original article

EARLY DETECTION OF SMOKING INDUCED LUNG DAMAGE IN PATIENTS WITH NORMAL PULMONARY FUNCTION TESTS: EVALUATION WITH HIGH RESOLUTION COMPUTED TOMOGRAM (HRCT) CHEST

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Abstract

Background: Spirometry is accepted universally to diagnose chronic obstructive pulmonary disease. However, many current and former smokers who do not meet the spirometric criteria for COPD may assume that they are disease free and may be having significant respiratory disease demonstrable by imaging.

Study design & Objective: It was a Cross-sectional observational study. To evaluate the possibility of detecting early COPD/smoking induced lung damage in current and former smokers having normal spirometry, by using HRCT chest.

Materials & Methods: Sixty-four patients either former or current smokers aged 40-70 years who had normal pulmonary function test were included in this study. The cases were subjected to detailed history, clinical examination including pulmonary function tests (PFT) and high-resolution computed tomography (HRCT) chest.

Results: Out of 64 cases 57 were current and 7 were former smokers. Around 64 % of smokers had one or more respiratory related symptoms. Around 12.5 % of smokers with normal PFT had significant emphysema on quantitative CT (QCT) measurements. Around 4.7 % smokers with normal PFT had significant air trapping on QCT. Almost 12.5 % of smokers had other CT chest findings other than emphysema & air trapping. There was a significant correlation between CT documented emphysema with age, pack years (> 35 pack years) & sputum production.

Conclusion: Relying exclusively on pulmonary function tests to diagnose COPD/ smoking related lung disease may underestimate significant early smoking related lung diseases, hence it is imperative to supplement patient evaluation with HRCT for identifying early disease and thus motivating current smokers to quit smoking.

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Introduction

There are around 1.3 billion smokers worldwide and on an average at present around 47.5% of men and 10.3% of women are current tobacco users. Tobacco continues to be the second major cause of death in the world around 8.8% of mortality and 4.1% of disability adjusted life years (DALY`s) are lost due to smoking related problems, in particular respiratory system related.[1] Tobacco addiction is one of the biggest public health threats the world has ever faced, killing more than 7 million people a year. By 2030, if current trends continue, smoking will kill over 9 million people annually.[2]

Smoking associated chemicals lead to lung irritation and mucus over production and thus contributing to various lung pathologies some of which last for short time and are sudden like pneumonia, cough, cold; some last long time and are chronic like emphysema, lung cancer, chronic obstructive pulmonary disease (COPD) etc. [3,4]Around 90% of overall lung cancer deaths and 80% of COPD related deaths are due to smoking.

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COPD, as a consequence of smoking is the third leading cause of death in the USA and a major cause of chronic disability. [5] The chronic airflow limitation that is characteristic of COPD is caused by a mixture of small airways disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person.[6]

Spirometry is a way of detecting the presence of airway obstruction and making a definitive diagnosis of asthma and COPD.[7] The spirometric definition of COPD typically requires a post bronchodilator response of forced expiratory volume in one second to forced vital capacity (FEV1/FVC) of less than 0.7. Although, Global Initiative for Obstructive Lung Disease (GOLD) do not currently include CT chest in the workup of COPD, there is a significant literature suggesting that HRCT chest is an important tool in relevant clinical setting.[8,9]

HRCT chest can reveal evidence of COPD i.e. pulmonary emphysema in asymptomatic smokers with normal pulmonary function tests. Also, HRCT chest can help distinguish between different causes of emphysema e.g. smoking disease (centri-lobular emphysema) and lesions associated with alpha-1-proteinase inhibitor deficiency. Another evidence of COPD which can be detected through HRCT chest in asymptomatic smokers which is hardly detectable with conventional PFT is air trapping. Air-trapping on HRCT chest in smokers and ex-smokers correlate with the inflammatory infiltration of peripheral airways. Air-trapping in an expiratory CT chest has been seen to strongly correlate with decrease in FEV1 and FEV1/FVC and is a surrogate of early smoking induced lung damage and COPD. Several studies have confirmed that airways smaller than 2mm in internal diameter (4th – 14th generation of trachea-bronchial tree branching) represent the major site of airway obstruction in patients with COPD. Airway trapping is a key finding for depicting small airway obstruction on HRCT scan. Airway trapping in current and former smokers have been shown to be correlating with inflammatory infiltration of peripheral airways. [8,9,10]

The third evidence of COPD which can be picked by HRCT chest in smokers with normal PFT is increased bronchial wall thickening. In addition, CT chest can reveal what PFTs often cannot, e.g. lesion that may mimic COPD. Conditions like bronchiectasis, upper airway disease, bronchiolar disease, pulmonary nodules, pleural based lesions and interstitial lung disease are often associated with COPD and HRCT chest can discriminate between different causes of airflow obstruction[10]. Presence of bronchiectasis on CT chest in COPD patients may provide a means of identifying those patients with COPD who are at risk of more severe disease exacerbations.

Cigarette smoking is a major factor associated with the development of emphysema and is also an independent risk factor for lung cancer. Because of the poor prognosis of both conditions, there are obvious medical and economic reasons justifying the detection of subclinical abnormalities in smokers in order to reinforce prevention and intensify smoking cessation campaigns. Therefore, the present study was conducted to detect early COPD/ smoking induced lung disease utilising HRCT chest in smokers who have normal PFT.

Aims & Objectives

• To evaluate the possibility of detecting early COPD/smoking induced lung damage in current and former smokers having normal spirometry, by using HRCT chest.

Materials & methods

The current study was conducted at Sher-i-Kashmir Institute of Medical Sciences and Sher-i-Kashmir Institute of Medical Sciences Medical College, Srinagar from September 2015 to August 2017 over a period of 24 months. Sixty-four subjects were included in this study. The study was prospective in design. All ethical considerations were taken care of during the study and the recruitment process was started only after ethical clearance from the Institutional Ethical Committee as per norms and all the individuals gave their informed consent to participate in the study. The informed consent was taken in local language.

Inclusion criteria

- Healthy smokers without pulmonary function abnormalities.
- Current smokers/former-smokers in age group 40-70yrs.

Exclusion criteria

Ischemic heart disease, respiratory diseases other than COPD, rheumatoid arthritis and collagen vascular diseases, haemoptysis of unknown origin, pneumothorax, unstable angina, recent eye surgery, recent thoraco-abdominal surgery, acute disorder affecting spirometry (nausea, vomiting), unstable cardiovascular status (e.g. myocardial infarction / pulmonary embolism), vertebral column / Neuromuscular abnormalities, subjects unwilling to participate, individuals younger than 40 years and older than 70 years, never smokers with abnormal spirometry and individuals with already diagnosed lung diseases like bronchiectasis, lung cancers, tuberculosis, bronchial asthma, interstitial lung disease were excluded from the study.

Spirometry

Before doing pre-drug spirometry, all the baseline parameters (height, weight, abdominal and hip circumference, pulse) were measured. The spirometer used during the study was Electronic desktop spirometer, Schiller spirovit. The spirometer fulfilled ATS and ERS criteria for accuracy and precision. The spirometry testing was performed according to the guidelines prescribed in American Thoracic Society (ATS) and European respiratory society (ERS) guidelines. Before doing spirometry testing, spirometry questionnaire was administered and spirometry was not performed on participants who had any of the contraindications for performing spirometry. The apparatus was calibrated daily. A maximum forced exhalation was carried out for a minimum of 6 seconds, while the subjects were in a sitting position. Testing was repeated until a minimum of three acceptable flow volume loops with a FEV1 and FVC within 150 ml were obtained. The HRCT chest was done within a week time after doing the PFT.

HRCT chest Non-contrast enhanced, HRCT chest was performed using a Siemens Somaton sensation 64 slice CT (Siemens, Erlangen, Germany). HRCT chest were done in a supine position. Volumetric CT scans were obtained for all participants after giving instructions and a proper demo about the standardized technique. The scans were obtained during deep inspiratory breath-hold at a standard CT dose, and at the end of a normal expiration (functional residual capacity) at reduced CT dose in a craniocaudal direction of the supine position. The typical CT parameters were as follows: submillimeter collimation (0.6–0.75 mm) and submillimeter reconstruction (thickness: 0.625–0.9 mm, interval: 0.45–0.625 mm) with both standard and high-frequency protocols, 120 kVp and 200 mAs for the inspiration scan and 50 mAs for the expiration scan and different parameters were drawn using Lung CARE software.

Inspiratory and expiratory CT scans of all the subjects in the study were evaluated. Measures examined included emphysema, defined as the percentage of low-attenuation areas ≤ –950 Hounsfield (HU) on inspiratory CT; air trapping, defined as the percentage of low attenuation areas ≤ –856 HU on expiratory CT. In both inspiratory and expiratory films, images were reconstructed, from -500 to +3095 HU so as remove structures other than lung parenchyma. The emphysema was considered significant if more than 5% of the total inspiratory volume and air trapping was significant if more than 20% of the total expiratory lung volume.

Results

A total of 64 smokers with normal PFT were included in the study. Fifty-seven patients were current smokers and 7 patients were former smokers. The demographic, clinical, PFT & HRCT chest characteristics of the study population is given in Table 1. The demographic, clinical, PFT & HRCT chest characteristics of the current and former smokers of the study population is given in Table 2.

Age (years) (Median (IQR))	55	14
BMI (Kg/m^2) (Mean ± SD)	24.18	9.67
Duration of symptoms (Years) (Median (IQR))	0.5	0.9
Pack Years (pack/years) (Mean ± SD)	25.84	10.42
Post FEV1 (Litres) (Mean ± SD)	3.16	0.78
Post FVC (Litres) (Mean ± SD)	4.12	1
Post FEV1/ FVC [Median (IQR)]	80.5	7.98
TLV Expiratory (Litres) (Mean ± SD)	4.28	0.92
TLV Inspiratory FRC (Litres) (Median [IQR)]	5.2	0.9
Quantification of emphysema in Litres [Median (IQR)]	62.5	119
Emphysema (percent) [Median (IQR)]	1.3	2.68

Table 1.*Demographic, clinical, PFT & HRCT chest findings of study population. BMI= Body mass index, FEV 1= Forced expiratory volume 1, FVC= Forced volume capacity, TLV= Total lung volume, FRC= Forced residual capacity, SD= Standard deviation, IQR = Interquartile range.*

Various abnormal HRCT chest findings of emphysema, air trapping and other abnormalities in the study population are mentioned in Table 3. Clinical symptoms of cough & breathlessness were statistically insignificant in patients with HRCT abnormalities. However, a smoking history of more than 35 pack years (p value=0.006) & history of mild sputum production (one teaspoonful/ day) was statistically significant (p = 0.05) in patients with HRCT findings of emphysema although there was no association of air trapping or other HRCT chest abnormalities with sputum production.

Fourteen patients had either one or more HRCT abnormalities that suggested COPD or smoking related lung injury. Emphysema was seen in 5 patients, 2 patients had air trapping, 4 patients had other HRCT abnormalities, 2 patients had emphysema & other HRCT abnormalities, 1 patient had air trapping & other HRCT chest abnormalities and 1 patient had all the three abnormalities i.e. emphysema, air trapping & other HRCT abnormalities.

	Normal	**Abnormal**
Emphysema volume	56 (87.5%)	8 (12.5%)
Air Trapping	61 (95.3%)	3 (4.7%)
Other CT Chest Abnormalities	56 (87.5%)	8 (12.5%)

Table 2. *Various abnormal HRCT chest findings in study population.*

HRCT chest	CT Normal	Emphysema	p value
Age [Median (IQR)]	55 (15)	60 (10)	0.035
BMI [Median (IQR)]	23.9 (3.18)	24.11 (5.78)	0.855
Pack years [Median (IQR)]	22 (17)	35.5 (19)	0.009
Duration (symptom) [Median (IQR)]	0.5 (1)	0.75 (2.5)	0.112
Post FEV1[Median (IQR)]	3.24 (.81)	2.93 (.68)	0.155
Post FVC [Median (IQR)]	4.18 (1.01)	3.79 (.84)	0.282
FEV1/FVC [Median (IQR)]	80.77 (7.53)	77.31 (5.85)	0.056

Table 3. *Demographic, clinical & PFT correlation of normal Vs abnormal HRCT chest findings.*

	Normal HRCT	Abnormal HRCT
Number	**50**	**14**
Percent	**78.12**	**21.88**

Table 4.*The percentage of abnormal HRCT chest in smokers with normal PFT.*

Pack years	<35 pack years	≥35 pack years	p value
HRCT Normal	40	10	0.006
HRCT Abnormal	6	8	

Table 5. *Relation of pack years with abnormal HRCT chest in smokers with normal PFT. Persons with smoking history of more than 35 pack years had significant changes suggestive of COPD on the HRCT chest. (p value=0.006)*

Discussion

Chronic obstructive pulmonary disease a common, preventable and treatable disease characterised by persistent respiratory symptoms and air flow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gasses. It should be considered in any patient having dyspnea, chronic cough or sputum production and/or history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis. The presence of post-bronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD. [6]

Many current and former smokers who do not meet the spirometric criteria for COPD may assume they are disease free may be having significant respiratory disease demonstrable by imaging. The demonstration of imaging abnormalities in asymptomatic patients may provide an early and possibly reversible window period of intervention before progressing to the irreversible stage demonstrable on spirometry. Spirometry may be insensitive to early disease or subclinical lung pathology in part because variations in the maximally attained FEV1 of young adulthood gives smokers with higher values a greater buffer before declining to defined disease levels. [11, 12, 13]

The total number of patients in this study were 64 comparable to that of a study carried by Betsuyaku et al. who studied the HRCT findings in asymptomatic smokers with normal PFT and detected low attenuation areas (emphysema) in a significant number of patients having lower FEV1 values though within normal range comparable to those without LAA.[14]

In our study the selected subjects were of the age group of 40 – 70 years with a mean age of 55 years comparable to that of study carried by Regan et al. [15] Although most of the smokers start smoking at much early age however the compromise of lung function progresses with age and COPD is more prevalent in elderly population.[16] Most of the population based studies including Indian for screening early COPD in smokers with normal PFT have taken subjects above 30-40 years of age. In DIDASCO (Differential Diagnosis between Asthma and COPD) a population-based study, individuals aged 35-70 years were subjected to spirometry for early diagnosis. [17, 18, 19]

The selected patients had minimum smoking exposure of 10 pack years with a mean pack year of 25.84 which was in accordance to study carried by Regan et al. and Yasunagaet al.[15, 20]

The skewed distribution of males versus females in this study may be explained by lower prevalence of smoking among females in our part of world due to socio-cultural reasons and stigma associated with smoking in females hindering their volunteering for participating in such studies.

This study demonstrated that 64% of patients who didn't meet the spirometric criteria for COPD had one or more respiratory system related symptoms (cough, exertional breathlessness and sputum production) supporting the association of these symptoms with effect of smoking on lung and general health which was in accordance to the study carried out by Regan et al. and Woodruff et al., where the prevalence of symptoms was 50%.[15, 21]

The slightly higher prevalence of respiratory symptoms may be explained on the basis of hospital rather than community-based study. The 40% of the patients having sputum production had emphysema on imaging as compared to 10.2% of patients with no sputum production, an observation that was statistically significant (p value < 0.05). There was no significant association of cough and breathlessness in patients with CT showing emphysema.

The former smokers with the spirometric values though within normal range had greater decline in FEV1 and FEV1% than the current smokers possibly

due to greater quantum of pack years in former smokers and a younger population in current smoker group. This was in accordance to study carried by Regan et al. [15]

Quantitative analysis of emphysema as defined by percentage of low-attenuation areas ≤ -950 HU on inspiratory CT; and air trapping as defined by the percentage of low-attenuation areas ≤ -856 HU on expiratory CT; was done and was consistent with studies carried out by Schroder et al., Arakawa et al., Busaker et al., who demonstrated a strong correlation of inspiratory emphysema and expiratory air trapping.[11, 12, 13, 22]

The percentage of patients with emphysema using QCT measurements was 12.5% in our study consistent with 12.4% using QCT scoring in a study by Regan et al.[15] The prevalence of emphysema on imaging was 25% in patients with pack years more than 40 as compared to 9.6% in patients with pack years less than 40.

The 4.7% of patients in this study who were current smokers had significant air trapping (more than 20%) on QTC scoring as compared to the study carried out by Regan et al,[15] in which the percentage was 14.5% using the same scoring system and Tanaka et al. where the overall frequency of air trapping in smokers with normal spirometry was as high as 64% though the percentage of patients with extensive air trapping was 16%. The discordant results could be explained by the high cut of levels of air trapping (more than 20%) in our study and the use of visual scoring system for air trapping rather than QCT scoring in other study. Genetic variations in our population and the use of alternative methods having intrinsic errors as compared to automatic software for quantifying the results in developed countries may also have reflected in our results in relation to air trapping.

Our study showed 8.3 % of smokers with pack years > 40 had gas trapping as against 3.8 % of smokers with pack years < 40 an observation which is in accordance to the study conducted by Liu Y& et al. [23]

In our study 12.5 % of current and former smokers with normal spirometry had other lesions (micro-nodules, ground-glass attenuation, pleura-based nodules) on imaging and the abnormalities were more common (16.7%) in patients with pack years more than 40 than in patients with pack year less than 40 (11.5%). These results are in contrast to the study carried out by Tanka et al. in which micro-nodules were seen in 27% of patients and ground-glass attenuation in 20% of patients. [24]

The findings in this study debunk the myth of the so-called healthy smokers and highlight the importance of smoking cessation to prevent lung disease and long-term effect of smoking. It would be worthwhile for physicians to discuss with smokers about benefits of getting lung CT done to detect early changes and institute appropriate measures for preventing irreversible damage.

Conclusion

Overall the findings point to limitation in the current spirometric diagnostic criteria for COPD and suggest that spirometry is insensitive in detecting early smoking induced lung damage. The current and former smokers having a normal spirometry may consider themselves disease free, yet they have an early smoking induced lung damage which if detected early may give an objective reason for the smokers to quit smoking and halt or reverse the progression of disease.

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