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COMPARISON OF SPIROMETRY AND IMAGING BIO-MARKERS IN EARLY DETECTION OF SMALL AIRWAY DISEASE

Radiology

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ABSTRACT

Background: Small Airway Diseases (SAD) are a group of disorders affecting airways with calibers < 2mm. They are significant contributors to morbidity in a range of lung pathologies. New Hydrofluroalkane (HFA) pressurized Metered Dose Inhalers (pMDI) now offer the possibility of targeted therapeutics for SAD. Early diagnosis is essential for rapid institution of therapy and improving long-term outcomes.However the appropriate investigation for screening of SAD remains unclear. In this study, we compare spirometry to HRCT for screening of SAD. **Methods:** Consecutively sampled patients suspected of SAD were made to undergo HRCT and Pulmonary Function Tests (PFT). HRCT images were interpreted with consensus reporting by two radiologists blinded to patient history and PFT findings. **Results:** The mean FEF_{25-75} values differed by 3.43 ± 7.27 between subjects with and without small airway disease. The difference however was not found to be statistically significant. $FEF_{25-75}$was found to have a sensitivity of 0.86 and positive predictive value of 0.42.There was no statistically significant relationship found between FEF_{25-75} and imaging bio-markers of small airway disease. **Conclusion:** The low specificity afforded by FEF_{25-75}makes it an inferior choice to HRCT. HRCT provides a one-stop-shop alternative for screening and confirmation of early SAD.

KEYWORDS

Small Airway Disease, Spirometry, High Resolution Computed Tomography, Peripheral Airways

INTRODUCTION

Small Airway Diseases (SAD) predominantly affect the distal airways supplying the secondary pulmonary lobule[1] and are silent but significant contributors to morbidity in a host of lung pathologies.[2] While High Resolution Computed Tomography (HRCT) and Pulmonary Function Tests provide complementary information, considerable ambiguity still remains in their role in diagnosis of early SAD.[3,4,5]

In this study, we compare the validity of FEF_{25-75}against imaging bio-markers in the diagnosis of early SAD. We hypothesize that imaging bio-markers may provide a superior alternative to spirometry in the initial assessment of suspected cases of Small Airway Disease.

MATERIALS AND METHODS

Cohort Selection

From 1st November 2018 to 31st March 2020, all patients clinically suspected of small airway dysfunction and presenting to the Department of Radiodiagnosis, were prospectively assessed. The study was approved by the Institutional Ethical Committee. Informed consent was obtained before inclusion of the participant into the study.

Detailed clinical, social and economic history was documented. History of cigarette consumption was sought from each participant and Brinkman Index was calculated. Each participant was clinically evaluated for symptoms such as cough and dyspnoea. Relevant clinical details collected included age, gender, height, weight, BMI, duration of smoking (in years) and duration since cessation of smoking (in months).

Patients with history of Pulmonary Tuberculosis or having gross fibro-calcific changes on CXR were excluded from the study. Subjects diagnosed with Small Vessel Disease, Pulmonary Arterial Hypertension or having moderate to severe dyspnoea, were also excluded. Participants who did not undergo all the steps of assessment were also excluded from final analysis.

The final cohort consisted of 55 individuals, who were made to undergo Pulmonary Functions Tests and HRCT examination within 4 weeks of the initial assessment.

Pulmonary Function Tests

A pneumotachygraph (Easy-on-PC; NDD Medical Technologies Inc., Zurich, Switzerland) was utilized to record expiratory flow volume curves. Instrument calibration, technique and curve selection was done in accordance to American Thoracic Guidelines.[6] Parameters obtained included: Forced Vital capacity (FVC), Forced Expiratory Volume in 1 second (FEV_1), FEV_1/FVC Ratio and Forced Expiratory Flow between 25% and 75% FVC (FEF_{25-75}). All findings were projected as percentages of predicted values using techniques laid down by Knudson et al.[7]

The participants were also subjected to Impulse Oscillometry using Impulse Oscillometry system (Jaeger MasterScreen Impulse Oscillometry system; Jaeger Co, Wurzburg, Germany). The instrument was calibrated for saturated gas pressure and body temperature. Impulses of multiple frequencies were used and measurements were made during tidal breathing over half minute intervals. Participants were encouraged and evaluated by trained technicians. Three artifact-free reproducible maneuvers were selected for analysis. Resistance of the airway was calculated at discrete frequencies of 6 – 20 Hz. The average of the three recordings was for final assessment.

High Resolution Computed Tomography

High Resolution Computed Tomography scanning was done using Somatom Definition Flash (Siemens, Erlangen, Germany). The protocol followed involved 0.625 slice thickness, 120 kv, 100 – 200 mAs, 1.5 – 3 mm collimation, 768 x 768 matrix size and a FOV of 35 cm. A high spatial frequency algorithm was used for image reconstruction.

Images were interpreted by at least two radiologists blinded to patient history and pulmonary function test results. Consensus reporting was in cases of incongruent interpretations. Scans were visually assessed for markers of small airway dysfunction. Each marker of small airway disease was categorized on the basis of conspicuity into mild, moderate and severe. Lesions involving 3 secondary pulmonary lobules or less were categorized as mild. Lesions involving more than 3 secondary pulmonary lobules but restricted to one segment were marked as 'Moderate'. Those lesions which were not limited to a single segment were labeled 'Severe'.

RESULTS

Cohort Characteristics

The general characteristics of the study group are summarized in Table 1. The mean age of the study group was 47.8 years with the largest fraction in the cohort stemming from the 4th decade [29%] followed by the 6th decade [27%].The cohort had a female preponderance with almost twice as many females as male subjects. Cough and breathlessness were the two most commonly reported symptoms. The median duration of cough was 24 months and that of breathlessness was 12 months. The pulmonary function test parameters are summarized in Table 1. Sub-optimal and incomplete Impulse Oscillometry examinations were excluded from the final analysis. The median R6 – R20 value was 17.12 [n=33].

Findings on HRCT

Of the 55 participants selected for the study, 30 [54.54%] were diagnosed with small airway disease on imaging. The distribution of imaging bio-markers of small airway disease is shown in Table 2. The most common marker of small airway disease amongst the cohort was found to be mosaic attenuation, seen in 29 patients [32.22%]. This was followed closely by ground glass opacities (11 patients [12.22%]) and bronchiolar wall thickening (10 patients [11.11%]).

Most of the findings were 'Severe' in conspicuity. Mosaic attenuation had the highest relative proportion of severe lesions with all 29 patients [100%] diagnosed with the marker having widespread lesions. Ground glass opacities were found to have the largest relative proportion of Mild category lesion [7.27%].

Comparison of Functional and Imaging Parameters

The mean FEF_{25-75} values differed by 3.43 ± 7.27 between subjects with and without small airway disease. The difference however was not found to be statistically significant. A cutoff of 0.60 was used to dichotomize the sub-cohort of small airway disease patients. $FEF_{25-75}$was found to have a sensitivity of 0.86 and positive predictive value of 0.42.

The three most prevalent imaging bio-markers, namely: mosaic attenuation, ground glass opacities and bronchial wall thickening were compared with FEF_{25-75} values. Using the above mentioned cutoff of 0.60, FEF_{25-75} had sensitivity of 0.89 and positive predictive value of 0.65 for detecting Mosaic Attenuation. For ground glass opacities, it had a sensitivity of 0.75 and likelihood ratio of 0.86. The findings are summarized in Table 2.

There was no statistically significant relationship found between FEF_{25-75} and imaging bio-markers of small airway disease.

Table 1: Cohort Characteristics (n=55)		
Age		47.85 ± 2.0 years
Weight		59.78 ± 3.0 kg
Height		157.3 ± 1.5 cm
Duration of Cough		33.13 ± 5.19 months
Duration of Dyspnoea		26.39 ± 5.25 months
Sex	Male	18 (32.7%)
	Female	37 (67.3%)
*Data represented as Mean ± Standard Error of Mean		
Pulmonary Function Test Results (n=55)		
FVC		60 ± 21.77
FEV_1		52.18 ± 22.81
FEV_1/FVC		86.82 ± 20.42
FEF_{25-75}		37.76 ± 22.79
R6 – R20†		16.72 ± 10.94
†n=33 *Results were expressed as a percentage of the predicted value and represented as Mean ± SD		

Table 2: Relative Distribution of Markers of Small Airway Disease (n=55*)

Conspicuity of Lesion	Mild		Moderate		Severe		Total	
Centrilobular Nodules	1	(1.81)	3	(5.45)	5	(9.09)	9	(16.36)
Tree-in-bud Opacities	2	(3.63)	1	(1.81)	3	(5.45)	6	(10.90)
Mosaic Attenuation	0	(0.00)	0	(0.00)	29	(52.72)	29	(52.72)
Air Trapping	1	(1.81)	1	(1.81)	5	(9.09)	7	(12.72)
Atelectasis	1	(1.81)	1	(1.81)	2	(3.63)	4	(7.27)
Ground Glass Opacities	4	(7.27)	1	(1.81)	6	(10.90)	11	(20)
Cylindrical Bronchiolectasis	1	(1.81)	0	(0.00)	6	(10.90)	7	(12.72)
Centrilobular Emphysema	1	(1.81)	1	(1.81)	4	(7.27)	6	(10.90)
Mucoid Impaction	0	(0.00)	1	(1.81)	0	(0.00)	1	(1.81)
Bronchiolar Wall Thickening	1	(1.81)	2	(3.63)	7	(12.72)	10	(18.18)

*Multiple Observations †Numbers in parenthesis denote relative percentages

Assessment of validity of FEF_{25-75} (Threshold = 0.60)

Imaging Biomarker	Sensitivity	Specificity	PPV	NPV	Likelihood Ratio
Mosaic attenuation	0.89 (0.72,0.96)	0.23 (0.09,0.47)	0.65 (0.49,0.78)	0.57 (0.25,0.84)	1.16
Ground glass opacity	0.75 (0.40,0.95)	0.13 (0.05,0.27)	0.15 (0.07,0.30)	0.71 (0.35,0.94)	0.86
Bronchial wall thickening	1.00 (0.72,1.00)	0.17 (0.08,0.32)	0.25 (0.14,0.41)	1.00 (0.60,1.00)	1.20
All bio-markers	0.86 (0.70,0.94)	0.27 (0.09,0.56)	0.76 (0.60,0.87)	0.42 (0.15,0.74)	1.19

*numbers in parenthesis are 95% CI

DISCUSSION

In this study, a group of 55 subjects clinically suspected of Small Airway dysfunction, were investigated with HRCT to document the markers of Small Airway Disease. The age distribution of the study population was bimodal with peaks at 4th and 6th decades [29% and 26% respectively].

The mean age for subjects with Small Airway Disease was 48.67 years while it was 46.88 years for those not diagnosed with Small Airway dysfunction. The difference in mean age was 1.78±4. This difference may be attributed to increasing peripheral airway obstruction with ageing. There has been limited research into the role of ageing in obstruction of the peripheral airways. Boudewijn et al was the first to investigate the effect of age on small airways.[8] They found a strong correlation between increasing age and PRMfsad as well as PRMemph and PRMpd. The mean age for their cohort was 40 years, similar to this study. Further evidence for this relationship was furnished by the SPIROMICS study, which revealed a significant association between the extent of PRMfsad and age, with a rise of 2.7% per decade.[9] The association between age and Small Airway Disease was not found to be statistically significant in our study. This is probably because aging may be causing sub-clinical peripheral airway damage which may not always culminate into pathological signs of Small Airway Disease on qualitative CT. While earlier studies have shown a correlation between quantitative air trapping and age, it remains to be seen if this is clinically relevant and translates into higher risk of precipitating frank Small Airway Disease.

The cohort in our study was composed of 67.27% females. Sex has not been investigated as a risk factor associated with Small Airway dysfunction. In this study, 22 of the 37 female subjects were found to have Small Airway Disease. However, the association was not found to be statistically significant [P = 0.389]. Despite this, our results establish that there was a definitive trend for females developing Small Airway Disease with 59.45% of females being affected compared to 44.44% of males. A larger cohort should be studied to evaluate the possibility of female sex predisposing to the development of peripheral lung obstruction.

Anthropometric data acquired at the time of examination reveals a canny picture. The median weight was found to be 54.50 kg. The median BMI of the group was 24.09. Though high BMI may put individuals at risk of developing peripheral airway obstruction, particularly due to aspiration pneumonia,[10] no such statistically significant association was found in our study group.

The subjects were also made to undergo pulmonary function tests whenever possible. Pulmonary function was assessed by Spirometry

and Impulse Oscillometry. The median FVC%pred was 0.56 with FEV1/FVC%pred of 0.87. The mean MEFR%pred value was 37.76% ±3.397. MEFR%pred is the most commonly implemented test parameter to detect Small Airway dysfunction. Values less than 60% [0.6] are considered to indicators of peripheral airway occlusion.

In this study, MEFR%pred was not found to be significantly associated with Small Airway Disease. The result is in agreement with work previously done by Mastora et al.[3] Small Airway Disease, nonetheless was present in 76.47% [n=34] of subjects with MEFR%pred<0.6. Subsequent investigation by Jain et al, using air trapping as a proxy quantitative marker for Small Airway Disease, has shown significant correlation with low MEFR values.[11] The sensitivity of MEFR%pred<0.6 in our investigation, was found to be 86.67% but specificity was poor, at 27.27%. The Positive Predictive Value was 76.47%. This roughly translates to 3 out of 4 subjects with MEFR%pred<0.6 having Small Airway Disease.

MEFR%pred was also evaluated for screening of Mosaic Attenuation, Ground Glass Opacities and Bronchial Wall Thickening. The sensitivity of MEFR%pred for diagnosis of the individual markers of Small Airway dysfunction was high, with 89.29%, 75% and 100% for Mosaic Attenuation, Ground Glass Opacities and Bronchial Wall Thickening respectively. Positive Predictive Values were found to be low, ranging from 65.79% for Mosaic Attenuation to 15.79% for Ground Glass Opacities. This again confirmed that, while MEFR values may be used to screen for these markers they were poor predictors of disease. No significant association was found between MEFR values and the three markers of Small Airway Disease. These findings are in line with observations made in previous studies.[3]

Evidence to use MEFR%pred to screen for Small Airway Disease remains inconclusive. This further strengthens the argument for HRCT as the lead modality for diagnosis of Small Airway Disease and may even hint to the possibility of its use as a screening tool in the future. However low cost and lack of detrimental ionizing radiation purports that it is unlikely to be replaced as the screening modality of choice in the near future.

33 patients also underwent Impulse Oscillometry to look for evidence of Small Airway obstruction. The R6-R20 value is usually indicative of peripheral resistance. Univariate analysis failed to determine any significant difference between the mean R6-R20 values of those diagnosed with Small Airway Disease and those without peripheral airway obstruction. This finding is in agreement with work done by Jain et al.[11] Impulse Oscillometry is a niche investigation, often inaccessible and requiring specifically trained staff. From our study, we can infer that limited, if any, value is derived from subjecting patients suspected of Small Airway Disease through the procedure and HRCT is often a reliable and easily accessible alternative.

Traditionally, diagnosis of Small Airway Disease on HRCT is established on the basis of 'Direct' and 'Indirect' markers.[12] The most common marker found in our cohort was Mosaic Attenuation [52.72%], followed by Ground Glass Opacities [20%], Bronchial Wall Thickening [18.18%] and Centrilobular Nodules [16.36%]. This is of particular interest as Centrilobular Nodules and Tree in Bud Opacities are taken to be direct markers of Small Airway Disease. Despite the over-emphasis on these two markers, they were not found in most cases of Small Airway Disease diagnosed in this study. On the other hand, Mosaic Attenuation which is relegated to the 'Indirect' category, was the most prevalent sign of peripheral airway dysfunction.

These findings were contradictory to the observations of Umer et al.[13] In their retrospective analysis of a cohort of 100 subjects, the most prevalent marker was Tree in Bud Opacities. The second most common marker was Mosaic Attenuation [22%] followed by Bronchial Wall thickening [13%]. The lack of 'Direct' markers in our study may be attributed to chance and a small sample size. It must also be noted, that we have not included the pediatric population in the study unlike Umer et al and this may have led to an inadvertent exclusion of a large number infective bronchiolitis cases, which were the main source of Tree in Bud Opacities in their study. This assumption is supported by the similarity in the trends of prevalence of 'Indirect' markers and the relatively high proportions of Mosaic Attenuation and Bronchial Wall Thickening in our study, which are in agreement with their findings. The association between Small Airway Disease and Mosaic Attenuation was found to be statistically significant [p <0.0001]. Subjects with demonstrable Mosaic Attenuation were found almost 6 times more likely to have Small Airway Disease [RR = 5.828].

The high prevalence of Ground Glass Opacities and Bronchial Wall Thickening in our study, closely reflects the findings of Mastora et al.[3] Among their 250 participants, the investigators found Ground Glass Opacities and Bronchial Wall Thickening in 47 subjects each [33%], making them the second most common finding of peripheral airway dysfunction.

Air trapping has been cited as the best indicator of Small Airway Disease on HRCT.[14] But diagnosis of air trapping warrants unnecessary exposure to additional radiation to acquire expiratory scans, and previous studies have argued its value in routine use.[15] In most cases of peripheral airway dysfunction, inspiratory scans often reveal one or more markers of disease and dedicated expiratory maneuvers do not add to the diagnosis.[3] Furthermore, air trapping has been consistently found in normal individuals, calling into question the interpretation of disease by its mere presence.[3,16] Based on our investigation, Mosaic Attenuation holds promise as a future direct marker for Small Airway Disease. Moreover it may also be quantified by Parametric Response Mapping and be used as marker of disease severity as air trapping is used today.

In our study, the search for 'Direct' markers did not yield any diagnostic advantages over the use of 'Indirect' markers. The high prevalence of Mosaic Attenuation, Ground Glass Opacity and Bronchial Wall Thickening in our study adds credence to the argument against differentiating between 'Direct' and 'Indirect' markers. The so called 'Direct' markers may not be as common and relying upon them heavily may reduce the sensitivity of the radiologist in detecting Small Airway Disease.

Our study had a few limitations. The study cohort lacked pediatric subjects. Logistical barriers meant the Pulmonary Function Tests could not be conducted on the same day as HRCT. Histo-pathological confirmation of imaging diagnosis was not possible.

CONCLUSION

In conclusion, Pulmonary Function Tests did not provide any additional advantage in the investigation of a Small Airway Disease suspect.The low specificity afforded by FEF_{25-75}makes it an inferior choice to HRCT for screening of early SAD. HRCT provides a good alternative to spirometry and may reduce time to treatment in such patients.Mosaic Attenuation was found to be a strongly correlated marker of Small Airway dysfunction on HRCT and may be used as a primary sign of disease on inspiratory HRCT.

REFERENCES

1. Ranga V, Kleinerman J. Structure and function of small airways in health and disease. Arch Pathol Lab Med 1978;102:609-17.
2. van den Berge M, ten Hacken NH, Cohen J, Douma WR, Postma DS. Small airway disease in asthma and COPD: clinical implications. Chest 2011;139:412-23.
3. Mastora I, Remy-Jardin M, Sobaszek A, Boulenguez C, Remy J, Edme JL. Thin-section CT finding in 250 volunteers: assessment of the relationship of CT findings with smoking history and pulmonary function test results. Radiology 2001;218:695-702.
4. Mets OM, Murphy K, Zanen P, Gietema HA, Lammers JW, Van Ginneken B, *et al*. The relationship between lung function impairment and quantitative computed tomography in chronic obstructive pulmonary disease. Eur. Radiol. 2012;22:120-8.
5. Schroeder JD, McKenzie AS, Zach JA, Wilson CG, Curran-Everett D, Stinson DS, *et al*. Relationships between airflow obstruction and quantitative CT measurements of emphysema, air trapping, and airways in subjects with and without chronic obstructive pulmonary disease. Am. J. Roentgenol. 2013;201:W460-70.
6. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL,*et al*. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Am. J. Respir. Crit. 2019;200:e70-88.
7. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am. J. Respir. Crit. Care Med. 1983;127:725-34.
8. Boudewijn IM, Postma DS, Telenga ED, ten Hacken NH, Timens W, Oudkerk M, *et al*. Effects of ageing and smoking on pulmonary computed tomography scans using parametric response mapping. Eur. Respir. J. 2015;46:1193-6.
9. Martinez CH, Diaz AA, Meldrum C, Curtis JL, Cooper CB, Pirozzi C, *et al*. Age and small airway imaging abnormalities in subjects with and without airflow obstruction in SPIROMICS. Am. J. Respir. Crit. Care Med. 2017;195:464-72.
10. Abbott GF, Rosado-de-Christenson ML, Rossi SE, Suster S. Imaging of small airways disease. Thorac Imaging 2009;24:285-98.
11. Jain N, Covar RA, Gleason MC, Newell Jr JD, Gelfand EW, Spahn JD. Quantitative computed tomography detects peripheral airway disease in asthmatic children. Pediatr. Pulmonol.2005;40:211-8.

12. Deepak D, Prasad A, Atwal SS, Agarwal K. Recognition of small airways obstruction in asthma and COPD-the road less travelled. J ClinDiagn Res 2017;11:TE01-05.
13. Umer US, Alam S, Gul S, Ghaus SG, Gul S, Farooq SU, *et al*. Imaging beyond the main air pipe: hrct signs of small airway diseases and bronchiolitis. Pak. J. Radiol. 2017;27.
14. Mahadeva R, Walsh G, Flower CD, Shneerson JM. Clinical and radiological characteristics of lung disease in inflammatory bowel disease. Eur. Respir. J. 2000;15:41-8.
15. Hansell DM. HRCT of obliterative bronchiolitis and other small airways diseases. Semin. Roentgenol. 2001;36:51-65.
16. Tanaka N, Matsumoto T, Miura G, Emoto T, Matsunaga N, Ueda K, *et al*. Air trapping at CT: high prevalence in asymptomatic subjects with normal pulmonary function. Radiology 2003;227:776-85.