ORIGNIAL ARTICLE

AIRWAY WALL THICKNESS IN PATIENTS WITH UNCONTROLLED ASTHMA

By

Aliaë AR Mohamed-Hussein,[1] Samy AA Sayed[2]

[1] Chest, ERS Scientific Council, [2] Radiology Departments, Assiut University Hospitals, Assiut, Egypt

Rationale: *Asthma is characterized by chronic inflammation and structural changes in the airways referred to as remodeling. Recently, high resolution CT (HRCT) has been used to indirectly assess airway remodeling in vivo, on the basis of findings such as airway wall thickening.*

Objectives: *1) To assess airway wall thickness by HRCT in patients with uncontrolled and partly controlled asthma and to compare these findings with normal healthy controls, 2) to investigate the association between disease duration and the degree of airflow limitation and airway wall thickness parameters.*

Design: *Prospective case- control study*

Subjects and methods: *Fifty -two patients with asthma and 23 healthy controls were recruited in the study. We measured airway luminal area (Ai) corrected by body surface area (Ai/√BSA), airway wall area (WA) corrected by body surface area (WA/√BSA), the percentage of wall area (WA %), absolute wall thickness (T)/√BSA, and thickness to diameter ratio (TDR) by HRCT. Spirometric tests were also performed.*

Results: *In patients with uncontrolled and partly controlled asthma, Ai/ BSA, WA/BSA, WA%, and T/√ BSA were all significantly greater than those in controlled and healthy control subjects. No significant difference in airway wall thickness parameters were found between controlled asthmatics and healthy controls. The degree of airway wall thickness was correlated to smoking, disease duration and percentage of predicted forced vital capacity (FVC %), forced expiratory volume in 1st second (FEV1%) and FEV1/FVC and post- bronchodilator reversibility in asthmatics.*

Conclusions: *The airways of uncontrolled and partly controlled asthmatics are thickened when compared to controlled asthmatics and healthy controls. Smoking and prolonged disease duration may be important factors in determining the airway wall thickness and hence the irreversibility of airway obstruction in this group of patients.*

Keywords: *remodeling; airway wall thickness; high resolution computed tomography; asthma.*

INTRODUCTION

Increased airway wall thickness has been recognized as a feature of asthma for almost a century.[1] Histological specimens obtained from necroscopic studies and bronchial biopsies showed that this airway wall thickening might be secondary to chronic inflammation.[2-3] This airway wall thickening results from mucosal infiltration with inflammatory cells, smooth muscle hyperplasia, deposition of connective tissue, and mucous gland hyperplasia. It involves all layers of the airway wall including the muscle membrane and the adventitia.[4]

Although remodeling of the airway wall has been evaluated at necropsy after death from asthma,[2] it has recently been assessed using bronchial biopsy specimen.[5] Biopsies can demonstrate several qualitative changes of the bronchial wall, but they can not assess precisely changes in airway smooth muscle or thickening of the whole airway wall, and is not likely to be representative to smaller airways.[6]

However, with the refinement of resolution of the high resolution CT (HRCT) it may now be possible to assess and quantify the extent of airway remodeling in- vivo.[7] Thin section CT has made it possible to measure airway dimensions accurately. Quantitative analysis of the bronchial wall thickness, airway narrowing and broncho-dilatation can be performed for measuring the airway dimension.[8] Confirmation that whole airway wall thickness parallels reticular basement membrane thickness and induces airflow obstruction in asthmatics may help to clarify the pathogenesis of irreversible or refractory airflow obstruction.[9]

Awadh et al.[10] described a relatively simple method of estimating airway wall thickness of segmental and sub-segmental bronchi by HRCT. Measurements of bronchial wall thickness and luminal diameter were averaged from all bronchi with a luminal diameter of >1 mm in five selected scans levels. From these values the ratio of airway wall thickness to total diameter (TDR) and the percentage wall area (PWA) were determined. They found that asthmatics have greater airway wall thickening than normal subjects and that those with severe disease have thicker airways than milder disease. Similar results of increase in TDR and PWA in patients with moderate and severe asthma were recorded by Mohamed-Hussein and co-workers in 2005.[11] These findings are in keeping with post mortem studies in asthma and would support the concept of chronic inflammation causing bronchial wall thickening and remodeling.[2-12]

Recently, measurements of airway wall dimensions are corrected by body surface area (BSA). Airway wall thickness, assessed by a validated CT technique measured wall area corrected by body surface area (WA/√BSA), the ratio of WA to outer wall area (WA%), and the absolute wall thickness corrected by √BSA (T/√BSA). The WA% and T/√BSA were positively correlated with post-bronchodilator values of mid-forced expiratory flow and maximum expiratory flow at the quartile of lung volume.[13]Also, WA/BSA, WA%, and T/√BSA were all significantly greater in patients with cough variant asthma than those in control subjects.[14]

The aim of this study was to quantify airway wall thickness and luminal area in uncontrolled and partly controlled asthmatics compared to controlled asthmatics and healthy control subjects, by HRCT. In addition, the relation of airway wall thickness to the clinical characteristics of the asthmatic patients, such as age, smoking, disease duration, degree of asthma control, and degree of airflow obstruction were investigated.

MATERIALS AND METHODS

Fifty- two patients with asthma and 23 healthy control subjects matched for age and sex were selected randomly from Chest Department and Chest out-patients clinic, Assiut University

Hospitals. Asthma was diagnosed and classified according to Global initiative for Asthma (GINA, 2006).[15] Uncontrolled asthma was defined as three or more features of partly controlled asthma present in any week and one exacerbation in any week. Partly controlled patients had daytime symptoms > twice/week, any limitation of activity, nocturnal symptoms/awakening, need for reliever/rescue treatment >twice/week, FEV1 or PEF<80% predicted and one or more exacerbation/year. Controlled asthmatics had none of these criteria and normal lung function.[15] The presence of chronic bronchitis, emphysema, bronchiectasis, and pulmonary tuberculosis were ruled out by history, clinical examination, and chest radiography.

Control subjects were healthy volunteers with no history of asthma and had normal spirometric results, none of them had any record of past or current major disease (heart or lung disease). Pregnancy was an exclusion criterion.

To minimize reversible changes such as inflammation and bronchospasm, all patients with uncontrolled or partly controlled asthma received 0.5 mg/kg prednisolone/ day orally for 2 weeks and inhaled salbutamol sulfate (2 puffs) 15 minutes before HRCT. It is believed that pretreatment with oral prednisolone and an inhaled ß2 agonist may suppress latent inflammation and airway spasm.[16]

Pulmonary function tests: Spirometric tests were performed with ZAN Spirometer (Messgeraete GmbH, Germany, Model GbI 3.00) to measure forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV1), FEV1/FVC % and Mid-expiratory flow (MEF25-75%). Each measurement was repeated at least three times and the highest acceptable measurement was compared with normal predicted values. FEV1 is used to evaluate the large airways, whereas MEF25-75 reflects the small airways.

HRCT scanning: The thoracic CT examination was performed with Toshiba X-press scanner. All examinations were performed from the apex to the base of the lungs, with the patient in supine position at end of inspiration (end-inspiratory volume) without use of contrast medium.

Image evaluation: We assessed the bronchial wall thickness as follows: all visible sections of the bronchi were counted at five levels in both pulmonary fields. All circular (complete circles or at least two thirds of a circle) and longitudinal bronchi except hilar bronchi were included. The five levels were 1 cm above the carina, 1cm below the carina, right pulmonary vein, and 2-3cm below the top of the pulmonary vein and above the right side of the diaphragm. The images were reconstructed using a high-resolution algorithm and were visualized using a window width of 1500 to 1600 Hounsfield units (HU) and window level of (–440 to –500 HU), to analyze airway wall thickness.

Two or more bronchi in a single scanning slice were examined (a total ≥10 bronchi/ subject). Mean values from 10 or more measurements per subject were calculated and compared in patients and controls.

Magnified field of views on both lungs were reconstructed from raw data. We used anatomic landmarks (airway or vascular branching points) to match the sections obtained during the successive sets of measurements in each patient. We measured the internal and external bronchial diameters by using electronic calipers.

For each patient we computed the total sum of all cross sectional areas of selected bronchi and the following airway dimensions were assessed by validated HRCT techniques (Nakano et al., 2000, Niimi et al., 2000, Little et al., 2002.[17-19]

We measured airway wall area (WA) corrected by body surface area (BSA), the percentage of wall area [WA%= { [π (D/2)2 -π (L/2)2]/ π(D/2)2 }.100]), absolute wall thickness corrected by BSA, (T/√BSA), thickness to diameter ratio (TDR) and airway luminal area (Ai) and Ai/√BSA .Body

surface area was computed using the Dubois formula: BSA(m2)= 0.20247 x Height(m) 0.755 x Weight (kg) 0.425

Statistical Analysis: The SPSS version 11 for windows for statistical analysis of data was used. The means for groups were compared using the Mann- Whitney's test. Differences between groups and subgroups were assessed by analysis of variance (ANOVA). The Spearman-rho tests were used to determine correlation between age, smoking, duration, asthma severity, PFTs parameters, and bronchial wall thickening parameters in HRCT.

Ethical consideration: The Assiut University's Ethics Committee approved the study and all subjects gave written informed consent.

RESULTS

Fifty-tow asthmatic patients and 23 controls were recruited in this prospective study. They included 21 uncontrolled asthmatics, 14 partly controlled and 17 controlled asthma. The characteristics of the patients and control subjects are presented in Table 1. There is significant difference in smoking index, disease duration, and in the mean PFTs parameters (pretreatment) between the studied groups.

The findings of HRCT scan measurements are shown in Table 2. The Ai, Ai/√BSA, WA, WA/√BSA, WA%, TDR and T/√BSA, are significantly higher in patients with uncontrolled and partly controlled asthma than in controlled asthmatics and healthy controls.

No correlation is observed between airway wall thickness parameters with age. However, significant positive correlation between Ai, Ai/√BSA, WA, WA%, WA/√BSA and T/√BSA and smoking and duration of asthma. The FVC%, FEV1 %, FEV1/FVC% and reversibility were negatively correlated with airway wall thickness parameters, Table 3.

DISCUSSION

The main findings in this study are: 1) the airway wall thickness increases in uncontrolled and partly controlled asthma, 2) Smokers and patients with more prolonged asthma duration has more prominent airway wall thickness, 3) increase airway wall thickness was associated with more airflow obstruction and reduced reversibility.

Airway remodeling is often considered to contribute to the element of irreversible airflow obstruction, which is a feature of some patients with asthma.[9] Many attempts have been made to analyze airway remodeling and bronchial wall thickening quantitatively by HRCT. Boulet et al., measured the thickness of the intermediate bronchus with an electronic caliper and calculated the ratio of wall thickness to outer diameter.[8] Okazawa et al., measured the airway wall area and airway wall percentage, [(airway wall area / total area) x 100].[20] Awadh et al.[10] and Niimi et al.[18] applied a slightly modified version of this technique to adults with asthma. We chose a modified HRCT technique to assess airway dimensions in patients with asthma by using the previous techniques with image amplification.

The WA, WA/√BSA, WA%, T/√BSA and TDR were significantly higher in uncontrolled and partly controlled asthmatics compared with patients with controlled asthma and healthy controls. These data support that remodeling with irreversible thickening of whole airway wall, causes irreversible functional changes and progressive airflow limitation in asthmatics. This agrees with studies involving quantitative analysis of HRCT scans in asthmatics[10-11-18-21] These studies have shown that: all groups of patients with mild to severe asthma, defined according to clinical[10-11-18] or functional[11-21] criteria have airway walls that are thicker than those of healthy subjects. Subjects with more severe asthma display a greater amount of airway wall thickening than those with milder asthma.

Similarly, Kasahara et al[9] illustrated that reticular basement membrane (Rbm) thickness in bronchial

biopsy specimens, PWA and WT% in HRCT scans, were significantly and negatively correlated with FEV1%. Previous studies have also shown that thickening of either the bronchial Rbm or the airway wall was correlated with disease severity, decreases in respiratory function, and airway hyper-responsiveness in asthmatics.[9-23-24] Severe thickness in subbasement membrane (SBM) was a characteristic feature for patients with refractory asthma and had significant positive correlation with the period of refractory course, decline in FEV1% of predicted and the number of admissions both to hospital and ICU in refractory asthma group.[25]

In contrast, other studies have reported that airway wall thickening was not correlated with airflow obstruction. In asthma, many factors in addition to irreversible airway wall thickening may contribute to airflow obstruction including airway wall edema, inflammation, mucus secretion, and bronchial smooth muscle spasm.[8-21]

This study showed that there was no significant correlation between WA, WA%, WA/√BSA, T/√BSA and TDR with age. Awadh et al,[10] reported that the T/D ratio showed no significant correlation with aging. Similarly, Matsuoka et al., found no significant correlation between broncho-arterial ratio and T/D ratio and age. They added that the bronchial wall thickness was only significantly higher in the elderly smokers who had higher smoking index and stated that this might be related to the synergistic effect between aging and smoking.[11-26]

Cigarette smoking is a major risk factor for airflow limitation. Recently, data from HRCT of airway dimensions in smokers were reported, and abnormal bronchial wall thickness was observed with greater frequency in smokers than non-smokers.[26-29] In the present study positive correlations were found between WA, WA%, WA/√BSA, T/√BSA and TDR and smoking in both asthmatics and healthy controls. The differences in smoking pack/years between asthmatic groups and between control groups may have had an effect on the wall thickness and degree airflow limitation and degree of asthma control. This may be explained by the known interaction between smoking and asthma on lung function.

We examined the correlation between airway wall thickness parameters and the duration and the degree of airflow obstruction. We found significant positive correlation between the duration of asthma and significant negative correlation between FVC%, FEV1%and FEV1/FVC% with indices of airway wall thickness. Awadh et al.,[10] found that the WA and WA/BSA, significantly correlated with the duration (although weakly), and severity of asthma. Similar findings supported the hypothesis that there is a progressive increase in airway wall thickening with increasing duration as well as severity of asthma.[11]

Also, significant negative correlation was found between WA or WA/BSA and FEV1, FEV1/FVC, or FEF25-75% and between PWA and FEV1.[7-10] This does not seem to apply to the relation between WA and WA/BSA in healthy control subjects.[30] Mehanna et al., demonstrated significant relation between the degree of bronchial wall thickening, degree of large and small airway obstruction in 22 bronchiectatic patients.[31]

We observed a significant negative correlation between post bronchodilator reversibility and WA, WA%, WA/√BSA, T/√BSA and TDR. These findings and those of earlier studies suggest that some patients with asthma have irreversible or partially reversible airway obstruction, which may cause refractory airway obstruction and greater decline in respiratory function, despite intensive treatment including inhaled steroids, bronchodilators, and other anti-inflammatory drugs. Such airway obstruction may results from structural alterations of the bronchi.[8-11-25- 32]

Lastly, we noticed that the luminal area (Ai), Ai/√BSA were increased in cases with

uncontrolled and partly controlled asthma than in controlled asthmatics and controls. This phenomenon is difficult to interpret but could be explained at least partly by the following speculations: a) the presence of bronchial dilatation has been reported in many CT studies in asthma especially in severe cases,[8-22-33] b) another possibility involves the effect of lung volumes on airway dimensions. Lung volumes increase with increasing severity in asthmatic patients and airway luminal area becomes larger as lung volume increase,[34] c) or due to thickening extending outward, rather than encroaching on the lumen, although encroachment on the lumen might be expected in cases of asthma where there is fixed airflow obstruction, as in COPD.[35]

In conclusion, we have shown with the use of HRCT that patients with uncontrolled and partly controlled asthma have more airway wall thickening than controlled asthmatics and normal controls. Smoking and prolonged disease duration may be important factors in determining the degree of airway wall thickness and hence the irreversibility of airway obstruction in asthma. The HRCT could be used in association with clinical and spirometric data to identify patients with a higher risk of remodeling. Further studies should be performed to further define the role of HRCT in the follow–up of asthmatic specially those with long history of asthma.

Table 1. Clinical characteristics in the control subjects and the asthmatic subgroups.

Variable	Uncontrolled asthma n= 21	Partly controlled asthma n=14	Controlled asthma n=17	Controls n=23
Gender				
Male, n (%)	10 (43.4)	9 (64.3)	10 (58.8)	13 (56.5)
Female, n (%)	11 (46.6)	5 (35.7)	7 (41.2)	10 (43.5)
Age, years, mean (SD)	46.6 (8.4)	47.3 (16)	46.7 (19)	44.7(12)
BSA, m2, mean(SD)	1.59 (0.16)	1.64 (0.13)	1.62 (0.17)	1.54 (0.19)
-Smokers and ex-smokers, n (%)	8 (38.1)	7 (50)	6 (35.2)	10 (43.5)
Smoking index (pack. year), mean (SD)	15.4 (2) P1<0.01	14.3 (1) P2<0.01	2.7 (3) P3=NS P4<0.01	2.5 (8)
Duration of asthma, years, mean (SD)	11.9 (2.7)	8.1(1.2)	7.9(1.8) P4<0.05	-
FVC% of predicted, Mean (SD)	35.1 (9) P1<0.001	69 (8) P2<0.001	95 (3) P3=NS P4<0.001	101(2)
FEV1% of predicted, Mean (SD)	29.7 (9) P1<0.001	74.1(6) P2<0.001	94.3 (16.6) P3=NS P4<0.001	107.7
FEV1/FVC%,	39.6 (8)	67.4 (2)	76.9 (9.9)	81.1 ± 5.3

Table 1. Clinical characteristics in the control subjects and the asthmatic subgroups.

Variable	Uncontrolled asthma n= 21	Partly controlled asthma n=14	Controlled asthma n=17	Controls n=23
Mean (SD)	P1<0.01	P2<0.01	P3=NS P4<0.01	
FEF25-75% , Mean (SD)	23.8 (12) P1<0.001	48.2(18) P2<0.01	96.2 (5) P3=NS P4<0.01	97.8 (20.3)
Reversibility %, Mean (SD)	12.4 (0.3)	16.2 (3.1)	Not tested	Not tested
Medication used on admission				
- Inhaled B2 agonists, n (%)	17 (73.9)	14 (100)	None	None
- ICS, n (%)	10 (43.4)	9 (64.3)		
- Theophylline SR, n (%)	20 (95.3)	6 (42.8)		
- Oral steroids, n (%)	21(100)	7(50)		

ICS= Inhaled steroids were recorded if the patients were on regular inhaled steroids for more than 6 months, SR= sustained release.
Data are expressed in mean (SD). Significance was considered at P-values <0.05.
NS= Non-significant.
P1=uncontrolled asthma versus controls.
P2=partly controlled asthma versus controls.
P3= controlled asthma versus controls.
P4= uncontrolled and partly controlled versus controlled asthma.

Table 2. Airway wall thickness parameters as measured by HRCT scanning.

Variable	Uncontrolled asthma n= 21	Partly controlled asthma n=14	Controlled asthma n=17	Controls n=23
Ai, mm2, Mean (SD)	16.4 (7.9) P1<0.05	15.9 (5.6) P2<0.05	14.1 (7.2) P3=NS P4<0.05	14.4 (4.3)
Ai/BSA, mm2/m2, Mean (SD)	13.18 (0.4) P1<0.001	12.4 (5.1) P2<0.001	9.2 (4.5) P3=NS P4<0.01	9.7 (4.1)
WA, mm2, Mean (SD)	31.3 (8.2) P1<0.001	26.3 (8.3) P2<0.001	20.7 (4.2) P3<0.05 P4<0.001	17.6 (4.3)
WA/BSA, mm2/m2	24.9 (5.0) P1<0.001	18.8 (3.1) P2<0.001	12.4 (3.2) P3=NS P4<0.01	11.6 (2.0)

Table 2. Airway wall thickness parameters as measured by HRCT scanning.

Variable	Uncontrolled asthma n= 21	Partly controlled asthma n=14	Controlled asthma n=17	Controls n=23
WA% (%)	87.9 (5.4) P1<0.01	86.8 (2.1) P2<0.01	81.2 (0.3) P3<0.05 P4<0.01	77.8(0.9)
TDR, Mean (SD)	0.46 (0.01) P1<0.01	0.43(0.06) P2<0.01	0.34(0.01) P3=NS P4<0.01	0.32(0.09)
Absolute T/BSA mm/m2	4.2(0.3) P1<0.001	3.7(0.02) P2<0.001	1.3 (0.4) P3=NS P4<0.01	1.4(0.3)

Ai = luminal area, BSA= body surface area, WA= wall area, WA% = WA/(WA + luminal area) × 100; T = thickness; TDR= thickness to diameter ratio.

Data are expressed in mean (SD). Significance was considered at P-values <0.05. NS: Non-significant.

P1=uncontrolled asthma versus controls.

P2=partly controlled asthma versus controls.

P3= controlled asthma versus controls.

P4= uncontrolled and partly controlled versus controlled asthma.

There was significant difference between uncontrolled, partly controlled asthma and healthy controls , and both groups were significantly greater than controlled asthmatics.

Table 3. Correlation coefficients (r) between airway wall thickness and clinical indices in all asthmatic patients.

Variable	Ai	Ai/BSA	T/BSA	TDR	WA%	WA/BSA
Age	0.132	0.083	0.012	0.127	0.105	0.213
Smoking (pack/year)	0.598**	0.498**	0.327*	0.152	0.145	0.322*
Duration of asthma, yrs	0.323**	0.531**	0.313*	0.373*	0.468**	0.548**
FVC% of predicted	-0.421**	-0.650**	-0.532**	-0.512**	-0.409**	-0.503**
FEV1% of predicted	-0.648**	-0.289*	-0.546**	-0.517**	-0.422**	-0.436**
Ratio	-0.398*	-0.461**	-0.393*	-0.317**	-0.399**	-0.365*
FEF 25-75% of predicted	-0.433**	-0.288*	0.327*	0.218 *	0.258**	-0.544**
Reversibility	-0.769**	-0.381*	-0.409**	-0.582**	- 0. 382*	-0.765**

FEF25-75% = forced expiratory flow during the middle half of the FVC, TDR =thickness to diameter ratio, PWA = percentage wall area. Severity scored as: uncontrolled=4, partly controlled =3, controlled asthma=2, healthy control= 1. Pearson's correlation coefficients were done for parametric variables. Spearman's correlation was analyzed for other variables.

** = Correlation significant at the level < 0.01 (2- tailed).

* = Correlation significant at the level < 0.05 (2- tailed).

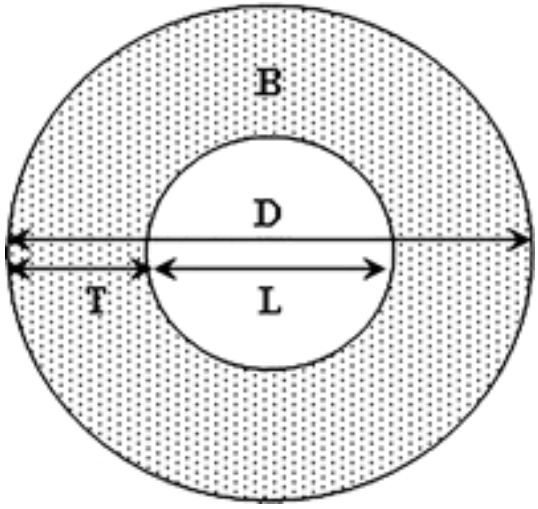

*Fig 1. Schematic drawing of airway measurements. T= wall thickness, D=bronchial external diameter, L= bronchial lumen diameter. The WA%=[WA%= ([π (D/2)2 -π (L/2)2) / π(D/2)2) *100]) where π(D/2)2 is the total area and luminal area, Ai= π(L/2)2 (Matsuoka et al, 2005).*

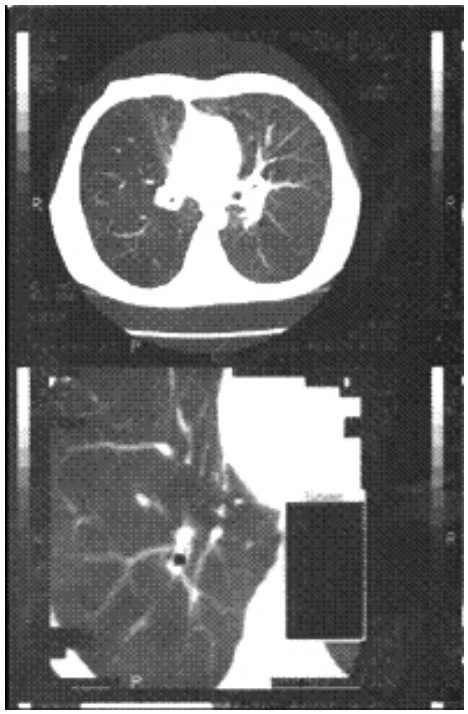

Fig 2. HRCT scans obtained from 39 years old male with partly controlled asthma, 1cm below the carina. All circular visible bronchi were counted and measurements were obtained from the magnified images.

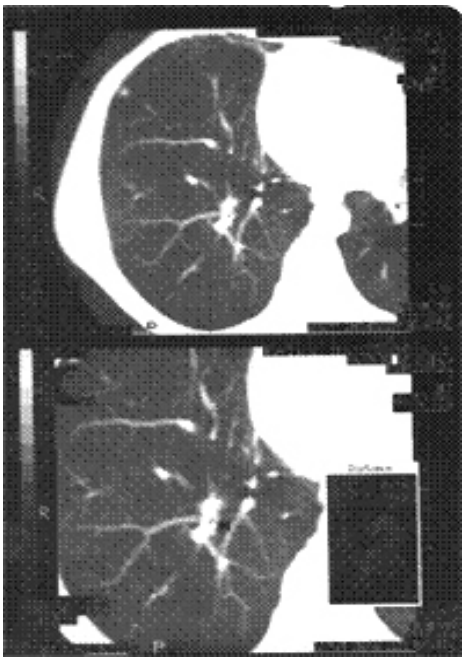

Fig 3. HRCT scan of 46 years old male with uncontrolled asthma at the level of right pulmonary vein. L=lumen (white arrow).

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