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RESEARCH ARTICLE

ROLE OF CHEST COMPUTED TOMOGRAPHY IN EVALUATION AND MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract

Chronic obstructive pulmonary disease (COPD) exhibits significant heterogeneity in its clinical presentation and rate of disease progression among affected individuals, owing at least in part to differing pulmonary morphologic abnormalities. Symptom assessment, spirometric evaluation, and frequency of respiratory exacerbations have traditionally been used to determine disease severity and guide management. ChestComputed Tomography (CT) scanning provides clear and exact in vivo assessments of organs, and from these data, we can extract subjective and objective features such as parenchymal remodeling, airway dilatation, and vascular calcification. These features can be used to detect the extent of the disease, its severity and also predict its clinical course. However, despite the increasing use and widespread availability of chest CT scans, the wealth of information from Chest CT scans is not consistently used in routine practice and has not yet been incorporated into clinical guidelines for COPD diagnosis, management or prognosis.This article reviews the role of CT in differentiating different phenotypes of Chronic Obstructive Pulmonary Disease (COPD), its clinical implications of emphysema, airway disease, air trapping, and pulmonary vasculature and, highlight the potential value of assessing nonpulmonary structures such as coronary arteries and vertebral bone to provide better comprehensive care for patients with COPD.

Introduction:-

The most recent update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) defined Chronic Obstructive Pulmonary Disease (COPD)as a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due toairway and/or alveolar abnormalities usually caused by significant exposure to noxious particles orgases and influenced by host factors including abnormal lung development.[1] Chronic obstructive pulmonary disease (COPD) exhibits significant heterogeneity in its clinical presentation. Symptom assessment,spirometric evaluation, and frequency of respiratory exacerbations have traditionally been used to determine disease severity and guide its management. Chest computed tomography (CT) is a noninvasive imaging modality that shows structural and pathophysiologic features, leading to a better understanding of disease and further characterization of COPD phenotypes.[2-3] Many patients with and at risk for COPD undergo a chest CT in the outpatient setting for lung cancer screening, evaluation of pulmonary nodules detected on chest X-ray, assessment of concurrent interstitial lung disease, or planning for surgical options such as lung transplantation and Lung Volume Reduction Surgery (LVRS).CT imaging can also help to decide on therapy

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that may be disease-modifying.CT scans are frequently done for chest pain and dyspnea in patients with COPD to rule out pulmonary embolism, cardiovascular disease, or infection. Although Chest CT scans are increasingly used and easily available,yet they are not used in the diagnosis, management and prognosis of COPD patients in routine practice.[4]This article reviews the role of CT in differentiating different phenotypes of Chronic Obstructive Pulmonary Disease(COPD), its clinical implications of pulmonary parameters like emphysema, airway disease, air trapping, and pulmonary vasculature and highlight the potential value of assessing nonpulmonary structures such as coronary arteries and vertebral bone to provide better comprehensive care for patients with COPD.

Pulmonary Parameters:-

Emphysema:-

Pulmonary emphysema is characterized by abnormal and permanent dilatation of air spaces and destruction of their walls distal to terminal bronchioles.[5] It can be visualized on CT by areas of low attenuation as well as vascular distortion and thinning. Emphysema is divided into three anatomic subtypes depending on its location within the secondary pulmonary lobules: centriacinar, panlobular/acinar, and paraseptal. Centrilobular emphysema is the most common form of smoking-related emphysema. It starts in the central portion of the secondary pulmonary lobules, initially as small holes that become more confluent as the disease progresses. It is typically upper lung predominant and is characterized by the obliteration or narrowing of distal bronchioles. Panlobular emphysema is predominant in the lower lobes of individuals with alpha-1 antitrypsin deficiency, involves each secondary lobule diffusely, and is accelerated in severity and age of onset in the presence of cigarette smoking. Bronchiolar lumen is generally preserved in pan-lobular emphysema. Paraseptal emphysema most commonly involves the upper lobes and affects the secondary pulmonary lobules along with the mediastinal, costal, and fissural pleural surfaces. Patients with centrilobular emphysema experience more dyspnea,have less exertional tolerance, and show evidence of hyperinflation and decrease diffusion capacity, [6] while patients with paraseptal emphysema tend to be male and asymptomatic and have unremarkable pulmonary function tests. Therefore, visual assessment and quantitative evaluation of emphysema on CT may be complementary. Increased compliance in emphysema and increased resistance from small airway disease contribute to airflow limitation in COPD. CT has the potential to identify COPD at an early stage because the narrowing and loss of terminal bronchioles occur before the development of emphysema. Expiratory CT scans are more sensitive in the routine practice of visual assessment of air trapping especially in the presence of emphysema. Chest CT seenhelps the determination of subtype of emphysema and is a validated tool for estimation of the extent of emphysema, but it is time-consuming and has interobserver variability.[7-9]Automated densitometry provides more reliable quantification of emphysema and are more sensitive for homogeneous changes in the lung parenchyma. [10] as calculating the percentage of lung voxels at or below a given attenuation threshold, which is referred to as the percent emphysema or percent low attenuation area for which optimal cut off is estimated to be between -950 and -970 Hounsfield units (HU)on basis of comparisons with macroscopic or microscopic morphometry of pathological specimens.[11-12]The clinical use of CT densitometry has been well demonstrated in patients with alpha-1 antitrypsin deficiency. In patients with alpha-1 antitrypsin deficiency, upper lung zone emphysema score was found to be an independent predictor of mortality on chest CT. [13-14] Quantitative methods are not able to distinguish between emphysema subtypes as centrilobular emphysema may be present in patients without quantitative emphysema, similarly, panlobular disease may be missed by visual inspection but detected on quantitative measurements.[15] So quantitative analysis and visual inspection on CT are complimentary for the evaluation of emphysema. Patients and CT-related factors such as obesity, adequacy of deep inspiration, and CT model and calibration can affect lung densitometry. Through adequate parameters such as spatial and temporal resolution, inspiratory breath-holding techniques, scanner calibration, and minimizing radiation exposure [16] in serial monitoring is always a goal. Recently use of dose optimization protocol with reconstruction techniques allowed to obtain CT scans at a fraction of the standard of clinical dose whilst still producing a quantitative measurement of emphysema, air trapping, and airway dimensions.[17-18] The advanced scanners provide optimism that radiation exposure from a quantitative chest CT reduced as much as an anterior-posterior and lateral digital chest radiographic examination.[19]

Airway Disease:-

Radiologic assessment of Airway disease severity is more challenging and has been less well studied and validated than the quantification of emphysema and visual assessment of airway wall thickness is subject to significant interobserver variability.[9] With recent advancement in CT technology of whole lung imaging at a slice thickness of less than 1mm within a single breath-hold allowed the development of three-dimensionalmodels of the central airway tree and the measurement of segmental and subsegmental airway wall thickness and luminal area. Airway size within and between subjects have variability which can affect these measurements. A useful measure known as

Pi10 takes advantage of the known linear relation between the square root of airway wall area and the internal perimeter of the airway,[20] hypothetically airway with an internal perimeter of 10mm.This measure in combination with quantitative emphysema and airway trapping assessment has been found to be a useful predictor of the presence of COPD.[21]Until the reproducibility, clinical validity, and ease of use of airway measurements can be further demonstrated.These quantitative methods are primarily limited to research and are not available at this time.Quantitative visual inspection of airways including measurement of bronchial wall thickening, bronchiectasisand expiratory central airway collapse, still remains the standard in routine clinical practice.

Air Trapping and Functional Small Airway Disease:-

Airflow limitation in COPD is contributed due to both increased compliance from emphysema and increased resistance from the small airway disease. Because the narrowing and loss of the terminal bronchioles occur before the development of emphysema, assessment of small airway disease severity is necessary to identify COPD at an early stage.[22] Although airways less than 2mm in diameter are the main site of airflow obstruction [23] which falls below the resolution limit of chest CT for direct evaluation. For this reason, investigators have useddifferent measures of air trapping on expiratory CT assurrogates for the estimation of functional small airway disease. These include the ratio of expiratory toinspiratory mean volume change of voxels with attenuation between -860 and -950 HU, [24] and the percentage of voxels below -856 HU in expiration.[25]However, each of these imaging techniques has its advantages and limitations and it remains to be determined which one correlates best with clinical outcomes. Onepromising application, parametric response mapping detects attenuation changes for individual voxels between co-registered volumetric inspiratory and expiratory CT scans to classify each voxel as normal lung, emphysema, and functional airway disease.[26]Not only does this technology allows for radiologic components of COPD to be geographically mapped but has the potential to further characterize phenotypes of COPD, monitordisease progression and assess response to therapy.[27-28]Another application, the air-trapping index depends on attenuation difference per voxel on co-registered inspiratory and expiratory CT scans.[29-30]Software programs for the detection of functional small airway disease are now clinically available and are more sensitive than the routine practice of visual assessment of air trapping on expiratory CT scans especially in the presence of emphysema.

Pulmonary Vasculature:-

Pulmonary vascular damage in patients with COPD is prevalent and maymanifest as pulmonary hypertension, especially in advanced diseases.[31]However little is known about pulmonary vascular changes early in COPD pathogenesis. New quantitative CT methods are being developed to better understand the relationship between these changes and emphysema. Smokers with early emphysema showed increased heterogeneity in pulmonary perfusion compared with never-smokers and smokers without emphysema by using multidetector-row CT perfusion imaging.[32] The pulmonary vascular remodeling through the distal pruning of small intraparenchymal blood vessels was demonstrated in a study by Estepar and colleagues using volumetric CT scans in smokers.[33] These findings suggest that inflammation associated with patches of emphysematous tissue may cause endothelial dysfunction and damage or promote local areas of hypoxic vasoconstriction, thereby resulting in perfusion heterogeneity. More recent work further shows that this pulmonary blood flow can be reversed with the use of sildenafil.[34]Althoughclinical significance of these findings still needs to be clarified. In clinical practice, many radiologists measureand report central pulmonary artery size butsoftware quantifying the entire intrapulmonary vascular volume is not routinely available.

Clinical Correlationsof CHEST CT Pulmonary Parameters:-

Emphysema, airway disease, air trapping, and pulmonary vascular abnormalities are common in smokers with and without COPD [35] and are associated with a number of clinically important outcomes.

Respiratory symptoms and health status:-

Increased dyspnea has been independently associated with both emphysema and airway disease identified on chest CT scans of subjects with COPD [36, 37]. Even among individuals without COPD, emphysema on chest CT has been associated with dyspnea[38], and airway wall thickening has been associated with higher COPD Assessment Test scores [39]. When examined together, however, the relative contribution of airway disease to worse health status seems to be greater than that of emphysema when adjusted for FEV1 percent predicted [40]. Hence, although assessing symptoms in smokers clearly does not require a CT scan, if one is available, clinicians should be aware that even among patients without spirometrically defined COPD, emphysema and airway wall thickening can be associated with increased respiratory symptoms and poorer health status.

Lung function and disease progression:-

In patients with COPD, FEV1 percent predicted on spirometry inversely correlates with emphysema and air trapping on chest CT [41, 42]. The relationship between lung function and airway disease identified on CT is more ambiguous due to inconsistent results that are influenced by the specific airway measure used and the size of the assessed airways [41-43]. Longitudinal studies designed to evaluate lung function decline found that emphysema detected on chest CT is independently associated with the rate of annual FEV1 decrease [44, 45]. Although Bhatt and coworkers confirmed this relationship, they also found that functional small airway disease on parametric response mapping was even more correlated with lung function decline than emphysema, especially in individuals with Global Initiative for Chronic Obstructive Lung Disease stage I or II COPD [46]. Furthermore, increased small airway abnormality was found even among current and former smokers without airflow obstruction. These results suggest that subjects with mild to moderate COPD and smokers with a preserved pulmonary function who have evidence of emphysema or air trapping on chest CT may be at increased risk for disease progression. Total lung capacity (TLC) is another metric commonly available from inspiratory CT. Although CT-based measures of TLC demonstrate a good correlation with TLC measured by plethysmography, the former may be underestimated, particularly in the presence of air trapping [47]. Thus, a normal TLC on chest CT suggests the absence of restrictive lung physiology, and a high TLC likely indicates the presence of hyperinflation.

COPD exacerbations:-

A multivariate analysis of the COPDGene cohort demonstrated that a 5% increase in emphysema in subjects with at least 35% total emphysema and a 1-mm increase in bronchial wall thickness was associated with an increase in annual COPD exacerbations by 1.18 and 1.84 times, respectively, regardless of the degree of airflow limitation [48]. Similar findings were observed in a prospective cohort of smokers for both qualitatively and quantitatively defined emphysema [49]. In other analyses, subjects with COPD with visually identified bronchiectasis on chest CT were found to have more frequent severe respiratory exacerbations when assessed by the need for hospitalization [50] or the duration of symptoms [51]. In a study of current and former smokers, central airway collapse greater than 50% on expiration was associated with a higher frequency of respiratory exacerbations [52]. Moreover, a ratio of the pulmonary artery diameter to the aorta diameter greater than 1 has also been demonstrated to be a strong and independent predictor of severe exacerbations [53], even when adjusted for lung function and prior history of exacerbations. For the clinician, these findings suggest that CT-quantified emphysema, airway disease, and pulmonary artery dilation provide additional information regarding increased COPD exacerbation risk beyond other readily available clinical and physiologic metrics. It still remains to be determined whether the exacerbation mechanisms differ between those three phenotypes and what implications this would have on prevention and treatment.

Lung cancer:-

Low-dose chest CT screening has been shown to decrease lung cancer mortality [54] and improve the detection of early-stage malignancy [55]. Subjects enrolled in the National Lung Screening Trial (NLST) were 55 to 74 years of age, with at least a 30 pack-year smoking history, and were either current smokers or former smokers who had not quit more than 15 years ago. Multiple studies have validated the independent association between visually assessed emphysema on chest CT and the risk of lung cancer in current, former, and never smokers [56–58]. Moreover, lung cancer was found to have a predilection for lobes with more severe emphysema [59]. This relationship has important clinical consequences, as the addition of emphysema to the NLST screening criteria led to fewer missed malignancies [60].

Mortality:-

Although the presence of bronchiectasis on CT portends a worse survival [61], airway wall thickness as measured by Pi10 has not been related to increased mortality [62]. On the other hand, both visual and quantitative assessments of emphysema have been shown to be independent predictors of all-cause, respiratory, or cardiovascular mortality in smokers with and, notably, without COPD [62–65]. This association further supports the known relationship between worse emphysema and higher scores on the body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index, which is a well-validated predictor of mortality in subjects with COPD [66]. In terms of therapy, LVRS confers a survival advantage in selected patients with predominantly upper-lobe emphysema and poor exercise capacity [67]. A chest CT to assess emphysema distribution and fissural integrity is required to evaluate a patient's candidacy for LVRS and advancedbronchoscopic interventions, respectively. Even though endobronchial coils and valves can improve lung function, exercise tolerance, and quality of life in patients with either

homogeneous or heterogeneous emphysema, their long-term outcomes and safety still need to be determined [68–72]. None of these devices are currently approved for use in the United States.

Nonpulmonary Structures:-

Coronary Arteries:-

Ischemic heart disease is a common comorbidity in COPD [73]. Myocardial infarction occurs more frequently and carries worse mortality in patients with COPD, even after accounting for shared risk factors like age and smoking [74, 75]. Therefore, the early identification of coronary artery disease and the institution of appropriate preventive strategies have the potential to improve outcomes in this patient population. The measurement of coronary artery calcium (CAC) on chest CT provides a noninvasive and accurate assessment of coronary atherosclerosis. An elevated CAC score has been shown to be an independent predictor of future cardiovascular events and deaths in both symptomatic and asymptomatic patients [76–78]. CAC scores were found to be higher in subjects with COPD than in nonsmokers and smokers with normal spirometry and were associated with increased mortality [79]. Visual assessment of CAC (classified as mild, moderate, or severe calcification) performed as well as quantitative measurements such as Agatston scoring with respect to predicting cardiovascular death [80]. Although an electrocardiographically gated CT is usually the study of choice to measure CAC, Budoff and colleagues showed low-dose ungated CT scans to be a reliable alternative [81]. Thus, chest CT scans performed in patients with COPD for noncardiac reasons, such as lung cancer screening or pulmonary embolism exclusion, provide an opportunity to evaluate coronary atherosclerosis. However, because CAC is typically recommended for screening of asymptomatic adults with intermediate cardiovascular risk, the clinical implications of this measurement reported on chest CT scan ordered for other reasons in an unselected population need to be further elucidated. At this time, when available, a CAC score should be integrated with each patient's other cardiac risk factors to guide individual management.

Vertebral Bone:-

Osteoporosis is prevalent in COPD, as the two conditions share common clinical factors such as smoking, low body mass index, physical inactivity, steroid use, and vitamin D deficiency [82]. More importantly, a diagnosis of severe COPD was associated with significantly increased 1-year mortality in patients with osteoporotic hip fractures [83]. Although dual-energy X-ray absorptiometry (DXA) of the lumbar spine and hip is currently the gold standard for the screening and diagnosis of osteoporosis, quantitative CT (QCT) is emerging as an alternative for assessing bone mineral density (BMD) [84, 85] and predicting future vertebral fractures [86], particularly in smokers who had a chest CT performed for other purposes. Although DXA yields an area measure of BMD (in milligrams per square centimetre) that sums both cortical and cancellous values, QCT uses a three-dimensional technique that reports a volumetric assessment (in mg/cm3) and provides information on osseous architecture by identifying cancellous versus cortical bone. Because most vertebral compression fractures occur in the mid to lower thoracic region, chest CT provides a good window for the evaluation of thoracic BMD and vertebral fractures. Jaramillo and coworkers showed that COPD, and more specifically the emphysema phenotype, was associated with low vertebral volumetric BMD measured on chest CT even after accounting for traditional risk factors of osteoporosis [87]. Low vertebral bone attenuation detected on chest CT was also shown to be an independent predictor of increased morbidity in patients with COPD, including higher rates of respiratory exacerbations and hospitalizations [88]. In addition, vertebral compression fractures can result in decreased vital capacity [89]. More studies are needed to determine whether vertebral BMD assessed on QCT is adequate to predict fractures prospectively and whether it can be used to initiate treatment. At this time, further evaluation of patients with low QCT vertebral bone attenuation values should be considered using standard DXA measurements to determine T scores and make treatment decisions.

Conclusions:-

Although chest CT is not currently considered standard of care in the diagnosis and management of mild to moderate COPD, its expanding use for other purposes now demands that clinicians understand how to treat radiologic information that becomes available. For subjects with established COPD, chest CT provides data on the risk of lung function decline, respiratory exacerbations, and death, independently and incrementally to routinely used studies, such as pulmonary function tests and symptom measures. In patients with end-stage disease, chest CT has clear utility in identifying those who would benefit from interventions such as LVRS and lung transplants. Chest CT should be more frequently integrated in COPD clinical trials to determine the effect of existing or new therapies on patients with different imaging phenotypes, as has been shown with LVRS. In smokers being screened for lung cancer, CT-quantified emphysema and air trapping, along with certain clinical variables, can be used to identify individuals with airflow obstruction. Therefore, one could argue that any significant amount of emphysema, airway disease, or air trapping noted by a radiologist on a chest CT performed for any reason should raise the clinician's

suspicion for COPD if spirometry has not already been performed. Beyond the assessment of airways and lung parenchyma, images from existing chest CT scans also provide information on extrapulmonary parameters and comorbidities, including coronary artery disease and osteoporosis, which are recognized as an essential aspect of COPD care. In that context, chest CT clearly has the potential to become a powerful tool in the quest for personalized medicine in COPD. Whether it is incorporated into routine assessment for patients with COPD will ultimately depend on our ability to demonstrate that this information changes management and improves outcomes.

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