vibrates and magnifies the airways. This mechanism can be connected to nebulizer and with potential improvement of removing the secretion. When the percussive bursts of air go inside the lungs with maintaining of continuing pressure, the high velocity percussive inflow opens airways and promote intra-bronchial mobilization of sputum. (Vargas et al., 2005).

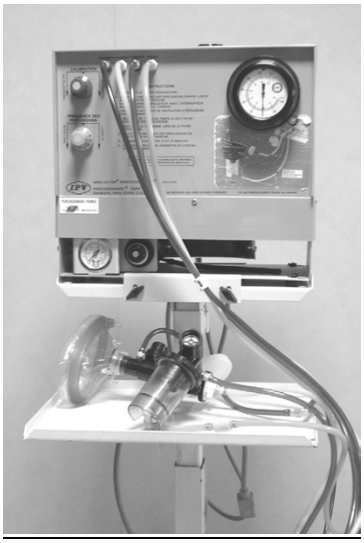

Figure 10. Intrapulmonary percussive ventilation IPV device (Percussionaire Corp., Sandpoint, ID, USA) with face mask (Vargas et al., 2005)

2.9.2.12. High frequency chest wall oscillation (HFCWO):

The high-frequency chest wall oscillation (HFCWO) is also one of ACTs. It is composed of an air-pulse generator that connect with inflatable vest that suits around the trunk of individual. The pulses air can be transferred to the vest with high frequency that generate oscillatory chest wall compressions. Nowadays, the most prescription of HFCWO instrument creates oscillations with a sine waveform. Lately, a new instrument was developed that generates oscillations with a triangular waveform. This amendment of the waveforms is assumed to produce higher improved mechanical shear forces that can be generated into airways to remove the secretions. (Kempainen, 2007)

Figure 11. Vest airway clearance system used to deliver high-frequency chest wall oscillations. Note the air compressor connected by tubing to the vest. (Darbee et al. 2005)

3. Methodology

The thesis is a literature review completely from relevant researches about the efficacy of airway clearance techniques on patient with Chronic Obstructive Pulmonary Disease. To make the thesis more valid and reliable, the recent research studies have been selected with experimental designs. The main measure in this literature review that all patients have the problem of COPD that cause accumulation of sputum in the airway, and then evaluate the effects of physiotherapy interventions to clear the airway based on lung function measurements, and quality of life measurement according to St. George's Respiratory Questionnaire, and then evaluate the differences of effects from each technique and assess the P-values from each article.

3.1. Literature research, study selection, and data extraction

The database has been searched broad range to identify published researches for patients with chronic obstructive pulmonary diseases. The articles have been chosen according to importance and related to the topic that can support this research and make it stronger.

The database that been searched to the issue from year 2000 until 2017 were:

- PubMed
- Medline
- PEDro
- CINAHL
- Cochrane
- Embase

3.2. Goals of thesis

- Identify the recent available physiotherapy practice of airway clearance techniques and the most frequent have been used.

- Analyze the efficacy of these techniques on patients with Chronic Obstructive Pulmonary Disease.
- Identify the most effective of these techniques on patients that can keep the airway clear longer with integrity of lung function and quality of life.

3.3. Research question

What is the effect of airway clearance techniques on patients with chronic obstructive pulmonary disease?

3.4. Inclusion criteria

- Patients with COPD and acute exacerbation COPD
- Airway Clearance techniques including postural drainage, percussion, vibration, huff and cough, abdominal thrust, active cycle breathing technique, positive expiratory pressure, and autogenic drainage
- Research studies are from all over the world
- Hospitalized patient whether in Intensive Care Unit, in wards, or as an outpatient
- Both genders
- No age restrictions
- Using pulmonary function tests: FEV_1, FVC, FEV_1/FVC ratio, TLC, RV, PEF, FEF, and ERV
- Quality of Life measurement according to St. George Respiratory Questionnaire
- Research studies that published from 2000 to 2017
- All articles in English version
- Combination of airway clearance techniques with breathing exercises.

3.5. Exclusion criteria

- Patients with cystic fibrosis
- Patients with pneumonia and pneumothorax
- Patients with heart failure or other cardiac pathologies
- Presence of history of thoracic or abdominal surgery
- COPD with respiratory failure or lung cancer
- Patients with asthma or bronchiectasis alone
- Patients with neurological pathologies
- Articles and journals had been established before the year of 2000
- Patients with hemodynamic instability

3.6. Key words

- Chronic Obstructive Pulmonary Disease
- Airway clearance techniques
- Chest physiotherapy
- Nonpharmacological management
- Respiratory care
- Pulmonary function tests
- Quality of Life measurement
- Positive expiratory pressure
- Mucus clearance

4. Results

A total of 117 articles were identified by searching on database of that were selected according to the title and establishment date at the beginning. According to full reviewing of each article, 23 articles were eligible depend on inclusion criteria, exclusion criteria, and outcome measures as a pulmonary function tests, and quality of life measurements according to St. George Respiratory questionnaire that are varied from author to another. The measurements that been found were FEV_1, FVC, FEV_1/FVC ratio, PEF, FEF, ERV, TLC, and RV. Quality of Life measurement has also found by using St. George's Respiratory Questionnaire. The SGRQ scores have been identified as symptoms, activity, impact, and total scores. The predicted patients' ages were ranged between 30 and 91 years old.

The range of published dates have been found between 2000 and 2017. The participants were hospitalized and as outpatients with total of all articles 1509 patients (male and female) whether that patients were in intervention group or control group. They were diagnosed by chronic obstructive pulmonary disease and exacerbation COPD or combined with other disease. They had been eligible for trial with evidence of sputum production. Thirteen of findings are designed by randomized control trial, randomized cross-over trail, randomizations into different groups, cross-sectional study, and as retrospective study. The types of therapy were variable. They used active cycle breathing technique, positive expiratory pressure, temporary positive expiratory pressure, oscillating positive expiratory pressure (flutter and RC-Cornet), slow expiration with the glottis opened in a lateral posture, postural drainage, vibration, and percussion.

The regions that the authors have performed their experiments were in Italy, Brazil, Unites States of America, India, Australia, Turkey, Taiwan, Lebanon, Canada, Pakistan, United Kingdom, and Germany. The selected patients of the studies were as inpatient and outpatient departments. The treatments have planned as long or short terms. The total duration studies ranged between 1 week and 6 months. Also, the pulmonary function tests and SGRQ have been selected as a primary or secondary outcome measures.

4.1. Pulmonary function measurements

The pulmonary function measurements, according to inclusion criteria, have found and done by different devices. The devices had been used in the selected studies were: standard spirometry 6200 Auto-box pulmonary function lab sensor medics, calibrated pneumotachograph, computerized spirometry, computerized body plethysmograph, vitalograph, spirometer EasyOne, simple spirometer, and even peak flow meter for PEFR. However Jahan, Kumar, and Ahmed (2015) and Osadnik et al. (2014a) didn't mention the type of pulmonary function measurement device.

4.1.1. Positive expiratory pressure (PEP)

Regarding to D'Abrosca et al. (2017), the results of FEV_1 and FVC depict statistical improvement after PEP technique in compare with the results before PEP ($P<0.001$ for both). However, FEV_1/FVC ratio showed no differences ($P>0.05$). The positive expiratory flow revealed $P<0.006$, but the $FEF_{25-75\%}$, $FEF_{50\%}$, and $FEF_{75\%}$ had no differences. In the article of Su et al. (2007), PEP and forced expiratory technique have been used together in one group and gave significant difference in FEV_1 and FVC in compare with baseline ($P<0.001$). The PEF and $FEF_{25-75\%}$ was also significant ($P<0.01$ and $P<0.05$ in respect). The other pulmonary function test didn't give any differences (FEV_1/FVC ratio, $FEF_{75\%}$, $FEF_{50\%}$, TLC, & RV). As Tout, Tayara, and Halimi (2013) explained that PEP has been used in combination with chest physiotherapy (which includes ELTGOL, diaphragmatic rehabilitation, lower limb training, psychological, and educational sessions) as a second group, and another group (the third) that combined PEP + CPT + IMT (inspiratory muscle training). The second and third group had no significance differences in FEV_1 and PEFR in comparison with pre-test pulmonary measurements ($P>0.05$ for both). Relating to Osadnik et al. (2014a), the FEV_1 wasn't improved ($P=0.941$). Also, Osadnik et al. (2014b), the FEV_1, FVC and FEV_1/FVC ratio, RV, and TLC depicted no differences in comparison with controlled experiment that used huff and cough techniques.

4.1.2. Temporary positive expiratory pressure (T-PEP)

According to D'Abrosca et al. (2017), FEV_1 and FVC showed significant difference in group that been used T-PEP in comparative with pre-test pulmonary measurement ($P<0.001$). Also, PEF had significance difference by $P<0.006$. The $FEF_{25-75\%}$, $FEF_{75\%}$ were no significant different because it was apart of the borderline ($P=0.05$, 0.046 in respect), $FEF_{50\%}$ ($P>0.05$). However, FEV_1/FVC ratio had not been significant change ($P>0.05$). Nikolini et al. (2017) stated no changes of FEV_1 with group that used TPEP (G1) in compare with OPEP (G2) and controlled (G3) group (G1 vs. G2 P= 0.18 in liters, P=0.22 in percentages), (G1 vs G3 P= 0.16 in liters, P=0.2 in percentages). In addition, FVC didn't change the results statistically (G1 vs G3 P= 0.2 in milliliter, P= 0.14 in percentages), (G1 vs. G2 P= 0.22 in milliliter, P= 0.24 in percentages). Also, FEV_1/FVC ratio was (G1 vs. G2 P=0.2), (G1 vs. G3 P= 0.24). Furthermore, the TLC had statistical differences in comparison with control group (P=0.02 in L and percentages), but there were no differences in comparison with OPEP (P=0.14 in L and 0.26 in percentage). In addition, RV did some statistical changes (G1 vs. G2 P= P=0.3 in L, and P= 0.18 in percentage), but in comparison with control group (P= 0.02 in both units).

In respect the study of Venturelli et al. (2012), the TPEP had been used for 78 with COPD and 20 with bronchiectasis patients. There were significant differences in FEV_1/FVC in 3rd and 10th day of treatment in comparison with controlled group ($P<0.05$ and $P<0.01$ respectively), and in FEV_1 in 10th day only ($P<0.05$). However, FVC didn't provide any noteworthy changes. The study of Mascardi et al. (2016) has also some statistical differences. The group that used T-PEP in the hospital result in crucial differences in comparison with control group in FEV_1, TLC, and RV ($P<0.0001$, $P<0.0001$, $P=0.02$ respectively), but the great changes in comparison with T-PEP at home was just in TLC ($P<0.0001$).

4.1.3. Oscillating positive expiratory pressure (O-PEP)

Gastaldi et al. (2015) clarified with no improvement in FEV_1, FVC, FEV_1/FVC ratio, PEF, TLC, & RV whether the group that been used the flutter or flutter with bronchodilator

in comparison with baseline on each group (P>0.05). According to Nicolini et al. (2017), the results have not changed in FEV_1 with group that used OPEP (G2) in comparison with TPEP (G1) and controlled (G3) group (G2 vs. G1 P= 0.18 [in L], P=0.22 [in %]), (G2 vs G3 P= 0.14 in L, P=0.8 in percentages). In addition, FVC didn't also change the results in statistics (G2 vs G1 P= 0.22 in milliliter, P= 0.24 in percentages), (G2 vs. G3 P= 0.18 in milliliter, P= 0.18 in percentages). Furthermore, FEV_1/FVC ratio was (G2 vs. G1 P=0.2), (G2 vs. G3 P= 0.26). In addition, TLC was made some changes G2 vs. G1 (P= 0.14 [L] and P= 0.26 [%]), but in comparison with control group (P= 0.02 [L], and P= 0.04 [%]). Furthermore, RV there were no significant differences in comparison with T-PEP in bother (L) and (%), (G2 vs. G1 P=0.3, P=0.18 respectively), but presents important differences in comparison with control group (P= 0.04 & 0.02 respectively). In respect of Cegla et al. (2001), the group that used RC-Cornet device made statistical differences in comparison with ipratropium bromide inhalation group (P<0.0161), but the residual volume didn't accomplish statistical differences (P<0.0555). According to Svenningsen et al. (2016), there was improvement in FVC on 14 COPD patients who were sputum producers in comparison with baseline (P= 0.01), but the FEV_1 and FEV_1/FVC did not produce any differences (P= 0.12 & 0.1 respectively).

In respect of Wolkove, Kamel, Rotaple, and Baltzan (2002), it has make the pulmonary function tests after the flutter immediately and after using the bronchodilator by 30, 60, and 120 minutes. There was slight improvement in FEV_1 after MCD in 11±24% (P<0.05), and significant difference after BD in all periods at baseline. In comparison with sham-MCD, no changes have been found until 120 min post bronchodilator which the MCD is greater in statistics 36±23% than sham-MCD 24±18% (P<0.05). About the FVC, there was statistical improvement after MCD immediately by mean 199±300 mL (P<0.05), but it did not make important changes in comparison with sham-MCD (65±300), (P= 0.33). And after bronchodilator, both group made significant improvement at baseline. However, there was no statistical improvement in comparison with after BD even after 120 minutes although the MCD is greater than sham-MCD (P=0.09). Furthermore, in the study of Wolkove et al. (2004), there was improvement in FVC at baseline after MCD and BD within 120 minutes to 2.22±0.63 L and after 1 week to 2.37±0.61L. the improvement has been found at baseline

and after 1 week in comparison with SMCD (P<0.05). Although there was improvement for both groups and pros of MCD are greater than SMCD, the advantages were the similar over 1 week of use for both time points. There was slight improvement in FEV_1 after using the MCD in comparison with SMCD. Also, there was significant differences in changes after using the bronchodilator within 30, 60, and 120 minutes at baseline, and after 1 week within 60 and 120 minutes (P<0.05 for all). At baseline and after using MCD with BD, the percentages of FEV_1 were reached to 60±28% (P<0.05), and after 1 week the FEV_1 reached to 43±20% (P<0.05). Although there is great improvement in MCS in comparison with sham-MCD, in one week measurement was slightly lower than the baseline. Regarding Jahan et al. (2015), the results of peak expiratory flow rate of using flutter groups in comparison with autogenic drainage and diaphragmatic breathing exercise by using ANOVA between group did not make any statistical changes (P-value for PEFR1PO= 0.383, PEFR2PO= 0.602, PEFR3PO= 0.664, PEFR4PO= 0.642, PEFR5PO= 0.731).

4.1.4. Slow expiration with glottis opened in lateral posture (ELTGOL)

Kodric et al. (2009) expressed a significant difference in FEV_1 in comparison with admission result (P= 0.001), but didn't make any changes in FEV_1/FVC (P=0.127) and even the result of FEV_1 and FEV_1/FVC ratio comparison with the controlled group (P=0.405 and 0.152 respectively). Tout et al. (2013) explained chest physiotherapy have been used (which includes ELTGOL, diaphragmatic rehabilitation, lower limb training, psychological, and educational sessions) with inspiratory muscle training as a first group in the study. There was significant difference in FEV_1 and PEF in comparison with pre-test pulmonary function results (P= 0.03 and 0.01 respectively). The study of Lanza, Alves, dos Santos, de Camargo, and Dal Corso (2015) has categorized the patients according to the severity of COPD and by recruiting thoracic and abdominal compression. However, there was no difference in results of ERV in mild, moderate, and severe (P= 0.34, 0.43, and 0.39 respectively).

4.1.5. Active cycle of breathing technique (ACBT)

The active cycle breathing technique has been used with Melam, Zakaria, Buragadda, Sharma, and Alghamdi (2012), it resulted in significant differences in FEV_1, FVC, and PEFR

in comparison with controlled group by using one-way ANOVA ($P<0.01$ for all). Savci, Ince, and Arikan (2000) explained that group of using ACBT group in the study had no changes of FEV_1 and PEF at baseline ($P>0.05$), some changes differences in PEF and FVC ($P<0.05$). In respect to the study of Basri, Tahir, and Naseem (2017), it was done by using independent T-test between ACBT and controlled group resulted in significant difference in PEF ($P<0.05$).

4.1.6. Other airway clearance techniques (ACTs)

In autogenic drainage technique, Melam et al. (2012) stated significant difference compared with controlled group in FEV_1, FVC, PEFR ($P<0.01$ for all parameters). Also, Savci et al. (2000) used AD and the result had some change differences in comparison with baseline for FEV_1, FVC, PEF, and FEF_{25-75} ($P<0.05$). In addition, the conventional huffing and coughing techniques have been recruited with Osadnik et al. (2014b) didn't change the differences wither in 8-week follow up and 6-month follow up results of FEV_1, FVC, FEV_1/FVC ratio, TLC, and RV in compare with positive expiratory pressure ($P>0.05$). As Singh, Khandelwal, Khandelwal, and Abusaria (2003) had made combination of walking, breathing exercise, and postural drainage, controlled coughing and changes in lifestyle activities did make any important changes the differences in FEV_1 and FEV_1/FVC statistically ($P>0.05$). Finally, Mahajan et al. (2011) did not reveal any statistical changes of FEV_1 after using high frequency chest wall oscillation in comparison with sham group ($P>0.05$).

4.2. Quality of Life measurement by St. George Respiratory Questionnaire

Cross et al. (2012) expressed no significant differences in results of symptom, activity, impact, and total scores in by using active cycle breathing technique in comparison with controlled group at six-month randomization ($P= 0.695, 0.836, 0.822, 0.753$ respectively). In the study of Deepak, Mohapatra, Janmeja, Sood, and Gupta (2014), the results have been taken before and after 3 months of using postural drainage, diaphragmatic breathing, pursed lip breathing exercise, and there were significant differences in all SGRQ scores at baseline ($P< 0.001$), and even in comparison with CTWPR ($P<0.05$). Kodric et al.

(2009) depicts that the expiration with the glottis open in lateral posture did not change the differences results of SGRQ on patients with acute exacerbation COPD in comparison with controlled group whether in 8-week and 6-month follow up (P= 0.961). According to Osadnik et al. (2014a), the positive expiratory pressure also did not make any changes in results in combination with physical exercises for 8 weeks, in comparison with 6 months follow up (P-value of symptom= 0.909, activity= 0.899, impact= 0.783, total= 0.871). Tout et al. (2013) demonstrated that all quality of life scores had been resulted important differences in all groups (G1: chest physiotherapy + inspiratory muscle training, G2: CPT+ PEP, G3: CPT+ PEP+ IMT, G4: controlled). Symptoms (P-value G1= 0.013, G2= 0.015, G3= 0.01), Activity (P-value G1= 0.014, G2= 0.009, G3= 0.01), impact (P-value of G1= 0.015), total (P-value of G1= 0.012, G2= 0.04, G3= 0.02) except the impact results of the G2 and G3 (P>0.05) without significant differences. According to Svenningsen et al. (2016), there was improvement in the total score of the questionnaire on sputum producer group in comparison before the treatment (P=0.01).

4.3. Tables of study finding contents

Table 4. Patients' characteristics of included studies, type of therapy, design of the study, and outcome measures

First Author, year	Condition	Number of Participants	Age in Years	Type of Therapy	Design	Outcome Measures
Basri R, 2017	AECOPD	60	45-60	ACBT	Double blind RCT	- PEFR -Breathlessness VAS - SaO_2
Cegla UH, 2001	COPD	35	65±10	RC-Cornet	Randomized crossover trial	- RV - VC - FEV_1
Cross J, 2012	COPD	372	34-91	ACBT	RCT	- QOL - BCSS
D'Abrosca F, 2017	COPD (60%) Bronchiectasis (40%)	162	35-89	- PEP - T-PEP	Retrospective study	- Spirometry - Arterial blood gas
Deepak TH, 2014	AECOPD	60	CTWPR: 59.4±6.7 PEPR: 58.4±6.8	CTWPR (30) PEPR (30)	RCT	- QOL - 6MWT
Gastaldi AC, 2015	COPD	15	67.3±9.1	Flutter (OPEP)	Randomized crossover trial	- Impulse oscillometry - Spirometer - FeNO - Cough and secretions
Jahan S, 2015	Moderate to severe COPD	30	40-60 - 56.7% (>50) - 43.3% (<50)	G1: Flutter G2: AD	Randomized into 2 groups	- PEFR - O_2 saturation - Respiratory rate - Pulse rate - Heart rate

Kordic K, 2009	COPD exacerbation	59	ETGOL: 71.3± 8.4 Control: 69.1±8.3	ELTGOL	RCT	- Spirometer - Arterial oxygen saturation - ABG - Dyspnea measurement: A- MRC scale B- Borg scale - QOL - Sputum weight
Lanza FC, 2015	COPD	32	30–70	ELTGOL	Randomized cross-sectional study	ERV
Mahajan AK, 2011	COPD (2/3) Asthma (1/3)	52	Active HFCWO: 46.5 [38.6, 52.8] Sham: 50.4 [43.9, 60.7]	HFCWO	Randomized, multicenter, double-masked phase II control trial	- Borg scale - Satisfaction questionnaire - Sputum production - FEV_1
Mascardi V, 2016	Severe COPD	99	71.1±5.7	TPEP	Parallel RCT	Respiratory measurements
Melam GR, 2012	Moderate COPD	30	40-60	- ACBT - AD	RCT	- FEV_1 - FVC - PEFR
Nicolini A, 2017	Severe COPD	104	- T-PEP (72.15±1.2) - O-PEP (70.67±2.1) - Controlled (71.13±1.9)	- T-PEP - O-PEP	RCT	- Number of exacerbations - Respiratory functional parameters
Osadnik CR, 2014a	AECOPD	90	Control: 67.8±11.6 PEP: 69.5±9.8	PEP+ physical exercises	Multicenter RCT	- SGRQ - Exercise tolerance - Cough and sputum - Airflow and dyspnea
Osadnik CR, 2014b	Moderate and stable COPD	12	66.1±8.6	- PEP mask -Huffing and coughing	Randomized crossover trial	- Sacin - Second - FRC, IC - RV, TLC - FEV_1
Savci S, 2000	Stable COPD	30	G1: 48-76 G2: 44-72	AD ACBT	Randomized into two groups	- Pulmonary function tests - Arterial blood gas - 6MWT - Modified Borg scale

Singh V, 2003	COPD	40	48-75	- Postural drainage controlled coughing and changes in life style activities - Walking - Breathing exercise	RCT	- 6MWT - FEV_1 - CRDQ
Su CL, 2007	COPD	37	G1:59.1±11.6 G2: 64.6±9.5	- PEP + FET - FET only	Prospective RCT	- Pulmonary functions - 6MWT - Subjective cough difficulty scores
Svenningsen S, 2016	COPD	14 (sputum producers) 13 (non-sputum producers)	40-85	OPEP	Randomized crossover trial	- SGRQ - 6MWT - PEQ - MRI - Pulmonary functions
Tout R, 2013	COPD	40	60.38±8.02	- Respiratory muscle training in inspiration and expiration - PEP threshold	RCT	- Spirometery - 6MWT - SGRQ - Respiratory pressure
Venturelli E, 2012	Stable COPD and bronchiectasis	COPD= 78 Bronchiectasis= 20	G1: 70.1±10.8 G2: 71.6±8.7	G1: T-PEP G2: controlled	Single blind multicenter RCT	- Arterial oxygenation index - Lung volumes - Respiratory muscle strength
Wolkove N, 2002	Severe COPD	23	71.7±6.3	MCD (Flutter) + bronchodilator	Randomized crossover trial	- Spirometery - 6MWT
Wolkove N, 2004	COPD	15	71±10	MCD (flutter) + bronchodilator	Randomized crossover trial	- FEV_1 - FVC - 6MWT

Table 5. Table (A) for the final results of pulmonary functions tests in experimental trials

First Author, year	Type of Therapy	FEV_1	FVC	FEV_1/FVC Ratio	PEF or PEFR	FEF	P-value
Basri R, 2017	G1: Controlled G2: ACBT	------	------	------	- PEFR G2= 1.38 L/sec - G2 (paired t-test) = -5.35±5.35 - PEFR between groups (group A and B) using the 95% CI = (1.53, -6.7, -25.65) respectively	------	- Paired t-test (ACBT) P= 0.02 - independent t-test (between 2 groups) P<0.05
D'Abrosca F, 2017	T-PEP	1.21±0.54 L/s 52.22±23.97%	2.18±0.66 L 73.73±21.93%	55.02±12.64	3.63±1.42 L/sec 54.45±20.25%	$FEF_{25-75\%}$= 22.22±17.31% FEF50= 21.39±18.94% FEF75= 23.75±17.28%	Pre vs. post: FEV_1 P<0.001 FVC (L): P<0.001 FVC (%): P= 0.015 PEF: P<0.006 FEV_1/FVC: P>0.05 compared to pre-test - TPEP vs. PEP: P>0.05 for all except: FEF_{25-75}: P=0.05 FEF_{50}: P=0.046
	PEP	1.27±0.52 L/s 58.41±24.10%	2.21±0.70 L 74.78±23.72%	58.54±15.33	3.88±2.59 L/sec 56.32±20.59 %	FEF_{25-75}= 30.80±25.73% FEF_{50}= 29.85±26.73% FEF_{75}= 31.95±26.33%	FEV_1 P<0.001 FVC (L): P<0.001 FVC (%): P= 0.015 PEF P<0.006 All FEF=NS FEV_1/FVC= NS
Gastaldi AC, 2015	G1: Flutter-sham G2: Flutter exercise G3: Flutter + BD	G2= 66.0±15.5% G3= 60.3±17.1%	G2= 107.3±18.1% G3= 102±118.0%	G2= 51.0±12.5 G3= 48.9±12.8	-------	------	No significant difference compared to baseline

Cegla UH, 2001	G1: RC-Cornet G2: Controlled	RC-Cornet= - 20 min. after 2nd stroke with Salbulair Autohaler= 1.24±0.43 L/s - 25 min. after inhalation of ipratropium bromide= 1.34±0.51 L/s	------	------	-------	------	G1 vs. G2: P<0.0161
Jahan S, 2015	G1: Flutter G2: AD + diaphragmatic breathing exercise+ huffing/blowing nose	------	------	------	By ANOVA Between group: - PEFR1PO: G1=142.00±21.778 G2=155.00±52.474 - PEFR2PO G1=148.67±29.244 G2=156.67±50.943 - PEFR3PO G1=154.00±29.952 G2=161.33±57.305 - PEFR4PO G1=156.67±21.269 G2=163.33±50.662 - PEFR5PO G1=166.67±38.110 G2=172.67±54.963	------	Between group analysis in respect: P= 0.383, 0.602, 0.664, 0.642, 0.731 Within group analysis: G1: - PEFR1PR and PEFR5PR P= 0.0001 - PEFR1PO and PEFR5PO P=0.001 G2: - PEFR1PR and PEFR5PR P= 0.0001 - PEFR1PO and PEFR5PO P=0.001
Kodric M, 2009	G1: Controlled G2: ELTGOL	ELTGOL= 64.4±34.0 %	------	ELTGOL= 52.9±14.6	------	------	To baseline: FEV_1 P=0.001 FEV_1/FVC P= 0.127 G1 vs. G2 FEV_1 P= 0.405 FEV_1/FVC P=0.152
Mahajan AK, 2011	G1: Active HFCWO G2: Sham HFCWO	Active HFCWO: - Median= 0% - Interquartile range= [-2, 8%]	------	------	------	------	Comparison between 2 groups P > 0.05

Mascardi V, 2016	G1: Hospital TPEP G2: Home TPEP G3: Controlled	By median (95% CI) G1= 7.5 (6; 9) % G2= 7.2 (5.7; 8.6) %	By median (95%CI) G1=13.3 (10.5;16.2) % G2= 9.2 (6.5;12) %	------	------	------	FEV_1: G1 vs. G2: P= 0.8 G1 vs. G3: P<0.0001 G2 vs. G3: P<0.0001 FVC: G1 vs. G2: P= 0.04 G1 vs. G3: P<0.0001 G2 vs. G3: P<0.0001
Melam GR, 2012	G1: AD G2: ACBT G3: Controlled	One-way ANOVA Between: SS= 0.48445 Df= 2 MS= 0.2422 F= 1149.4 Fcritical= 3.3541 Within: SS= 0.00569 Df= 27 MS= 0.0002	By One-way ANOVA Between: SS= 0.44426 Df=2 MS= 0.2221 F= 996.26 F critical= 3.3541 Within: SS=0.00602 Df=27 MS= 0.0002	------	By One-way ANOVA Between group: SS= 0.90669 Df= 2 MS= 0.4533 F= 1072.5 F critical= 3.3541 Within group: SS= 0.0047 Df= 27 MS= 0.0002	------	FEV_1, FVC, and PEFR P<0.01 for G1 and G2 compared to G3
Nicolini A, 2017	G1: TPEP G2: OPEP G3: Controlled	G1: Δ= 163±113 L Δ= 7.3±4.6 % G2: Δ= 184±154 L Δ= 7.4±6.6 %	TPEP: Δ= 499±389mL Δ= 15.3±11.5% OPEP: Δ=417±365mL Δ= 11.5±9.0 %	TPEP= 4.169.8 OPEP= 1.968.5	------	------	ANCOVA p-value: FVC G1 vs. G3: (in mL) = 0.20 (in %)= 0.14 FVC G2 vs. G3: 0 .18 (mL) 0.18 (%) FVC G1 vs. G2 (in mL) = 0.22 (in %)= 0.24 FEV_1 G1vs. G3: (in L) = 0.16 (in %)= 0.20 FEV_1 G2 vs. G3: (in L) = 0.14 (in %)= 0.18 FEV_1 G1 vs. G2: (in L) = 0.18 (in %)= 0.22

							FEV_1/FVC: G1vs. G3= 0.24 G2 vs. G3= 0.26 G1 vs. G2= 0.20
Osadnik CR, 2014a	G1: PEP G2: Controlled	- Discharged (PEP)= 35.6±1.4% - 8-week follow-up= 36.5±1.6% - 6-month follow-up= 36.4±1.9%	------	------	------	------	G1 vs. G2 (interaction effect) P= 0.941
Osadnik CR, 2014b	T1: Baseline G1: PEP G2: Controlled (huff and cough) G2 & G3 crossed over	PEP: T2= 1.35 L T3= 1.30 L Control: T2= 1.37 L T3= 1.32 L	PEP: T2= 3.53L T3= 3.49L Control: T2= 3.56L T3= 3.53L	PEP: T2= 0.38 T3= 0.38 Control: T2= 3.64 T3= 0.37	------	------	No significant differences between 2 groups
Savci S, 2000	G1: AD G2: ACBT	G1= 51±18 % G2= 44±17 %	G1= 75±16% G2= 70±25%	------	G1= 69±16% G2= 54±17%	(G1) 25-75%= 27±15 % (G1) 75-85%= 49±18 % (G2) 25-75%= 22±11 % (G2) 75-85%= 43-51 %	G1: FVC, FEV_1, PEF, $FEF_{25-75\%}$ (P<0.05) G2: FVC & PEF: P<0.05 FEV_1 & FEF: P>0.05 All compared to baseline
Singh V, 2003	G1: Walking, breathing exercise, postural drainage, controlled coughing, and changes in life style activities G2: Controlled	29.1 ± 10.4%	------	48±10.4 %	------	------	The difference was not significant statistically pre and post treatment
Su CL, 2007	G1: PEP+FET G2: FET	G1= 1.4±0.6L G2= 1.2±0.4L	G1= 2.4±0.9L G2= 2.1±0.6L	------	G1= 4.1±1.5 L/sec G2= 3.8±1.3 L/sec	(G1) 25–75%= 0.8±0.4 L/sec (G2) 25–75%= 0.7±0.3 L/sec	G1: FVC+FEV_1 P<0.001 FEF P<.05 PEF P<0.01 G2: FVC P<0.05

Svenningsen S, 2016	G1: OPEP for sputum producers G2: OPEP for non-sputum producers	OPEP for Sputum producers= 59±20%	OPEP for Sputum producers= 87±21%	OPEP for Sputum producers= 51±9	-------	-------	Pre. vs. post. FEV_1: P=0.12 FVC: P=0.01 FEV_1/FVC ratio: P= 0.1
Tout R, 2013	G1: CPT + IMT G2: CPT + PEP G3: CPT + PEP + IMT G4: CPT (controlled) CPT= ELTGOL + diaphragmatic rehabilitation + lower limb training + psychological and educational sessions	G1= 1.44±0.57 L G2= 0.04±0.36 L G3= 1.06±0.47 L	------	------	G1= 0.76±0.16 L/sec G2= 1.25±0.56 L/sec G3= 1.44±0.65 L/sec	------	FEV_1: G1: P=0.03 G2: P> 0.05 G3: P> 0.05 PEF: G1: P=0.01 G2: P> 0.05 G3: P > 0.05
Vetrurelli E, 2012	G1: T-PEP G2: Controlled	T-PEP: day 3= 61.2 ± 29.1% day 10= 64.9 ± 27.0%	T-PEP: Day 3= 81.9±24.1% Day 10= 84.1±24.4%	T-PEP: Day 3= 44.0±13.4% Day 10= 53.7±16.6%	------	------	G1 vs G2 FEV_1: Day 3: NS Day 10: P<0.05 FVC: Day 3 and 10: NS FEV_1/FVC: Day3: P<0.05 Day 10: P<0.01
Wolkove N, 2002	G1: MCD (flutter) G2: Sham MCD	Flutter after 120 min after BD= 45±22%	Flutter after 120 min= 44±47%	------	------	------	FEV_1 P < 0.05 compared to baseline and sham group FVC P= 0.09 compared to sham after 120 min
Wolkove N, 2004	G1: Flutter G2: Controlled	At baseline: flutter after 120 min= 60±28% After 1 week: flutter after 120 min= 43±26%	At baseline: flutter after 120 min= 2.22±0.63L After 1 week: flutter after 120 min= 2.37±0.61L	------	------	------	FEV_1 and FVC at baseline and after 1 week: P<0.05 G1 vs. G2 at baseline and after 1 week P<0.05

Table 6. Table (B) for the final results of pulmonary functions in experimental trials

First author	Type of Therapy	TLC	RV	ERV	P-value
Cegla UH, 2001	G1: RC-Cornet G2: controlled	------	RC-Cornet: - 20 min. after 2nd stroke with Salbulair Autohaler= 3.98±0.98 L - 25 min after inhalation of ipratropium bromide= 3.9±1.01 L	------	G1 vs. G2: P<0.0555
Lanza FC, 2015	G1: ELTGOL by PT1 G2: ELTGOL by PT2 G3: ELTGOL by subject	------	------	One-way ANOVA PT1: Mild: 65.7±25.4% Moderate: 48.5±24.0% Severe: 47.7±24.1% PT2: Mild: 73.1±38.4% Moderate: 53.1±30.5% Severe: 41.0±24.2% Subject: Mild: 64.5±20.2% Moderate: 57.9±31.9% Severe: 44.3±25.4%	All Mild P= 0.34 All Moderate P= 0.43 All Severe P= 0.39
Mascardi V, 2016	G1: Hospital TPEP G2: Home TPEP G3: Control	Median (95% CI) G1: −14.1 (−18; −10.1) % G2: −13 (−16.9; −9.1) %	Median (95% CI) G1: −30 (−51.7; −8.3) % G2: −19.2 (−40.6; 2.2) %	------	TLC: G1 vs. G2: P= 0.7 G1 vs. G3: P<0.0001 G2 vs. G3: P<0.0001 RV: G1 vs. G2: P= 0.5 G1 vs. G3: P= 0.02 G2 vs. G3: P=0.09

Nicolini A, 2017	G1: TPEP G2: OPEP G3: Controlled	G1: Δ: -949±1193 L Δ: -13.9±16.2 % G2: Δ: -831±1172 L Δ: -13.6±17.5 %	G1: Δ: - 1020±976 L Δ: - 32.2±25.4 % G2: Δ: - 1207±1208 L Δ: - 30.4±108.5 %	------	TLC (L): G1 vs. G2: P= 0.14 G1 vs. G3: P= 0.02 G2 vs. G3: P= 0.02 TLC (%): G1 vs. G2: P= 0.26 G1 vs. G3: P= 0.02 G2 vs. G3: P= 0.04 RV (L): G1 vs. G2: P= 0.3 G1 vs. G3: P= 0.02 G2 vs. G3: P= 0.04 RV (%): G1 vs. G2: P= 0.18 G1 vs. G3: P= 0.02 G2 vs. G3: P= 0.02
Osadnik CR, 2014b	T1: Baseline G1: PEP G2: Controlled (huff and cough) G2 &G3 crossed over	PEP: T2= 7.55 T3= 7.63 Controlled: T2= 7.63 T3= 7.59	PEP: T2= 3.74 T3= 3.84 Controlled: T2= 3.76 T3= 3.75	------	No significant differences
Su CL, 2007	G1: PEP+FET G2: FET	G1: 6.3 ± 1.0 L G2: 5.7 ± 1.2 L	G1: 3.8 ± 1.0 L G2: 3.3 ± 0.9 L	------	G1 & G2: P>0.05

Table 7. The final results of Quality of Life measurement according to SGRQ on experimental trials

First author, year	Type of therapy	Symptom score	Activity score	Impact score	Total score	P-value
Cross J, 2012	ACBT	68.38 ± 23.13	82.49 ± 18.81	51.53 ± 22.58	63.88 ± 19.05	Symptom P= 0.695 Activity P= 0.836 Impact P=0.822 Total P= 0.753 (Adjusted analysis no MCP vs. MCP)
Deepak TH, 2014	G1: Postural drainage, diaphragmatic breathing, pursed lip breathing G2: Controlled	51.51±15.28	56.15±15.75	25.36±13.67	39.04±12.91	Pre vs. post (G1): P<0.001 PEPR vs. CTWPR: P<0.05
Kodric M, 2009	G1: controlled G2: ELTGOL	------	------	------	ELTGOL= 54.7 ± 17.7	G1 vs. G2: P= 0.961
Osadnik CR, 2014a	PEP + physical exercise A: 8-week follow up B: 6-month follow up	A= 55.8±3.4 B= 58.4±3.4	A= 46.9±3.6 B= 45.5±3.6	A= 34.2±2.6 B= 34.9±2.6	A= 41.6±2.6 B= 42.1±2.6	A vs. B Symptom P=0.909 Activity P=0.899 Impact P=0.783 Total P=0.872
Svenningsen S, 2016	G1: OPEP (sputum producers) G2: OPEP (non-sputum producers)	-------	--------	-------	G1: 40±12	Pre. vs. post P=0.01
Tout R, 2013	G1: CPT + IMT G2: CPT + PEP G3: CPT + PEP + IMT G4: CPT (controlled) CPT= ELTGOL + diaphragmatic rehabilitation + lower limb training + psychological and educational sessions	G1= 31.23±7.93 G2= 31.67±8.16 G3= 34.16±8.5	G1= 17.11±2.45 G2= 16.98±2.27 G3= 17.18±2.43	G1= 31.23±8.16 G2= 34.65±8.12 G3= 28.14±8.5	G1= 25.92±6.12 G2= 29.34±7.35 G3= 27.19±5.4	(Pre vs. post) Symptom: G1 P= 0.013 G2 P= 0.015 G3 P= 0.01 Activity: G1 P= 0.014 G2 P= 0.009 G3 P= 0.01 Impact: G1 P= 0.015 G2 P≥ 0.05 G3 P≥ 0.05 Total: G1 P= 0.012 G2 P= 0.04 G3 P= 0.02

5. Discussion

There is poor evidence for the effectiveness of airway clearance technique on patients with chronic obstructive pulmonary disease. Although there are varied techniques in the recent studies which established in the year of 2000 until 2017, the twenty-one of findings that used different techniques for COPD had used pulmonary function tests FEV_1, FVC, FEV_1/FVC ratio, PEF, FEF, ERV, TLC, and RV, and 6 used St. George Respiratory Questionnaire as a health-related quality of life measurement (4 of the total had been used both outcome measures). All pulmonary function parameters and SGRQ results in tables have been recorded after treatment session/sessions depends on each article's data.

5.1. Discussion of airway clearance techniques

The explanation of airway clearance techniques has been different because some of them used a single technique in one group and others combined more than one technique or medical treatment on the same group. Singh et al. (2003) combined walking, breathing exercise, postural drainage, controlled coughing, and alteration in the activity of lifestyle together in comparison with controlled group although there was improvement in quality of life by using chronic respiratory disease questionnaire (in respect $P>0.05$, $P<0.001$). Su et al. (2007) mixed positive expiratory pressure with forced expiratory technique group and resulted in significant differences in FVC and FEV_1 ($P<0.001$), FEF ($P<0.05$), and PEF ($P<0.01$) after comparison with baseline. Also, Tout et al. (2013) has complex 4 groups. First group has been treated with chest physiotherapy (that includes ELTGOL+ diaphragmatic breathing exercise + lower limb training + psychological and educational sessions) with inspiratory muscle training. The second group with CPT + PEP, and third with CPT+ PEP+ IMT. There were only significant differences in FEV_1 and PEFR with first group and in quality of life for all experimental groups. In study of Jahan et al. (2015), the mixture was the autogenic drainage with diaphragmatic breathing exercise and huffing/blowing nose as one group, but they didn't make important changes in comparison with flutter group. Furthermore, Gastaldi et al. (2015) combined flutter with bronchodilator in his third group

of treatments, but there was no significance improvement in comparison to the baseline. The conventional physical therapy techniques were historical to combine with other technique (Van Der Schan, 2007). Venturelli et al. (2012) illustrated that temporary 15 minutes of positive expiratory pressure has been used with 20 minutes' cycles of manually assisted breathing techniques that includes ELTGOL and forced expiration each day.

In respect of using the ACTs with bronchodilator, Wolkove et al. (2002) has been make the pulmonary function tests after the flutter immediately and after using the bronchodilator by 30, 60, and 120 minutes. There was slight improvement in FEV_1 after MCD ($P<0.05$), and significant difference after BD in all intervals at baseline. However, no significant changes have been found in comparison with sham-MCD until 120 min post bronchodilator which the MCD is greater in statistics 36±23% than sham-MCD 24±18% ($P<0.05$). About the FVC, there was statistical improvement after MCD immediately by mean 199±300 mL ($P<0.05$), but it did not make important changes in comparison with sham-MCD ($P= 0.33$). And after bronchodilator, both group had important improvement at baseline. However, there was no statistical improvement in comparison with after BD even after 120 minutes although the MCD is greater than sham-MCD ($P=0.09$). In crossover study of Wolkove et al. (2004), there was improvement in FVC at baseline after MCD and BD within 120 minutes to 2.22±0.63 L and after 1 week to 2.37±0.61L. the improvement has been found at baseline and after 1 week in comparison with SMCD ($P<0.05$). Although there was improvement for both groups and pros of MCD are greater than SMCD, the advantages were the similar over 1 week of use for both time points. There was slight improvement in FEV_1 after using the MCD in comparison with SMCD. Also, there was significant differences in changes after using the bronchodilator within 30, 60, and 120 minutes at baseline, and after 1 week within 60 and 120 minutes ($P<0.05$ for all). At baseline and after using MCD with BD, the percentages of FEV_1 were reached to 60±28% ($P<0.05$), and after 1 week the FEV_1 reached to 43±20% ($P<0.05$). Although there is great improvement in MCS in comparison with sham-MCD, in one week measurement was slightly lower than what was at baseline. In contrast, the volume results of improvement were similar for both times of measurement. Therefore, the pros of MCD use over sham MCD use was preserved during one week of use, but there was no additional advantage, as measured the FVC in using in

one week at home. The quality of the latest evidence was low in evaluation the techniques effectiveness according to Cochrane reviews: some RCTs have been given and the longest period of treatment was 3 months. (Wong et al., 2018)

5.2. Discussion of pulmonary function parameters

Another limitation has been found is that the authors did not use all the aforementioned parameters of pulmonary function. Also, the results of the pulmonary functions were different in enumeration; Lanza et al. (2015); Melam et al. (2012); and Jahan et al. (2015) used one-way ANOVA statistical analysis, Mahajan et al. (2011) explained the results according to median and interquartile range for FEV_1, Nicolini et al. (2017) demonstrated the results by accumulation together and presents the probability values according to ANCOVA. Basri et al. (2017) expressed the values of PEFR after active cycle breathing techniques by using paired t-test and 95% confidence interval ($P= 0.02$), and even used independent t-test in comparison with controlled medical treatment group ($P<0.05$). In addition, the other authors revealed the results of pulmonary function tests in liters or predicted percentages by mean and standard deviation. These may affect the comparison of the effectiveness of techniques on COPD patients because the differences of recitation results.

5.3. Discussion of smoking history

Regarding to smoking history, Tout et al. (2013) explained that 20% of experimental patients have already stopped smoking for around 6 months, 70% still in smoking during the study, but 8% were non-smokers. Wolkove et al. (2004) expressed that all patients with severe chronic obstructive pulmonary disease were smoker previously except one patient who was smoking during the study. In 162 patients of experimental study of D'Abrosca et al. (2017), 20% were current smokers, and 47%of them were former smoker, but 53% of those patients had never smoked. Gastaldi et al. (2015) illustrates that all COPD patient in his study had a history of smoking with mean 27.6±6.7 pack/years. In addition, ten of stable

and moderate COPD patients in Osadnik et al. (2014b) study had been former smoker and two had smoking during study by mean 67.4±60.9 pack/years. Savci et al. (2000) explained that the patients who received autogenic drainage technique had smoked 38.9±17.3 packs per year and the other group who received ACBT had smoked 35.9±24.7 packs each year. Singh et al. (2003) did not reveal the details about history, but the methodology and criteria included all patients who had given up the smoking for at least 2 months prior to study. The case and controlled group of Deepak et al. (2014) study had history of smoking cigarettes by mean 43.1 and 33.9 pack per year respectively. Venturelli et al. (2012) revealed that 28 patients of COPD and bronchiectasis had sill in smoking, 34 patients had been smoker and stopped, and 36 had never smoked. Cegla et al. (2001) mentioned that all selected patients were not-smokers in the last 5 years. Regarding Svenningsen et al. (2016), the group of sputum producers had a history of smoking around 59±34 pack per year. However, there were no mentions of smoking history in all of rest studies (12). Therefore, the history of smoking and even currently can make effect on the pulmonary function and quality of life results specially the patients who are still using cigarette even throughout the study. In study of Allinson et al. (2016), it illustrates that the representation of the beginning phase of COPD development is related with chronic mucus hypersecretion CMH in smokers in the middle age (between 36 and 43 years old) from 7.6±2.0% to 13.0±62.6%. The study also explained that the longer the CMH has been present, the increasing of FEV_1 declining.

5.4. Discussion of COPD severity

The severity of COPD and combination with other diagnosis in studies were varied because there were differences in selecting patients in each article. Four of studies have selected acute exacerbation COPD patients (Deepak et al., 2014; Osadnik et al., 2014a; Basri et al., 2017; Kodric et al., 2009). Two articles had severe COPD (Nicolini et al., 2017; Wolkove et al., 2002), one had selected moderate to severe (Jahan et al., 2015), and 1 moderate cases (Melam et al., 2012). One study has selected COPD 60% and 40% bronchiectasis (D'Abrosca et al., 2017). Other selected 1/3 with COPD and 2/3 with asthma (Mahajan et al., 2011). Venturelli et al. (2012) has selected 78 stable COPD and 20 bronchiectasis patients for active and controlled groups. However, the other authors selected

COPD without mentioning the severity. Therefore, the variation of severity and with other diagnosis may change on the effectiveness of airway clearance techniques and statistical analysis with probability value.

5.5. Discussion of St. George Respiratory Questionnaire

Regarding the health-related quality of life measurement by using St. George Respiratory Questionnaire, it has been selected to be concerned with health status in patients with COPD. There was lack of evidence in respect with using ACTs. In national survey of Jingar et al. (2013), around the India and out of 800 questionnaires, 85% of 342 of experienced cardiopulmonary physiotherapists assigned that they have used conventional airway clearance techniques and reducing dyspnea as a management of patients with COPD in inpatients wards and in intensive care units. Also, 83% of them had given physical exercises for upper and lower limbs. However, there was a slight solicitude in respect with health-related quality of life. Many of studies have been used the SGRQ in respect to management of dyspnea in COPD patients by using breathing exercises. In double-blind RCT of Borge et al. (2015) of using guided deep breathing exercise on COPD for four weeks as a double-blind RCT. Although there was statistical significant difference on symptom scores within group after using guided deep breathing in comparison with baseline, but there were no changes in other scores, there was no changes between-group in comparison with MLG and SSG. With regard the systematic review of Jones and Rowe,(2000) of bronchopulmonary physical therapy for patients with bronchiectasis and COPD, the study couldn't be conclusive because there was poor of evidence with low level quality, and it needs more excremental studies.

5.6. Discussion of risk of bias

In the review of Osadnik et al. (2012), it demonstrated that there is some risk of bias in the included studies: In the study of Kodric et al. (2009), there was high risk of bias by no information of blinding in detection and performance that can impact on FEV_1, FEV_1/FVC,

and SGRQ, and unclear risk of bias due to vague in the complete comparisons, in all participants, at baseline in all parameters. In respect to Wolkove et al. (2002), there is unclear selection bias of allocation concealment, even in attrition bias because of no explicitly states of the results of outcomes, but the risk is higher in blinding of patients and the treatment provider because there is no data. However, there is low risk of reporting bias due to reporting of all outcomes data. In other study of Wolkove et al. (2004), there is a vague of random sequence generation as an unclear selection bias. In addition, there is no information of blinding whether of patients and personnel nor the assessment of outcome. Finally, there are other potential bias in the finding studies that need more and wide investigations in future researches. In respect of Cegla et al. (2001), the selection bias was unclear due to insufficient information provided, the performance detection bias had high risk of bias because of no data provided. However, the attrition and reporting bias were in low risk of bias because of complete of all outcome reports.

5.7. Discussion of some relevant studies

Regarding the techniques of airway clearance, there were other studies that were not eligible according to inclusion and exclusion criteria and to make the review more clarified. Van der Schans (2016) demonstrates that the directed coughing technique as a conventional CPT was the most effective after reviewing the conventional techniques on patients with COPD or cystic fibrosis. In respect of the Australian survey study of Osadnik et al. (2013) on experienced physiotherapists who did ACT on patient with AECOPD, it expressed that the most techniques have been used between 189 therapists were forced expiratory technique by 81 percent, physical exercises by 89 percent, and active cycle of breathing technique by 79 percent. The non-invasive ventilation, singing and chest stroking, and mechanical vibration were not prescribed on their patients. The almost duration of application the treatment ranged from 5 to 20 minutes. In study of Martins, de Andrade, Britto, Lara, and Parreira (2012), there was using ELTGOL on patients with chronic bronchitis with most of them had mild to moderate COPD. There was significant airway clearance specially in the peripheral parts in lungs by observing scintigraphy images ($P<0.05$). Regarding to Vargas et al. (2005), the intrapulmonary percussive ventilation had been recruited twice a day in 16

patients with AECOPD with period of 3±1 days. In physiological parameters, there were statistical improvement in PaO2, PaCO2, and respiratory rate ($P<0.05$) with no changes in arterial pH. Also, there were increasing of exacerbations in 6 out of 17 of controlled subjects in comparison with zero complaining in IPV group. Furthermore, Morsch, Amorim, Barbieri, Santoro, and Fernandes (2008) showed the impact of oscillating positive expiratory pressure on patients with 10 who had COPD and 16 asthmatic patients. There were significant differences in excremental group for sputum sample weight and total cell counts in COPD patients ($P= 0.41$ by student t-test), total cell count ($P= 0.02$ by Mann-Whitney test), and cell viability ($P= 0.23$ by Mann-Whitney test). In respect of Cegla et al. (2002), the group that used RC-Cornet device didn't produce statistical differences in VC and FEV_1 after 2 years of treatment, and there was significant difference in medication group in comparison with RC-Cornet in vital capacity, but Osadnik et al. (2012) illustrated the presence of bias because there was a vague of the reason of excluding 3 patients randomly from the study to make the groups even in numbers, and there is no sufficient information for the participants nor outcome measures that may affect the FEV_1 and VC.

In respect to Bellone, Lascioli, Raschi, Guzzi, and Adone (2000) depicts the comparisons between the flutter, ELTGOL, and postural drainage on 10 male patients with chronic bronchitis. Although there is important increase in sputum production in all patients in all techniques ($P<0.01$ for all), there were no significance differences in FEV_1 and SO_2. In the pilot of randomized control crossover of Narayanan et al. (2014) study on 20 patients with COPD and bronchiectasis ($n= 8$ and 12 respectively), conventional chest physiotherapy percussion and mechanical percussion have been used into two groups and crossed over. There was high increasing of dry and wet sputum elicitation after using CCPT in comparison with MP (in dry sputum $P= 0.002$, and wet sputum $P<0.001$). However, Van der Schans (2017) illustrates that the considerable problem is not the quantity of sputum being expectorated, but the amount of secretions not removed and kept in the airways. The volume of expectorated secretion may not be a reliable outcome measure, because pulmonary secretions may be swallowed by the patient, and those that are expectorated also slobber.

In the systematic review of Tang, Taylor, and Blackstock (2010), it concluded that PEP and IPPV can raise expectoration of sputum for hospitalized patients with AECOPD, proposing that the therapists should consider utilizing the physiotherapy techniques with patients manifesting a high expectoration of sputum or hardness of sputum expectoration, instead of routine treatment for all patients. There was moderate evidence that the submitting of a walking program is helpful and that chest physiotherapy techniques other than percussion are safe to manage this condition. Furthermore, there was moderate evidence that percussion is not beneficial for patients, and it should be excluded from the part of the therapy. Wong et al. (2018) revealed that the present international guidelines advise ACTs as part of routine treatment for even bronchiectasis patients.

6. Conclusion

The objective of this study was to expose and evaluate the efficacy of airway clearance techniques on patients with Chronic Obstructive Pulmonary Disease by using pulmonary functions and Quality of Life measurements from recent studies. The results of the parameters have been compared with statistical P-values.

With respect the research question that to identify the effectiveness of airway clearance techniques on patients with chronic obstructive pulmonary disease, the availability of experimental studies is still poor. Although using the positive expiratory pressure and its modifications, that are oscillating PEP and temporary PEP, have been the frequent techniques from the recent studies, not all confirms that can give statistical and crucial improvement.

Due to the importance of airway clearance techniques, I recommend more researches for techniques in combination with cautious breathing exercises to exhibit positive adverse events of pulmonary functions, improve quality of life according to St. George Respiratory Questionnaire, and provide high level quality evidence of techniques with long term goal of effect. The combination can increase the management effect of removing sputum and decrease or manage the breathlessness of patients with Chronic Obstructive Pulmonary Disease.

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