IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Emerging Diagnostic Tools And Techniques For Chronic Obstructive Pulmonary Disease (COPD)

[1] Prathamesh A. Dabadghav, [2] Nakul W. Palkhade, [3]Om S. Kale, [4] Kunal D. Sharma , [5] Hariom G. Bonde.

[1]Student , [2]Student , [3]Student,[4]Student,[5]Student

[1] Bachelor of pharmacy

[1] Rajarshi Shahu College of pharmacy Buldhana, India,

[2] Bachelor of pharmacy,

[2] Shri Sant Gajanan Maharaj College of Pharmacy, Sagwan Buldhana, India,

[3] Bachelor of pharmacy,

[3] Dr. Rajendra Gode College of Pharmacy, Amravati, India,

[4] Bachelor of pharmacy,

[4] Laddhad College of Pharmacy, Yelgaon, Buldhana, India,

[5] Bachelor of pharmacy,

[5] Dr. Rajendra Gode Institute of Pharmacy, Amravati,India.

Abstract: COPD is a long-term respiratory disease characterized by airway limitations and reduced air-volume change, mainly due to emphysema and acute exacerbation. These exacerbations increase oxidative stress and inflammation in the lungs, and causes continuous deterioration of the lung functions. COPD depends on certain factors such as; age, environmental factors, genetics and presence of other diseases including asthma. Thus, the timely diagnose of COPD is an essential step to successful management and treatment. This review's aim is to describe the existing approaches, including traditional spirometry, and novel techniques including forced oscillometry, phase contrast imaging, and electrical impedance tomography. Spirometry is still the reference technique in the evaluation and staging of COPD, however, it has weak points especially when it comes to the identification and follow – up of the milder cases. Some of the new imaging methods include X-ray phase contrast imaging and electrical impedance tomography which, may allow lung function assessment in real time or more detailed regional analysis.It is important to present new developments in the diagnostics following COPD with stressing the role of new technologies for overcoming existing difficulties. Such advancements seeks to strengthening early detection, specific treatment approaches, and by extension, patients' quality of life by addressing issues with standard diagnostic practices.

Index Terms **- Chronic Obstructive Pulmonary Disease (COPD), Acute exacerbations (AE-COPD), Respiratory dysfunctions, Emphysema, Alpha-1 antitrypsin deficiency (AATD).**

I. INTRODUCTION

The hallmarks of chronic obstructive pulmonary disease (COPD) include airway blockage and restricted airflow, which are brought on by damage to the alveoli (emphysema) and made worse by recurrent infections or acute exacerbations (AE-COPD). AE-COPD increases innate reactions to oxidative stress and inflammation that compromise airway healing and protection mechanisms, which cause the lung function to gradually deteriorate [1]. In short, inflammation of the airway (bronchitis), which is affected by factors such as age, the environment, and/or Emphysema progression and COPD pathogenesis are initiated by genetic risk factors. There are COPD patients with different severity levels that are under the Global Initiative for Chronic Stages of Obstructive Lung Disease (GOLD) according to the severity of lung impairment of function [2].

Exposure is the main risk factor for the pathophysiology of COPD. to toxic gasses or particles, like those in biomass or cigarette smoke. Consequently, It is well established that smokers develop respiratory dysfunctions associated with COPD, restricted airflow and a greater death rate [3]. In the same way, dangerous chemicals, dusts, and air ,The amount of environmental contaminants or biomass smoke has also been seen to rise inflammation of the airways [4], from which emphysema might develop if exposed repeatedly. Comorbidities can further hasten the pathophysiology of COPD. For instance, It was discovered that people with a history of asthma had a 10-to 30-fold higher chance of acquiring COPD [5]. Additionally, genetic variables like alpha-1 antitrypsin deficiency (AATD), discovered in about 5% of those with COPD are at risk of developing emphysema. In summary, the liver is the primary organ that produces alpha-1 antitrypsin, a serine protease inhibitor to shield organs from harm brought on by infection and the ensuing inflammation, where the lack of AAT and/or the participants' history of recurrent respiratory exacerbations in causes underlying inflammation to destroy lung tissue, which results in COPD and emphysema pathophysiology [6]. It's interesting to observe that none of the AATD subjects acquire COPD. Emphasizing the need for a trigger, such as illness, first- or second-hand smoking, additional inflammatory/toxic substances, etc. Furthermore, while researching COPD from an epi The Boston Early-Onset COPD study showed, from a demiological standpoint, that smokers that have first-degree relatives with early-onset, severe COPD had a threefold increased risk. Airway restriction in comparison to smokers without a history of COPD in their families [7], confirming the part genetic predisposition plays in the pathophysiology of COPD. Additionally, impairments in lung Development and/or growth are also associated with more exposure to environmental and/or hereditary risk factors, in particular, those with lower maximum achieved lung function have restricted airway, which over time causes COPD to develop [8]. Furthermore, a common diagnosis of COPD is an irreversible obstructive lung disease. After hours. On the other hand, asthma is a commonly recognized reversible obstructive lung condition. Early, enabling prompt action. Despite the fact that COPD can be managed to either It is a progressive lung illness that lessens symptoms and exacerbations, when recurring or Over time, there is a sharp loss in lung function due to recurrent bouts of acute exacerbations[9] as one grows into stages of severe and deadly emphysema, requiring a lung transplant to avoid deadly consequences [10]. Therefore, it is essential to stop COPD from progressing to the deadly phases that therapy is started as soon as possible, before the condition significantly worsens and becomes serious asthma. This makes real-time lung health monitoring and diagnostics necessary. Techniques that can detect early alterations in the lungs of at-risk individuals before they advance to phases of severe emphysema[11]. Regretfully, diagnostics according to standards of care (SOC) are Not well-suited to achieve this aim. 2018 had 16 million adult US patients receiving diagnoses for COPD, however it was projected that over 14 million adult Americans still have lung disease. Function test (PFT), which the current gold SOC diagnosis was unable to diagnose. Consequently, as a result of the inadequate diagnosis to identify COPD early, the state of the subjects' lungs conditions cannot be tracked for prompt treatment, which causes the disease to worsen that, with early attention, could have been avoided differently. Spirometry-based COPD clinical diagnosis is still the gold standard today. In summary, according to the current SOC, a person must score lower than The forced expiratory volume in the first second of breathing (FEV1) ratio is 0.70. vital capacity under duress (FVC) [12]. But frequently, this diagnostic instrument alone is insufficient to reliably anticipate the occurrence of COPD, particularly in the early phases of the illness. This is partly explained by spirometry's and PFT's failure to identify disease severity variations, as demonstrated by the Obstructive Lung Disease Northern Sweden According to a study [13], 50% of people with severe COPD were given a clinical diagnosis only 19% of patients with mild COPD obtained a clinical diagnosis using spirometry. Using spirometry, necessitating the development of more thorough screening protocols and emphasizing the unfulfilled need for a diagnostic tool that can spot early, subtle, or localized alterations in pulmonary function. Spirometry/PFT, to put it briefly, monitors changes in total lung function and it overlooks mild variations in lung function that are localized or in their early stages[14]. But there are further diagnostics that have been employed to thoroughly examine and confirm the existence of of COPD, such as the ability to diffuse carbon monoxide (DLCO) and arterial blood gas (ABG) analysis and lung imaging techniques, including computed tomography (CT) and X-rays magnetic resonance imaging (MRI), and scans, but the majority of these procedures utilized alone or in mixture overlooks illness in its early stages. examinations for screening, like the six-minute walk test (6MWT) and COPD questionnaires, while helpful in identifying COPD precursors, are not strong enough for clinical diagnosis and/or tracking the state of COPD development[15]. Quantifiable metrics for the prompt detection of minute alterations in lung function. Therefore, even while conventional diagnostic tools are helpful, they have numerous drawbacks. Some important restrictions that must be handled in order to be compiled for comparison analysis. As was previously said, one of the primary drawbacks of the SOC diagnostics used today is early illness identification. A noteworthy shortcoming of the SOC diagnostics used nowadays is that

because their primary emphasis is on breathing, they are unable to detect regional changes in the airway on measuring changes in lung function worldwide. Lung imaging techniques like MRI, CT, and X-ray Photoacoustic tomography (PAT), ray phase contrast, and other techniques do enable the observation of regional variations or structural alterations in the lungs, although doing so increases the risk of exposure to dangerous radiation or toxicity, making it unsuitable for regular and continuous monitoring and/or assistance[16]. Moreover, traditional imaging methods offer information about lung function by deriving conclusions from alterations in structure rather than by explicitly measuring alterations in lung function. But newer diagnostic techniques are starting to make up for these deficiencies. The forced oscillation technique (FOT) is one such example. pressure oscillations are used to monitor respiratory function, whereas impulse oscillometry system (IOS), a frequently employed forced oscillation method, has the ability to diagnose COPD through measuring the lung's reaction to various pressure frequencies [17]. Still, this makes the application of artificial intelligence (AI) to analysis critically necessary. Audio information from FOT/IOS to further automate and improve these diagnoses to accurately identify COPD [18]. Similarly, further cutting-edge and safer lung imaging techniques include ultrasonography Another healthy substitute being explored is computed tomography (UCT), while For higher resolution, they will need to address the constraints on the signal to noise ratio. In Furthermore, electrical impedance tomography, or EIT, is exceptional in that it may non-invasively measure variations in localized lung function by 3D modeling and electrical info on impedance[19].

II. Assessment Methods for Detecting and Monitoring the Onset and Advancement of COPD

2.1. Questionnaires for Screening Chronic Obstructive Pulmonary Disease (COPD)

Various techniques are employed to examine and track signs and indications of the development and advancement of COPD. A commonly used tool for both initial diagnosis and monitoring of respiratory exacerbations is the COPD questionnaire. Nevertheless, there exist numerous variations of COPD questionnaires that can be utilized for assessment purposes.The impact of COPD on the subject's quality of life (QoL) and/or the severity of its effects. Progression of a medical condition. For instance, the Chronic Respiratory Questionnaire (CRQ) and the St. George's Respiratory Questionnaire (SGRQ) is quite comprehensive and provides detailed information.Nevertheless, they are lengthy and intricate for regular utilization [20]. On the other hand, the Clinical COPD questionnaire (CCQ) and the COPD Assessment Test (CAT) have a reduced length.Tests that can be done in around 2 minutes with a high level of reliability and accuracy. The validation process involves the use of quantitative data to diagnose and monitor COPD. Advancement. Both tests, recommended by the GOLD, are consistently responsive. By implementing interventions [21–23], it becomes possible to conduct an initial assessment of the therapeutic effectiveness in addition to its use as a tool for screening and monitoring diagnostic purposes. In addition, a direct comparison of the two surveys revealed that CAT is superior.
CCQ is less reliable than other factors in predicting future exacerbation occurrences. The CAT also possesses a threshold that is established based on clinical criteria.Regarding the severity of symptoms, the CCQ encompasses a wide spectrum of values ranging from 1.0 to 1.5. Suggesting that CAT is preferable to CCQ in the clinical environment when a precise threshold is required must be provided [24]. Although COPD surveys can be useful, their scope is typically restricted their capacity to measure or forecast alterations in the structure and/or function of the lung. In summary, These surveys assess the patient's respiratory health holistically, however, They lack the ability to directly perceive or anticipate alterations in lung function or anatomical abnormalities, therefore Restricting their usefulness as a supplementary test for functional or prognostic diagnosis[25].

2.2 Six Minute Walk Test

The 6MWT is a common method used to screen for early COPD. It can be done at home, at a point of care facility, or at a clinic. The American Thoracic Society (ATS) recommends that the 6-minute walk test (6MWT) be conducted inside on a lengthy, level, and straight surface measuring 30 meters in length. The distance is demarcated at intervals of 3 meters, and cones are positioned as turnaround checkpoints at both ends. Before the test, the patient reclines in a chair for approximately 10 minutes and thereafter ambulates up and down. The individual will walk around the cones in the corridor for a duration of 6 minutes, during which the number of laps completed will be documented. Assuming that it is possible to integrate a pulse oximeter to detect both heart rate and oxygen saturation.The abbreviation "SpO2" stands for peripheral capillary oxygen saturation. A decrease in the subject's walking distance is not only indicative of Both the existence and the

extent of COPD. A study demonstrated that a 6-minute walk test (6MWT) distance below a certain threshold A distance greater than 350 meters was found to be associated with a significantly higher risk of death and hospitalization [26,27]. Demonstrating the usefulness of the 6-minute walk test (6MWT) in predicting the occurrence of illness and death. Furthermore, the 6-minute walk test (6MWT) possesses An additional function as a prognosticator of recurring respiratory exacerbations, which are noteworthy. Factors that contribute to the reduction in lung function. For instance, a biennial investigation conducted in Brazil discovered that patients who achieved a score below 80% of the anticipated value of the 6-minute walk test (6MWT) were Twice as prone to experiencing repeated exacerbations [28].Nevertheless, the 6MWT is subject to specific constraints, including the potential influence on outcomes. Based on the pathophysiological characteristics of the individual subject, which may or may not be present, Pertaining to Chronic Obstructive Pulmonary Disease (COPD). Factors such as gender, age, sex, weight, and ethnicity can all influence An individual's capacity to sustain physical activity for prolonged durations. Thus, although a low 6MWT distance is associated with COPD, although it does not confirm COPD as the underlying cause [29]. Necessitating additional assessment by modern SOC diagnostics, such as spirometry-based pulmonary function testing (PFT).

III. Current Diagnostic Standards for COPD

3.1.Monitoring COPD Lung Function using Spirometry-Based Pulmonary Function Tests

Classical spirometry is the standard of care for diagnosing chronic COPD and the most often used PFT. The test has the advantage of posing minimal risk to the subject while providing an objective measure of overall changes.Lung function for COPD diagnosis. Briefly, spirometry examines lung function via Inhalation and exhalation breathing movements necessitate high patient compliance.

These measures are obtained at the peak of inspiration, at spirometry Can quantify variations in FVC and FEV1 to assess the subject's lung function. If the subject's FEV1/FVC ratio is less than 0.70, indicating a positive COPD diagnosis.Furthermore, FEV1 gives a mechanism for identifying different levels of COPD severity [30].GOLD classifies COPD patients as having a FEV1 greater than 80%. GOLDI has mild emphysema, and if FEV1 is less than 80% but greater than 50%, the individual is classed as GOLD II, with mild emphysema. Moreover, those with FEV1Less than 50% but more than 30% are classed as GOLD III stage COPD with severe. Emphysema and those with fewer than 30% FEV1 are classed as GOLD IV stage very severe emphysema.Despite the advantages of spirometry in staging and clinical diagnosis of COPD-emphysema it has limited efficacy and potential in early and complete diagnosis or monitoring.Monitoring modest or regional lung function changes. As found in Obstructive Lung Disease.In the Northern Sweden study mentioned above, 50% of the individuals with severe COPD obtained a clinical diagnosis with spirometry, while "only" 19% of individuals with moderate COPD received a similar Spirometry is more effective for clinical diagnosis, showing that Diagnosing severe COPD becomes increasingly unreliable with the FEV1/FVC ratio within the moderate to mild range [31–33]. In addition, various disorders with airflow restrictions, Asthma, for example, must be checked out [34], and it is possible to distinguish COPD from Asthma is a reversible lung illness that can be treated with a bronchodilator on a PFT.COPD is irreversible. One of the most important drawbacks of spirometry is that it assesses changes in overall lung function; it is not capable of identifying or quantifying alterations in regional lung function, leaving out early modest alterations. Since COPD is PFT does not account for a patchy lung disease caused by regional air flow limitation. Strong qualitative and quantitative data to evaluate the beginning and course of early-stage Disease requires timely intervention.

3.2. Diffusing Capacity for Analysis of Arterial Blood Gas and Carbon Monoxide

The DLCOtest measures the uptake of carbon monoxide (CO) per unit time per mm of driving pressure to assess overall lung function. This allows for the quantification of the lung's efficiency in transferring oxygen from inspired air into the blood cells. DLCO evaluates CO uptake rather than oxygen (O2) because CO has a far greater binding affinity for hemoglobin, making it possible to detect even minute functional changes. In a nutshell, the test involves having the participant breathe test gas including CO, tracer gas, O2, and nitrogen (N2) for 10 seconds before exhaling, and then using a DLCO analyzer to measure the concentration of CO and tracer gas in the exhaled gas. When the expected gas concentration is more than 75%, the test results for DLCO are normal; when it is less than 40%, the findings are mild, moderate, and severe [35, 36]. Furthermore, because DLCO is measured at full inflation, it evaluates total lung capacity in a manner equivalent to spirometry, which makes it a suitable diagnostic tool for determining alveolar volume and, consequently, emphysema[37–39].Therefore, while DLCO is adequate for measuring overall lung function, it cannot differentiate between

local or regional changes in lung function because it measures both the intake and the output of gas through exhalation in a comprehensive manner and only offers cumulative information on the subject's lung's absorption capacity of CO. As a result, this offers a broad indicator of changes in lung function worldwide but is evidently unable to detect localized alterations, impairments, or changes in the lung, making it unable to detect early stage disease. The ABG analysis test measures the lung's capacity to absorb oxygen, much like the DLCO test does. However, it does so by measuring the following: The partial pressure of oxygen (PaO2) measures the amount of oxygen that is transferred into the bloodstream; the partial pressure of carbon dioxide (PaCO2) measures the amount of CO2 that is removed from the bloodstream; the pH measures the presence of high CO2 levels; and the saturation of oxygen (SpO2) measures the amount of oxygen that is present in the arterial blood stream. In short, because CO2 combines with water (H2O) to generate carbonic acid (H2CO3), pH can be used to evaluate CO2 levels. The accumulation of CO2 will cause a buildup of H2CO3, which will significantly reduce the blood's pH if there is insufficient CO2 transfer out of the blood stream [40, 41]. Subjects with COPD are predicted to have lower PaO2 levels, higher PaCO2 levels, lower pH levels, and lower SpO2 levels compared to a person with healthy lungs because COPD restricts airflow. This provides a means for objectively classifying worldwide abnormalities in pulmonary function. Furthermore, ABG tests are the norm for giving extra oxygen to patients with COPD who have a PaO2 value of less than 55 mmHg, a SpO2 value of less than 88%, or a PaO2 value of between 55 and 60 mmHg in the case of subjects with erythrocytosis or right heart failure [42].Similar to the SOC diagnostics that were previously addressed, ABG has limited capabilities and can only anticipate changes in global lung function by examining the composition of arterial blood gas; it cannot measure changes in local or regional lung function. Its inadequacy as a reliable monitoring and diagnostic tool for the onset and progression of emphysema is further limited by the fact that ABG analysis is not a reliable indicator of the severity of COPD and is insufficient or ineffective for the diagnosis of the illness in its early stages [43].

3.3. Functional Lung Imaging Techniques to Assess the Advancement of COPD

In order to forecast the pathophysiology and course of COPD, lung imaging modalities are helpful diagnostic tools for evaluating structural alterations and making inferences about functional changes. To produce high-resolution tomographic images, one of the most often utilized modalities for lung imaging is the CT scan, which uses radiation's penetrating qualities. The patient is positioned between an X-ray source and X-ray detectors during the scan, which spin the detectors around the area of interest to measure the attenuation of X-ray signals via tissues. But because radiation exposure poses a serious risk, Although advances in low-X-ray dose CT scan resolution have shown potential application in evaluating COPD, CT scans are not routinely used for COPD monitoring and diagnosis in accordance with the GOLD guidelines. Instead, CTs are only used for bronchiectasis and lung cancer detection in high "at-risk" COPD subjects [44] of their capacity to precisely measure and locate artifacts like those connected to emphysema structural damage(s) by observing regions that are surrounded by noticeably reduced tissue density by healthy lung tissue to measure alterations in the pulmonary and airway vasculature [45–47].Because CT scans can visualize the features of lung damage regions, they are effective in providing information for interventions [48, 49]. Nevertheless, their capacity for routine or real-time disease monitoring for bedside interventions is limited. Consequently, CT scans can assist in identifying the cause of respiratory symptoms. Another common diagnostic method for imaging the lungs is the chest X-ray. This method involves sending X-rays to a target area, where they penetrate the body, and recording the data using a detector at the other end. To create a picture, the X-rays' attenuation after entering the target area is compared to the radiation that was applied initially. X-rays are often not helpful in diagnosing COPD and can only identify the disease when it is advanced, which restricts its monitoring and diagnostic potential.

Rather, X-rays are used to see larger lungs, rule out other potential reasons of respiratory problems, such as comorbidities, etc.

Another imaging technique that creates images of the tissue of interest without the use of ionizing X-ray radiation is magnetic resonance imaging (MRI), which uses radio waves and magnetic fields. Due to the low proton density of lung tissue and the quick signal decay brought on by artifacts, MRIs have not been used extensively in the past for lung imaging and COPD diagnosis [50]. Nevertheless, as technology develops, MRIs have the potential to challenge more established lung imaging modalities as a new COPD diagnostic. Recently, for instance, it has become possible to quantitatively assess lung function from MRI by placing contrast agents or hyperpolarized gases in the subject's airway. This enables high-resolution observation of changes in ventilation (V), perfusion (Q), and/or airflow [51]. This method has the advantage of monitoring V/Q changes rather than making assumptions based on structural changes in an image. Consequently, while functional analysis software advancements have made it possible to assess changes in regional lung function

using CT data, this evaluation still lacks real-time assessment and capability due to a lack of bedside equipment and a high risk of radiation exposure. Furthermore, the software's output data only serve as a prediction or inference of a structural change rather than a direct quantification of the regional or global lung function. Moreover, ionizing X-ray radiation, which is categorized as a carcinogen, is used in both CT scans and X-ray imaging. The severe health consequences for individuals with chronic illnesses limit the continuous use of these modalities for real-time surveillance of chronic lung disorders because there is a direct association between X-ray exposure and cancer development [52, 53]. As a healthier option, lower dosage radiation CTs are being developed; however, this comes at the expense of lower resolution, which restricts its monitoring and diagnostic potential. MRIs, on the other hand, do not use radiation; nonetheless, because of the low proton density in the lungs, they need hyperpolarized gases or contrast chemicals to record changes in V and/or Q. The use of magnetic resonance imaging (MRI) for routine disease progression monitoring is restricted due to the potential toxicity and side effects of these medications [54, 55]. MRI cannot be used often or for short periods of time. Moreover, these imaging modalities need sophisticated, pricy medical equipment that can only be found in clinics and hospitals with radiology departments. Furthermore, bedside or real-time monitoring of patients' lung conditions is not supported by these modalities.

IV. New COPD Diagnostics for Real-Time Evaluation of Lung Function

New diagnostic techniques that can detect COPD early and/or monitor the disease's course in real time have made significant advancements in the diagnosis of the condition. These methods, which each have particular benefits, are FOT/IOS, PAT, XPC, UCT, and EIT. and/or restrictions as depicted in Figure 1. Artificial intelligence (AI) that corresponds with it and As supplementary tools, validation software has also been created to attain resilience and Automated methods to get over the present clinical bedside translation constraints.

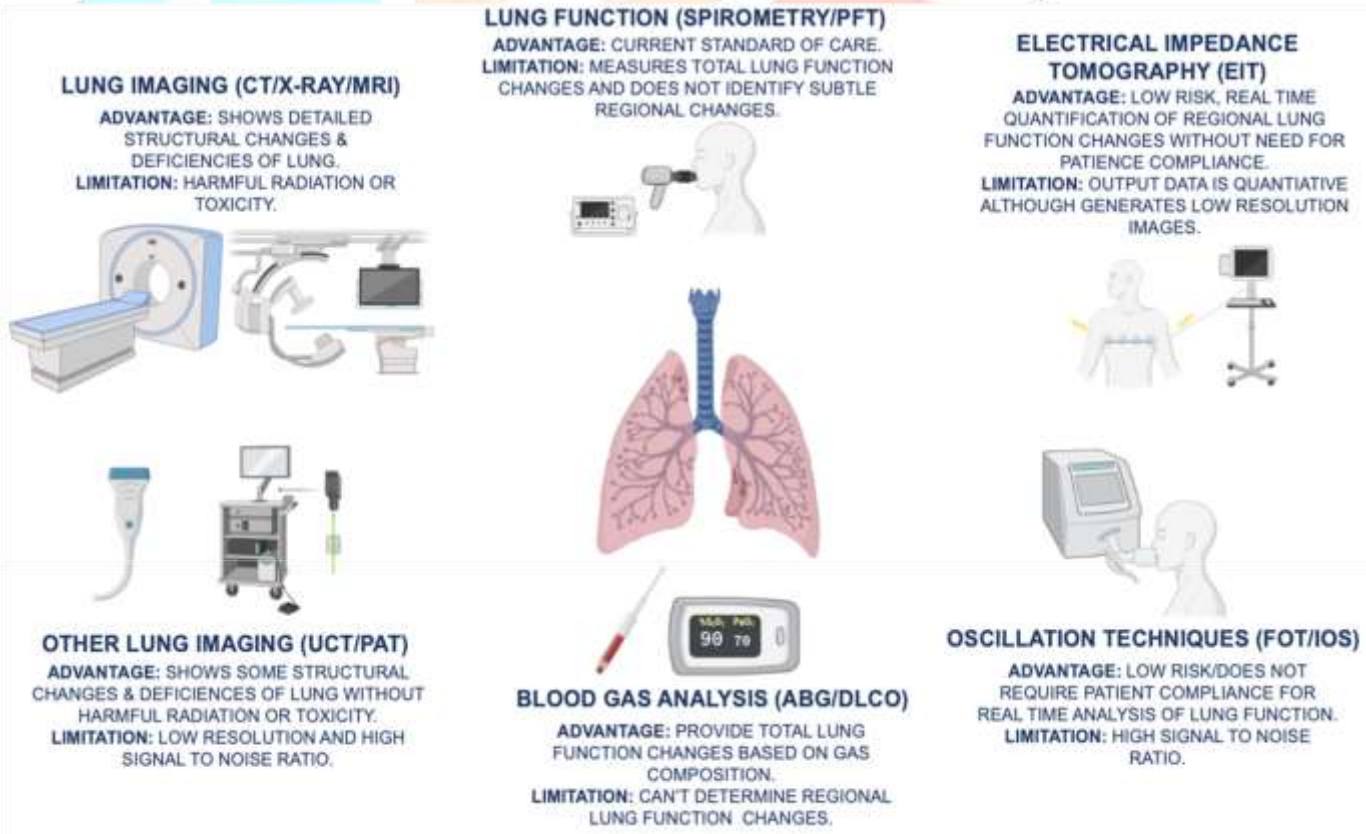

Fig.1 The benefits and drawbacks of the current diagnostic methods for COPD (chronic obstructive pulmonary disease) are discussed. These methods include spirometry/pulmonary function testing (PFT), arterial blood gas (ABG), diffusing capacity for carbon monoxide (DLCO), and lung imaging modalities like computed tomography (CT), X-ray, and magnetic resonance imaging (MRI). Furthermore, new and developing diagnostic methods like electrical impedance tomography (EIT), forced oscillation therapy (FOT), impulse oscillometry system (IOS), ultrasound computed tomography (UCT), and photoacoustic tomography (PAT) offer non-invasive, instantaneous evaluation of alterations in lung function.

4.1 Tomography and X-ray Phase Contrast Imaging for Functional Lung Imaging

Similar to low dose CT, X-ray phase contrast (XPC) shows promise as a novel diagnostic tool by measuring the shift in phase after X-rays pass through tissue. This allows XPC to detect weak X-ray absorbing properties that are not detected through conventional X-ray imaging [56]. In summary, XPC is an effective method for obtaining information about the lung that might reveal the existence of COPD or other lung abnormalities because of the comparatively large refractive index difference between lung tissue and air. For instance, an analyzer-based XPC was used in a preliminary clinical study to map airway regions in mice with mild and severe emphysema, successfully differentiating between the two conditions while maintaining a sensitivity of 0.80 and a specificity of 0.89. This demonstrated the accuracy of the technology and its potential use in pulmonary diagnostic processes, which still require significant clinical development. Furthermore, by taking dynamic lung images, XPC can quantify lung air volume capacity, enabling the observation of changes in lung function both locally and globally [57]. XPC imaging can be broadly classified into five categories: (1) propagation-based imaging; (2) analyzer-based imaging; (3) crystal-based interferometric methods; (4) grating interferometric methods; and (5) grating non-interferometric methods. While each has pros and limitations, all rely on the following for effective result acquisition: X-ray detector resolution, image reconstruction techniques, X-ray energy, and X-ray divergence [58]. To determine the best way to capture certain characteristics and functions of the lung consistent with COPD, a clinical context must be used to identify the specific advantages of various XPC imaging categories. Even with the capabilities of AI or algorithm-based analysis, resolution and radiation danger are still major barriers to the clinical application of XPC. Additionally, in order to intervene promptly, this strategy necessitates the use of sophisticated radiology equipment with a restricted real-time scope or routine bedside monitoring of the course of respiratory diseases, including COPD [59].

4.2 Measurement of lung function using force and impulse oscillometry techniques.

As previously mentioned, there is a clear and important need for diagnostic approaches for Chronic Obstructive Pulmonary Disease (COPD) that accurately measure real-time changes in lung function. These techniques would enable the early detection of COPD and allow for timely intervention. An emerging diagnostic method for COPD is Forced Oscillation Technique (FOT). FOT assesses lung function by measuring the lung's response to pressure oscillations during normal breathing. It quantifies this response as impedance, which is the resistance of airflow in the respiratory system. Impedance is calculated using the recorded pressure and airflow data obtained during the measurement [60]. IOS, or Impulse Oscillometry System, is a modified version of FOT, or Forced Oscillation Technique. While FOT transmits frequencies in a sequential manner, IOS transmits frequencies as an impulse that can be distinguished into different frequencies. This allows for a faster testing process and an improvement in the signal-to-noise ratio, which is the main drawback of this technique. The impedance measured in these tests indicates the sensitivity of the respiratory system, making Forced Oscillation Technique (FOT) and Impulse Oscillometry (IOS) a valuable diagnostic tool for measuring bronchial hyperresponsiveness, a common condition in patients with asthma and Chroni Obstructive Pulmonary Disease (COPD). The majority of studies on the clinical usage of FOT/IOS mostly concentrates on asthma and big airways. However, FOT/IOS analysis has proven to be valuable in identifying tiny airways for COPD diagnosis, depending on the frequency at which impedance is recorded [61]. Moreover, utilizing machine learning to analyze FOT/IOS data, following the program's training with FOT/IOS data from smokers, COPD patients, and healthy individuals, can enhance the ability to assess and measure quantitatively. Several studies have demonstrated the effectiveness of this advanced use of machine learning algorithms in accurately identifying pulmonary changes associated with early identification of COPD. The results indicate a high level of specificity and sensitivity, highlighting the ability of the algorithms to detect even modest changes in lung function [62]. In addition, FOT/IOS does not necessitate the subject to execute breathing maneuvers for measurements and only necessitates minimal compliance from the subject. This makes FOT/IOS advantageous over spirometry in situations where patient compliance is restricted, such as in young children, individuals with chronic illnesses, or the elderly [63]. Nevertheless, FOT does have limitations, such as the potential influence of extra-thoracic upper airway artefacts on measurements. These artefacts can distort the results when trying to identify small airway changes and COPD, ultimately hindering the precise quantification of lung function and structural changes. In addition, Forced Oscillation Technique (FOT) is unable to determine the specific causes of hyperresponsiveness. This is because other respiratory conditions, such asthma, can also lead to functional changes. Therefore, other diagnostic methods or the use of bronchodilators may be necessary to confirm the diagnosis of Chronic Obstructive Pulmonary Disease (COPD) [64]. FOT/IOS has limitations in accurately measuring regional lung function changes, since it

primarily assesses the overall impedance and hyperresponsiveness of the lung rather than specific areas. Furthermore, a particular constraint of IOS is that the impulse pressure may be excessively strong in comparison to the successive waves of the FOT, resulting in discomfort for the patient [65].

4.3 New Approaches to Lung Imaging: Photoacoustic and Ultrasound Tomography

PAT is another new diagnostic technique that is being used to diagnose COPD. It is an enhanced substitute for ionizing radiation-intensive CT scans. Low dose CT, on the other hand, can lower the radiation danger but at the expense of less resolution. PAT, on the other hand, uses signals from optical absorption to produce high-resolution images by using laser beams to excite endogenous chromophores or exogenous contrast agents. This causes the substances to absorb the optical energy and heat up, which expands the tissue and produces an ultrasound signal. After that, this signal is rebuilt using an algorithm to produce an image that records information about lung tissue destruction and airway characteristics. This image can then be examined to determine whether COPD or another pulmonary disease is present [66]. Due to light diffusion, other optical imaging techniques frequently have poor spatial resolution. This technique provides for enhanced spatial resolution. Moreover, visual contrasts and interference speckle artifacts found in other ultrasonic imaging modalities are absent from PAT. Furthermore, PAT is a healthier option than modalities that use dangerous ionizing radiation because it uses nonionizing radiation . However, because PAT's imaging depth depends on the tissue's limit of attenuation, its imaging capabilities are constrained. The longer imaging periods of PAT are further constrained by the laser beams' pulse repetition rate during optical excitation. Furthermore, PAT infers functional alterations based on morphological airway abnormalities, just like classical imaging modalities. Ultrasonic Computed Tomography (UCT) is a newer tomographic imaging technique that uses ultrasonic waves to create images. The waves are distorted in the tissue before being recorded by ultrasound transducers. UCT can record characteristics of the sample that other imaging modalities are unable to measure, such as the attenuation of sound waves, because it uses ultrasonic waves rather than radiation or magnets [67]. Furthermore, compared to conventional radiation-using modalities, UCT is a far healthier imaging technique because it spares the patient from dangerous ionizing radiation. Although UCT has shown promise, its application in pulmonary imaging has not been widespread. To prevent high signal to noise ratios and enhance resolution quality, major development of robust analysis techniques is necessary for UCT's potential usage in the diagnostic domain. Overall, the soft-tissue imaging properties and non-invasive imaging techniques demonstrate promise for routine use lung disease diagnostics in the future, but their capabilities are severely limited. This is because, like the current SOC diagnostic PFT, the current prototypes are unable to quantify regional or local function changes in order to detect early or subtle changes in lung function[68].

4.4. New Diagnostics for Regional Lung Function Analysis Using Electrical Impedance Tomography

Electrical impedance tomography (EIT) is an advanced diagnostic tool that can accurately measure and analyze regional changes in lung function. It achieves this by generating cross-sectional images of the lung's structure using low-dose current injections at a specific frequency. These injections are done non-invasively through surface electrodes, while changes in conductivity are measured. This technology exploits the fact that muscle and blood regions have lower impedance compared to areas of fat, bone, air, and lung tissue due to the presence of free ions. As a result, a ring of electrodes, typically consisting of 16 or 32 electrodes, is positioned around the 4th and 5th intercostal space to measure impedance variations in different lung regions, covering all lobes. Furthermore, an algorithm can utilize impedance data to reconstruct conductivity changes in V and Q, resulting in images that can be employed to assess COPD and estimate alterations in lung function by comprehensively evaluating the V/Q maps. The data can be examined utilizing innovative quantification software, algorithms, and artificial intelligence techniques to detect precise alterations in air or blood circulation. An approach to identify COPD using EIT involves the computation of the global heterogeneity Index (HI) [69]. This index is derived from the EIT V/Q or airflow (FEV1/FVC) heat maps obtained during tidal breathing. It enables the measurement of both ventilation heterogeneity and the evaluation of lung function. In summary, the comparison of Health Index (HI) between the COPD and non-COPD groups showed that the non-COPD group consistently had a lower overall HI than the COPD group. This indicates that EIT can effectively differentiate and identify individuals with COPD. Moreover, ventilation heterogeneity can be employed for COPD monitoring by utilizing inspiratory peaks and expiratory troughs from EIT measurements to create heating and cooling maps of expiratory time (tE), phase shift (PHASE), and amplitude of impedance signal (AMP). These maps can be used to demonstrate the corresponding heat intensity (HI) values. Evaluating the effectiveness of this measurement in identifying COPD revealed that individuals with COPD exhibited higher levels of ventilation heterogeneity and coefficient of variation. This demonstrates the ability of this tool to detect changes in lung function over time and quantify the progression of pulmonary

diseases. Moreover, the process of reconstructing EIT data is employed to compute regional or local FEV1/FVC ratios by measuring impedance values at various time points during an inspiration/expiration maneuver. This demonstrates its potential to generate standardized output measures with the ability to assess specific regions. EIT is a safer and more reliable option compared to traditional SOC methods (as depicted in Figure 2) for evaluating changes in regional lung function. This is because it avoids subjecting the patient to harmful radiation, toxic chemicals, or contrast agents. Consequently, it enables continuous real-time monitoring of regional lung function at the bedside or point of care, facilitating the tracking of disease progression[70].

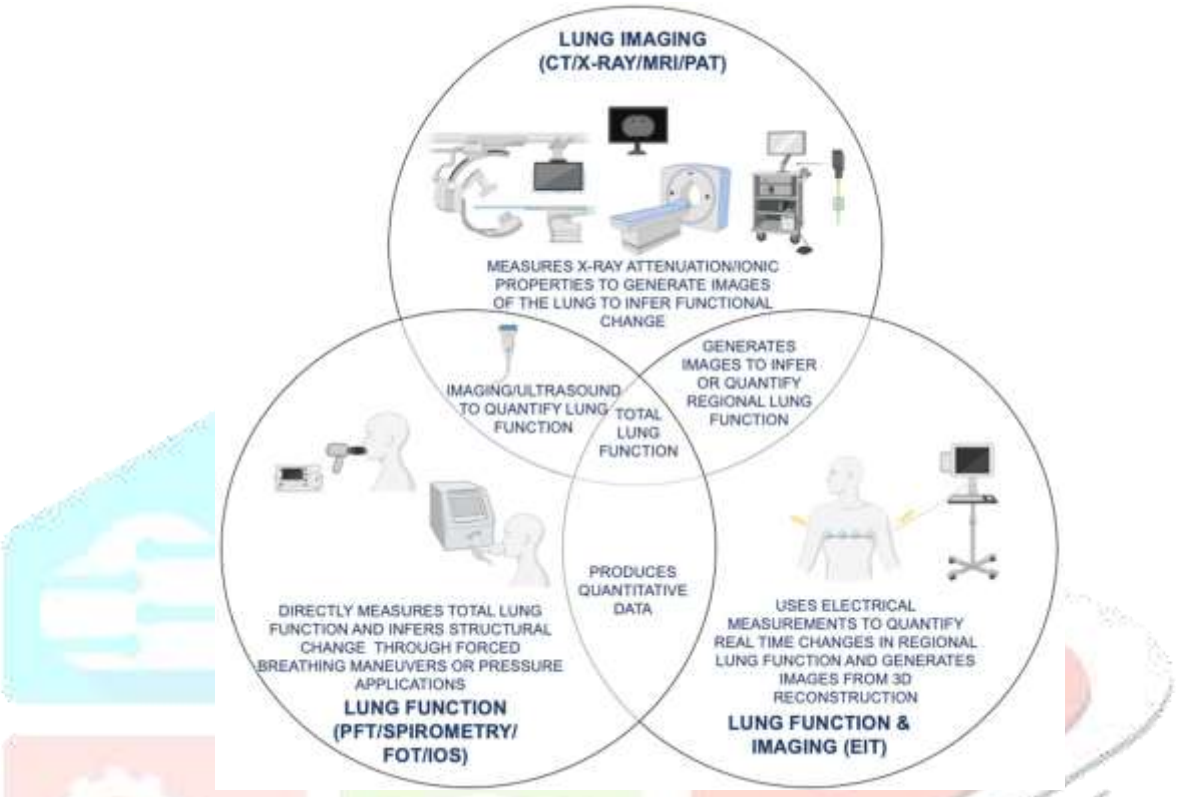

Fig.2 An analysis of the present lung imaging and lung function tests is conducted, comparing them with the new oscillation and tomography techniques for the diagnosis and monitoring of COPD (chronic obstructive pulmonary disease). The text demonstrates the functional similarities and differences between standard of care lung imaging techniques (CT, X-ray, MRI) and lung function tests (PFT, spirometry, FOT, IOS) in comparison to emerging novel modalities that combine lung function and imaging capabilities (EIT, UCT, PAT) for the diagnosis and monitoring of COPD.

The earliest prototypes of EIT had limited spatial resolution, which hindered its use as a diagnostic and monitoring tool. The reconstructed images were not as detailed as those produced by traditional imaging modalities. Nevertheless, EIT maintains a superior ability to measure changes over time and provide quantitative assessments, making it a valuable tool for monitoring regional changes. when compared to FOT/IOS, PAT, UCT, XPC, and other methods. Moreover, impedance measurements exhibit high sensitivity, enabling the detection of even little or limited alterations. Consequently, automation is required to reduce the variability between consecutive runs. Furthermore, the clinical EIT prototypes currently available solely capture cross-sectional data, therefore failing to provide conductivity measurements of lung areas along the z-axis. Nevertheless, this constraint can be readily resolved by employing electrode devices specifically created for 3D imaging. These devices can recreate corresponding cross-sections of the lung and measure them in relation to time, enabling a quantitative evaluation of regional lung function alterations [71].

V. PERSPECTIVE

COPD is a degenerative respiratory condition characterized by an expedited deterioration of lung function, often likened to the process of accelerated aging of the lungs. Ageing, together with exposure to environmental factors, leads to an increase in inflammatory-oxidative stress and cellular senescence. This ultimately causes irreversible progression of lung disease, ranging from mild to severe emphysema. Nevertheless, the

implementation of real-time diagnostics for monitoring lung health, along with appropriate therapies, can slow down the course of disease to severe emphysema and prevent fatal deterioration of lung function. Although COPD is widespread worldwide, the present standard of care (SOC) diagnostic methods have significant drawbacks that hinder prompt treatment. These limitations are outlined in Table 2 and will be further examined below.

COPD Diagnostic Comparison	Disease Details	Diagnostic Accuracy	Risks	Patient Compli-ance	Time
X-ray/XPC	Low	Low	Low radiation	No	15 min
CT/MRI	High	High	Radiation/Contrast Agents	No	20 min–2 h
PFT/Spirometry	Low	Moderate	Low	Yes	30 min–1 h
ABG/DLCO	Low	Moderate	Low	No	15 min
FOT/IOS	Low	Moderate	NA	No	Real Time
PAT	Moderate	Moderate	NA	No	Real time
UCT	Low	Moderate	Low	No	Real time
EIT	Moderate	High	NA	No	Real Time

Table No.1. The scope, hazards, and limits of present and developing diagnostic and monitoring approaches for chronic obstructive pulmonary disease (COPD).MRI stands for magnetic resonance imaging, CT stands for computed tomography, PFT stands for pulmonary function test, ABG/DLCO refers to arterial blood gas/diffusing capacity for carbon monoxide, FOT refers to forced oscillation technique, IOS stands for impulse oscillometry system, XPC refers to X-ray phase contrast, PAT stands for photoacoustic tomography, UCT refers to ultrasound computed tomography, and EIT stands for electrical impedance tomography.

One of the clear drawbacks of existing SOC diagnostics is their limited ability to detect COPD in its early to mild stages, resulting in a considerable underdiagnosis of COPD in the community. Spirometry/PFT, ABG analysis, and DLCO are effective in identifying COPD at advanced stages but are unable to detect subtle alterations that would enable the diagnosis of lung illness at its early onset. While CT scans can provide detailed information on the structure of the lungs, which can help predict the prognosis of COPD by indicating changes in pulmonary function, their regular usage is restricted because of the potential risks associated with radiation exposure. Furthermore, the capacity of structural modifications to infer conclusions, whether done manually by a radiologist or via the use of quantitative software that assesses alterations in pulmonary function, is constrained in its capability to accurately and consistently identify early minor changes. On the other hand, new diagnostic methods like FOT/IOS and EIT have the ability to identify and measure minor abnormalities in lung function more effectively when combined with appropriate AI and analysis tools. Moreover, numerous factors contribute to the high number of undiagnosed patients, with a primary factor being that individuals are generally not screened for COPD unless they display notable respiratory symptoms, by which time the disease has usually advanced to severe stages. Instead of relying on the appearance of symptoms, it is considered that instituting extensive screening tests for individuals at risk (such as smokers and those over 40 years old) can significantly reduce, if not completely eliminate, the number of undiagnosed cases utilizing the existing standard of care, including pulmonary function testing (PFT). Implementing an automatic COPD risk screening in a medical care system's online healthcare platform serves as a proof of concept and enables timely detection of the condition. Therefore, when a patient is entered into the system, regardless of whether they have COPD or other illnesses, their attributes, such as age and smoking status, are

automatically evaluated to determine their risk of developing COPD [72]. Additionally, it is crucial to closely observe the advancement of diseases in individuals who have already been diagnosed with COPD by identifying predictive markers of sudden or recurring exacerbations that may ultimately result in a significant reduction in lung function. By identifying these signs at an early stage, certain therapeutic interventions can be initiated to minimize the detrimental effects on the structure and function of the lungs. Additionally, there is a requirement for diagnostic instruments that can effectively and precisely detect early signs of COPD in patients who have not yet been identified, as well as evaluate possible future exacerbations in patients who have already been diagnosed, in order to track the evolution of COPD through reliable point-of-care (POC) and home-based lung health monitoring. Unlike diagnostic tests for individuals who are not people of color (non-POC), which require patient samples to be sent to laboratories for analysis, resulting in lengthy waiting periods, point-of-care (POC) tests are diagnostic procedures conducted at the location and time of patient care. This enables rapid results that promptly inform the treatment process. Moreover, if the diagnostic can be transferred to a home-based environment, it will enhance convenience and facilitate the monitoring of illness progression, enabling forecasts of respiratory exacerbations.
Another drawback of existing COPD standard of care (SOC) diagnostics is their inability to accurately measure small COPD-induced alterations in specific areas of the lung. This restriction hinders their effectiveness in monitoring the disease in real-time and implementing tailored therapies that are crucial for stopping the progression of the illness. The measurements obtained from spirometry/PFT, ABG analysis, and DLCO devices reflect the general functioning of the lungs[73]. However, they are unable to provide precise quantification of specific regional variations in the structure or function of the alveoli. Conventional imaging techniques like X-rays, CT scans, and MRIs can track changes in specific areas, but they rely on ionizing radiation or contrast chemicals, which restricts their usefulness for monitoring disease development in real-time at the patient's bedside. Nevertheless, novel techniques for monitoring lung health, such as Electrical Impedance Tomography (EIT), Forced Oscillation Technique (FOT), and Impulse Oscillometry System (IOS), have the capability to assess lung function in real-time. These tools have the potential to enable continuous, noninvasive, bedside, and/or Point-of-Care (POC) evaluation if they are put into practice. In addition, the advancement of innovative real-time technologies for monitoring chronic obstructive pulmonary disease (COPD) is facilitating the use of companion diagnostics (CDx) in the treatment of COPD. In essence, CDx refers to the simultaneous use of a diagnostic test alongside pharmaceuticals to determine the effectiveness of the treatment in a specific individual. This is necessary since the efficacy of the therapy can differ from one patient to another [74]. CDx has been employed in several cancer treatments as a demonstration of its feasibility. One such example is the utilization of trastuzumab, a medication that specifically targets the receptor tyrosine-protein kinase (HER2), which is frequently overexpressed in individuals with breast cancer. Physicians successfully determined the ideal therapy parameters and measured the levels of HER2 by modifying the dosage of trastuzumab based on the patient's reaction to the medicine [97,98]. On the other hand, the individualized therapy of COPD needs more clinical advancement, specifically in the creation of prognostic and inflammatory biomarkers that have demonstrated potential as diagnostic tools. During exacerbations, the airway with an abundance of eosinophils is frequently irritated, leading to elevated levels of eosinophils. The use of CDx involves utilizing the amounts of eosinophils to direct the administration of corticosteroids, aiming to
decrease exacerbations.

Nevertheless, the effectiveness of CDx in treating COPD is presently restricted due to the absence of suitable diagnostic and monitoring instruments. This emphasizes the urgent requirement for a real-time lung function monitoring equipment that can be used at the bedside or a prognosis test that can be conducted at home or at a point-of-care facility. In addition, CDx can be specifically tailored to monitor local or regional changes in pulmonary function in order to assess the effectiveness of the intervention in real-time. As previously mentioned, existing lung imaging techniques enable the measurement of lung function, but they do so indirectly by making assumptions based on anatomical changes rather than directly quantifying dynamic changes in lung function. For instance, CT scans can be used to analyze changes in pulmonary function by examining parameters such as lung density, V/Q ratio, or other measures of lung function. This analysis can help determine the presence of enlarged airspaces, obstruction, lung tissue destruction, and other factors that affect lung function. Instead of directly measuring changes in lung dynamics, these findings can be used to predict lung function [75]. On the other hand, EIT is becoming more recognized as an effective diagnostic technique that may directly observe small changes in lung function in specific areas of the lungs in real-time, without exposing the individual to radiation or causing severe discomfort. In summary, this technique allows for the immediate evaluation of lung function changes in different areas by analyzing data at a voxel level and creating a 3D

representation. This enables the precise measurement of small and dynamic alterations in air or blood flow, providing a quantitative assessment of lung function outcomes. This method offers a practical alternative to traditional lung imaging techniques. In addition, EIT can be conveniently used as a bedside monitoring diagnostic tool. It can be implemented using commercially available EIT devices, such as Dräger's PulmoVistaR 500 and Swisstom AG's Swisstom BB2. These devices simply require a sensor belt with electrodes and a computer or tablet equipped with software for impedance measurements. Furthermore, to ensure patient comfort, commercial EIT vests have been specifically created to easily and quickly attach to the subject without the need for patient cooperation, as is typically required in conventional PFT measurements. This enables the monitoring of lung and/or heart function at the patient's bedside or in real-time [76]. In addition, EIT may greatly leverage emerging AI and deep learning tools to enhance automation and resolution, resulting in a more user-friendly diagnostic solution.

VI. Conclusion

Chronic Obstructive Pulmonary Disease (COPD) represents a significant and escalating health challenge worldwide, characterized by progressive airway blockage and deteriorating lung function. This review underscores the multifaceted nature of COPD, with its development and progression being influenced by a blend of genetic, environmental, and lifestyle factors. Notably, smoking remains the primary risk factor, but exposure to various pollutants and pre-existing respiratory conditions also play a crucial role.The review highlights the diverse methods available for detecting and monitoring COPD, from traditional tools like spirometry and the six-minute walk test (6MWT) to more innovative approaches involving advanced imaging and diagnostic techniques. Spirometry remains the gold standard for assessing lung function and staging COPD severity, yet its limitations in early detection and monitoring have been acknowledged. Similarly, while the 6MWT offers valuable insights into physical capability and prognosis, it too has its constraints.

Recent advancements in diagnostic technologies, including X-ray phase contrast imaging, forced oscillation techniques, and electrical impedance tomography (EIT), show promise in addressing some of these limitations. These newer methods provide more nuanced, real-time data on lung function, which could enhance early detection, monitor disease progression more accurately, and tailor individualized treatment plans.The introduction of these advanced diagnostic tools marks a pivotal shift in the management of COPD, aiming to improve patient outcomes by offering a clearer understanding of the disease's progression and facilitating timely interventions. However, while these innovations bring hope, their implementation in clinical practice requires further validation and integration.In conclusion, the fight against COPD necessitates a multifaceted approach that includes not only advanced diagnostic techniques but also preventative strategies and effective management protocols. As research continues to evolve, the goal remains to harness these tools to slow disease progression, enhance patient quality of life, and ultimately reduce the burden of this debilitating condition.

References

1. Halpin, D.M.G.; Criner, G.J.; Papi, A.; Singh, D.; Anzueto, A.; Martinez, F.J.; Agusti, A.A.; Vogelmeier, C.F. Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. The 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **2021**, *203*, 24–36.
2. Hikichi, M.; Mizumura, K.; Maruoka, S.; Gon, Y. Pathogenesis of chronic obstructive pulmonary disease (COPD) induced by cigarette smoke. *J. Thorac. Dis.* **2019**, *11*, S2129–S2140.
3. Berend, N. Contribution of air pollution to COPD and small airway dysfunction. *Respirology* **2016**, *21*, 237–244.
4. Zuo, L.; He, F.; Sergakis, G.G.; Koozehchian, M.S.; Stimpfl, J.N.; Rong, Y.; Diaz, P.T.; Best, T.M. Interrelated role of cigarette smoking, oxidative stress, and immune response in COPD and corresponding treatments. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* **2014**, *307*, L205–L218.
5. Forey, B.A.; Thornton, A.J.; Lee, P.N. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. *BMC Pulm. Med.* **2011**, *11*, 36.
6. Davis, R.M.; Novotny, T.E. The epidemiology of cigarette smoking and its impact on chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* **1989**, *140*, S82–S84.
7. Halonen, J.I.; Lanki, T.; Yli-Tuomi, T.; Kulmala, M.; Tiittanen, P.; Pekkanen, J. Urban air pollution, and asthma and COPD hospital emergency room visits. *Thorax* **2008**, *63*, 635–641.
8. DeVries, R.; Kriebel, D.; Sama, S. Outdoor Air Pollution and COPD-Related Emergency Department Visits, Hospital Admissions, and Mortality: A Meta-Analysis. *COPD* **2017**, *14*, 113–121.

9. Ko, F.W.; Hui, D.S. Air pollution and chronic obstructive pulmonary disease. *Respirology* **2012**, *17*, 395–401.
10. 10. McGeachie, M.J. Childhood asthma is a risk factor for the development of chronic obstructive pulmonary disease. *Curr. Opin. Allergy Clin. Immunol.* **2017**, *17*, 104–109.
11. Brode, S.K.; Ling, S.C.; Chapman, K.R. Alpha-1 antitrypsin deficiency: A commonly overlooked cause of lung disease. *CMAJ* **2012**, *184*, 1365–1371.
12. Silverman, E.K. Genetics of COPD. *Annu. Rev. Physiol.* **2020**, *82*, 413–431.
13. Waschki, B.; Kirsten, A.M.; Holz, O.; Mueller, K.C.; Schaper, M.; Sack, A.L.; Meyer, T.; Rabe, K.F.; Magnussen, H.; Watz, H. Disease Progression and Changes in Physical Activity in Patients with Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **2015**, *192*, 295–306.
14. Tanabe, N.; Muro, S.; Hirai, T.; Oguma, T.; Terada, K.; Marumo, S.; Kinose, D.; Ogawa, E.; Hoshino, Y.; Mishima, M. Impact of exacerbations on emphysema progression in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2011**, *183*, 1653–1659.
15. Donaldson, G.C.; Seemungal, T.A.; Bhowmik, A.; Wedzicha, J.A. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* **2002**, *57*, 847–852.
16. Lindberg, A.; Bjerg, A.; Bjerg-Bäcklund, A.; Rönmark, E.; Larsson, L.G.; Lundbäck, B. Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking Report from the Obstructive Lung Disease in Northern Sweden Studies. *Respir. Med.* **2006**, *100*, 264–272.
17. Lipworth, B.J.; Jabbal, S. What can we learn about COPD from impulse oscillometry? *Respir. Med.* **2018**, *139*, 106–109.
18. Amaral, J.L.; Lopes, A.J.; Jansen, J.M.; Faria, A.C.; Melo, P.L. Machine learning algorithms and forced oscillation measurements applied to the automatic identification of chronic obstructive pulmonary disease. *Comput. Methods Programs Biomed.* **2012**, *105*, 183–193.
19. Wijkstra, P.J.; TenVergert, E.M.; Van Altena, R.; Otten, V.; Postma, D.S.; Kraan, J.; Koëter, G.H. Reliability and validity of the chronic respiratory questionnaire (CRQ). *Thorax* **1994**, *49*, 465–467.
20. Jones, P.W.; Quirk, F.H.; Baveystock, C.M. The St George's Respiratory Questionnaire. *Respir. Med.* **1991**, *85* (Suppl. B), 25–31; discussion 27–33.
21. Gupta, N.; Pinto, L.M.; Morogan, A.; Bourbeau, J. The COPD assessment test: A systematic review. *Eur. Respir. J.* **2014**, *44*, 873–884.
22. Zhou, Z.; Zhou, A.; Zhao, Y.; Chen, P. Evaluating the Clinical COPD Questionnaire: A systematic review. *Respirology* **2017**, *22*, 251–262.
23. Tsiligianni, I.G.; van der Molen, T.; Moraitaki, D.; Lopez, I.; Kocks, J.W.; Karagiannis, K.; Siafakas, N.; Tzanakis, N. Assessing health status in COPD. A head-to-head comparison between the COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ). *BMC Pulm. Med.* **2012**, *12*, 20.
24. Jo, Y.S.; Yoon, H.I.; Kim, D.K.; Yoo, C.G.; Lee, C.H. Comparison of COPD Assessment Test and Clinical COPD Questionnaire to predict the risk of exacerbation. *Int. J. Chronic Obstr. Pulm. Dis.* **2018**, *13*, 101–107.
25. Celli, B.; Tetzlaff, K.; Criner, G.; Polkey, M.I.; Sciurba, F.; Casaburi, R.; Tal-Singer, R.; Kawata, A.; Merrill, D.; Rennard, S.; et al. The 6-Minute-Walk Distance Test as a Chronic Obstructive Pulmonary Disease Stratification Tool. Insights from the COPD Biomarker Qualification Consortium. *Am. J. Respir. Crit. Care Med.* **2016**, *194*, 1483–1493.
26. Waatevik, M.; Johannessen, A.; Hardie, J.A.; Bjordal, J.M.; Aukrust, P.; Bakke, P.S.; Eagan, T.M. Different COPD disease characteristics are related to different outcomes in the 6-minute walk test. *COPD* **2012**, *9*, 227–234.
27. Marin, J.M.; Carrizo, S.J.; Gascon, M.; Sanchez, A.; Gallego, B.; Celli, B.R. Inspiratory capacity, dynamic hyperinflation, breathlessness, and exercise performance during the 6-minute-walk test in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2001**, *163*, 1395–1399.

28. Morakami, F.K.; Morita, A.A.; Bisca, G.W.; Felcar, J.M.; Ribeiro, M.; Furlanetto, K.C.; Hernandes, N.A.; Pitta, F. Can the six-minute walk distance predict the occurrence of acute exacerbations of COPD in patients in Brazil? *J. Bras. Pneumol.* **2017**, *43*, 280–284.
29. Heresi, G.A.; Dweik, R.A. Strengths and limitations of the six-minute-walk test: A model biomarker study in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* **2011**, *183*, 1122–1124.
30. Walker, P.P.; Mitchell, P.; Diamantea, F.; Warburton, C.J.; Davies, L. Effect of primary-care spirometry on the diagnosis and management of COPD. *Eur. Respir. J.* **2006**, *28*, 945–952.
31. Johns, D.P.; Walters, J.A.; Walters, E.H. Diagnosis and early detection of COPD using spirometry. *J. Thorac. Dis.* **2014**, *6*, 1557–1569.
32. Schermer, T.R.; Robberts, B.; Crockett, A.J.; Thoonen, B.P.; Lucas, A.; Grootens, J.; Smeele, I.J.; Thamrin, C.; Reddel, H.K. Should the diagnosis of COPD be based on a single spirometry test? *NPJ Prim. Care Respir. Med.* **2016**, *26*, 16059.
33. Enright, P.; Brusasco, V. Counterpoint: Should we abandon $FEV_1/FVC < 0.70$ to detect airway obstruction? Yes. *Chest* **2010**, *138*, 1040–1042; discussion 1042–1044.
34. Rogliani, P.; Ora, J.; Puxeddu, E.; Cazzola, M. Airflow obstruction: Is it asthma or is it COPD? *Int. J. Chronic Obstr. Pulm. Dis.* **2016**, *11*, 3007–3013.
35. Modi, P.; Cascella, M. Diffusing capacity of the lungs for carbon monoxide. Available online: https://pubmed.ncbi.nlm.nih.gov/ 32310609 (accessed on 28 October 2021).
36. Jensen, R.L.; Crapo, R.O. Diffusing capacity: How to get it right. *Respir. Care* **2003**, *48*, 777–782.
37. Hughes, J.M.; Pride, N.B. Examination of the carbon monoxide diffusing capacity (DL(CO)) in relation to its KCO and VA components. *Am. J. Respir. Crit. Care Med.* **2012**, *186*, 132–139.
38. Balasubramanian, A.; MacIntyre, N.R.; Henderson, R.J.; Jensen, R.L.; Kinney, G.; Stringer, W.W.; Hersh, C.P.; Bowler, R.P.; Casaburi, R.; Han, M.K.; et al. Diffusing Capacity of Carbon Monoxide in Assessment of COPD. *Chest* **2019**, *156*, 1111–1119.
39. Mahut, B.; Chevalier-Bidaud, B.; Plantier, L.; Essalhi, M.; Callens, E.; Graba, S.; Gillet-Juvin, K.; Valcke-Brossollet, J.; Delclaux, C. Diffusing capacity for carbon monoxide is linked to ventilatory demand in patients with chronic obstructive pulmonary disease. *COPD* **2012**, *9*, 16–21.
40. Sood, P.; Paul, G.; Puri, S. Interpretation of arterial blood gas. *Indian J. Crit. Care Med.* **2010**, *14*, 57–64.
41. Burri, E.; Potocki, M.; Drexler, B.; Schuetz, P.; Mebazaa, A.; Ahlfeld, U.; Balmelli, C.; Heinisch, C.; Noveanu, M.; Breidthardt, T.; et al. Value of arterial blood gas analysis in patients with acute dyspnea: An observational study. *Crit. Care* **2011**, *15*, R145.
42. Güell Rous, R. Long-term oxygen therapy: Are we prescribing appropriately? *Int. J. Chronic Obstr. Pulm. Dis.* **2008**, *3*, 231–237.
43. Singh, V.; Khatana, S.; Gupta, P. Blood gas analysis for bedside diagnosis. *Natl. J. Maxillofac. Surg.* **2013**, *4*, 136–141.
44. Ostridge, K.; Wilkinson, T.M. Present and future utility of computed tomography scanning in the assessment and management of COPD. *Eur. Respir. J.* **2016**, *48*, 216–228.
45. Labaki, W.W.; Martinez, C.H.; Martinez, F.J.; Galbán, C.J.; Ross, B.D.; Washko, G.R.; Barr, R.G.; Regan, E.A.; Coxson, H.O.; Hoffman, E.A.; et al. The Role of Chest Computed Tomography in the Evaluation and Management of the Patient with Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **2017**, *196*, 1372–1379.
46. Diaz, A.A.; Come, C.E.; Ross, J.C.; San José Estépar, R.; Han, M.K.; Loring, S.H.; Silverman, E.K.; Washko, G.R.; Investigators, C. Association between airway caliber changes with lung inflation and emphysema assessed by volumetric CT scan in subjects with COPD. *Chest* **2012**, *141*, 736–744.
47. Occhipinti, M.; Bruni, C.; Camiciottoli, G.; Bartolucci, M.; Bellando-Randone, S.; Bassetto, A.; Cuomo, G.; Giuggioli, D.; Ciardi, G.; Fabbrizzi, A.; et al. Quantitative analysis of pulmonary vasculature in systemic sclerosis at spirometry-gated chest CT. *Ann. Rheum. Dis.* **2020**, *79*, 1210–1217.
48. Washko, G.R. Diagnostic imaging in COPD. *Semin. Respir. Crit. Care Med.* **2010**, *31*, 276–285.

49. Haruna, A.; Muro, S.; Nakano, Y.; Ohara, T.; Hoshino, Y.; Ogawa, E.; Hirai, T.; Niimi, A.; Nishimura, K.; Chin, K.; et al. CT scan findings of emphysema predict mortality in COPD. *Chest* **2010**, *138*, 635–640.
50. Biederer, J.; Beer, M.; Hirsch, W.; Wild, J.; Fabel, M.; Puderbach, M.; Van Beek, E.J. MRI of the lung (2/3). Why . . . when . . . how? *Insights Imaging* **2012**, *3*, 355–371.
51. Sverzellati, N.; Molinari, F.; Pirronti, T.; Bonomo, L.; Spagnolo, P.; Zompatori, M. New insights on COPD imaging via CT and MRI. *Int. J. Chronic Obstr. Pulm. Dis.* **2007**, *2*, 301–312.
52. Sarma, A.; Heilbrun, M.E.; Conner, K.E.; Stevens, S.M.; Woller, S.C.; Elliott, C.G. Radiation and chest CT scan examinations: What do we know? *Chest* **2012**, *142*, 750–760.
53. Smith-Bindman, R.; Lipson, J.; Marcus, R.; Kim, K.P.; Mahesh, M.; Gould, R.; Berrington de González, A.; Miglioretti, D.L. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch. Intern. Med.* **2009**, *169*, 2078–2086.
54. Miller, G.W.; Mugler, J.P.; Sá, R.C.; Altes, T.A.; Prisk, G.K.; Hopkins, S.R. Advances in functional and structural imaging of the human lung using proton MRI. *NMR Biomed.* **2014**, *27*, 1542–1556.
55. Theilmann, R.J.; Arai, T.J.; Samiee, A.; Dubowitz, D.J.; Hopkins, S.R.; Buxton, R.B.; Prisk, G.K. Quantitative MRI measurement of lung density must account for the change in T(2) (*) with lung inflation. *J. Magn. Reson. Imaging* **2009**, *30*, 527–534.
56. Croton, L.C.P.; Morgan, K.S.; Paganin, D.M.; Kerr, L.T.; Wallace, M.J.; Crossley, K.J.; Miller, S.L.; Yagi, N.; Uesugi, K.; Hooper, S.B.; et al. In situ phase contrast X-ray brain CT. *Sci. Rep.* **2018**, *8*, 11412.
57. Kitchen, M.J.; Buckley, G.A.; Kerr, L.T.; Lee, K.L.; Uesugi, K.; Yagi, N.; Hooper, S.B. Emphysema quantified: Mapping regional airway dimensions using 2D phase contrast X-ray imaging. *Biomed. Opt. Express* **2020**, *11*, 4176–4190.
58. Kitchen, M.J.; Lewis, R.A.; Morgan, M.J.; Wallace, M.J.; Siew, M.L.; Siu, K.K.; Habib, A.; Fouras, A.; Yagi, N.; Uesugi, K.; et al. Dynamic measures of regional lung air volume using phase contrast x-ray imaging. *Phys. Med. Biol.* **2008**, *53*, 6065–6077.
    Lewis, R.A.; Yagi, N.; Kitchen, M.J.; Morgan, M.J.; Paganin, D.; Siu, K.K.; Pavlov, K.; Williams, I.; Uesugi, K.; Wallace, M.J.; et al. Dynamic imaging of the lungs using x-ray phase contrast. *Phys. Med. Biol.* **2005**, *50*, 5031–5040.
59. Bravin, A.; Coan, P.; Suortti, P. X-ray phase-contrast imaging: From pre-clinical applications towards clinics. *Phys. Med. Biol.* **2013**, *58*, R1–R35.
60. Zhou, W.; Majidi, K.; Brankov, J.G. Analyzer-based phase-contrast imaging system using a micro focus X-ray source. *Rev. Sci. Instrum.* **2014**, *85*, 085114.
61. Vij, N. Prognosis-Based Early Intervention Strategies to Resolve Exacerbation and Progressive Lung Function Decline in Cystic Fibrosis. *J. Pers. Med.* **2021**, *11*, 96.
62. Ribeiro, C.O.; Faria, A.C.D.; Lopes, A.J.; de Melo, P.L. Forced oscillation technique for early detection of the effects of smoking and COPD: Contribution of fractional-order modeling. *Int. J. Chronic Obstr. Pulm. Dis.* **2018**, *13*, 3281–3295.
63. Oostveen, E.; MacLeod, D.; Lorino, H.; Farré, R.; Hantos, Z.; Desager, K.; Marchal, F. The forced oscillation technique in clinical practice: Methodology, recommendations and future developments. *Eur. Respir. J.* **2003**, *22*, 1026–1041.
64. Desiraju, K.; Agrawal, A. Impulse oscillometry: The state-of-art for lung function testing. *Lung India* **2016**, *33*, 410–416.
65. Bickel, S.; Popler, J.; Lesnick, B.; Eid, N. Impulse oscillometry: Interpretation and practical applications. *Chest* **2014**, *146*, 841–847.
66. Bhattarai, P.; Myers, S.; Chia, C.; Weber, H.C.; Young, S.; Williams, A.D.; Sohal, S.S. Clinical Application of Forced Oscillation Technique (FOT) in Early Detection of Airway Changes in Smokers. *J. Clin. Med.* **2020**, *9*, 2778.
67. Li, L.Y.; Yan, T.S.; Yang, J.; Li, Y.Q.; Fu, L.X.; Lan, L.; Liang, B.M.; Wang, M.Y.; Luo, F.M. Impulse oscillometry for detection of small airway dysfunction in subjects with chronic respiratory symptoms and preserved pulmonary function. *Respir. Res.* **2021**, *22*,68.

68. Faria, A.C.; Lopes, A.J.; Jansen, J.M.; Melo, P.L. Evaluating the forced oscillation technique in the detection of early smokinginduced respiratory changes. *Biomed. Eng. Online* **2009**, *8*, 22.
69. Amaral, J.L.; Lopes, A.J.; Faria, A.C.; Melo, P.L. Machine learning algorithms and forced oscillation measurements to categorise the airway obstruction severity in chronic obstructive pulmonary disease. *Comput. Methods Programs Biomed.* **2015**, *118*, 186–197.
70. Malmberg, L.P.; Mieskonen, S.; Pelkonen, A.; Kari, A.; Sovijärvi, A.R.; Turpeinen, M. Lung function measured by the oscillometric method in prematurely born children with chronic lung disease. *Eur. Respir. J.* **2000**, *16*, 598–603.
71. Kalhoff, H.; Breidenbach, R.; Smith, H.J.; Marek, W. Impulse oscillometry in preschool children and association with body mass index. *Respirology* **2011**, *16*, 174–179.
72. Uchida, A.; Ito, S.; Suki, B.; Matsubara, H.; Hasegawa, Y. Influence of cheek support on respiratory impedance measured by forced oscillation technique. *Springerplus* **2013**, *2*, 342.
73. Kim, C.W.; Kim, J.S.; Park, J.W.; Hong, C.S. Clinical applications of forced oscillation techniques (FOT) in patients with bronchial asthma. *Korean J. Intern. Med.* **2001**, *16*, 80–86.
74. Xia, J.; Yao, J.; Wang, L.V. Photoacoustic tomography: Principles and advances. *Electromagn. Waves* **2014**, *147*, 1–22.
75. Hou, R.; Le, T.; Murgu, S.D.; Chen, Z.; Brenner, M. Recent advances in optical coherence tomography for the diagnoses of lung disorders. *Expert Rev. Respir. Med.* **2011**, *5*, 711–724.
76. Beard, P. Biomedical photoacoustic imaging. *Interface Focus* **2011**, *1*, 602–631.