ROLE OF RELATIVELY NEWER PULMONARY FUNCTION TESTS IN DIAGNOSIS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES IN INDIAN POPULATION.

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Abstract Background & objectives: This study primarily aims to show that relatively newer techniques like MIP (Maximum Inspiratory Pressure), MEP (Maximum Expiratory Pressure) and FOT (Forced Oscillation Technique) can be used to detect decrease in respiratory muscle strength along with increase in airway resistance in COPD patients. Furthermore, assessment of these parameters during different stages of COPD and its correlation with traditional spirometric parameters is done to understand the role of these techniques as additional diagnostic tools in the prognosis of COPD. One of these techniques MIP can also be used for COVID 19 patients following infection. **Methods:** Spirometry was done to diagnose COPD. MIP, MEP and FOT measurements were conducted. Unpaired t test, Pearson's correlation and SPSS version 23 were used. **Results:** 90 subjects with a mean age of 60.3 ± 14.76 years and percentage of forced expiratory volume in 1 second (FEV_1) of 89.67$\pm$9.92 L were recruited. The analysis of variance (ANOVA) showed significant difference for maximal inspiratory pressure (p=0.003) between different stages of COPD. The MIP results showed that there was a statistically significant difference between mild and very severe (p=0.0019) as well as between moderate and very severe (p=0.002). A significant positive correlation among maximal static pressure and FEV_1 % (r = 0.5) was also observed. FOT values had a good correlation (r=0.2) to the spirometric data. These techniques show good specificity and sensitivity (>80%) so testing their role in diagnosis can be noteworthy. **Interpretation & Conclusion:** Since performing FOT is very simple and effortless, it can be used along with conventional lung function test in the geriatric COPD population. FOT along with MIP and MEP showed good correlation with the spirometric data so these modalities can be used to assess pulmonary function in patients with COPD.

Key Words: Forced Oscillation Technique, COPD, MIP, MEP, Sensitivity, Specificity

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Introduction:

India contributes a growing percentage of COPD mortality which is estimated to be amongst the highest in the world.[1] Globally COPD is responsible for 6% of all deaths worldwide.[2] The traditional Gold test spirometry is used to evaluate respiratory obstruction in COPD.[3, 4] Although used frequently in almost all PFT labs, spirometry has the disadvantage of requiring much higher effort and great cooperation from the patients. Thus performing the test on some patients can be difficult especially in geriatric population.[5-7]

Spirometry is a mandatory tool for diagnosis and assessing severity in patients with COPD. It is used less effectively in geriatric patients.[8-9] The higher prevalence of functional impairment in elderly patients has rendered many of them incapable of performing a satisfactory forced expiratory maneuver in spirometry.[10-12]

FOT is less time-consuming and is measured when patients effortlessly breathe-in their tidal volume, requiring minimal patient cooperation. There are evidences which suggest that FOT parameters correlated well with forced expiratory volume in 1 second (FEV_1 %) and reflecting airway resistance more accurately.[13-16] It was also suggested to be a more sensitive marker for detection of airway hypersensitivity [17-20] as well as early airway disease. [21-22] Sensitivity of pulmonary function tests in the early stages critically decides the assessment of respiratory obstruction.[23] The importance of impedance in patients is now rapidly gaining acceptance, and promises to provide a more

comprehensible assessment of lung function than parameters derived from spirometry. [24]

Other techniques used in this study are maximal inspiratory (MIP) and expiratory pressure (MEP). Reduction of MIP and MEP has been associated with several neuromuscular diseases, but it is also possible to point lower values in patients with chronic obstructive pulmonary disease (COPD). [25-27]

Aim: The primary aim of this study was to evaluate Forced Oscillatory Technique, Maximum Inspiratory Pressure and Maximum Expiratory Pressure as additional diagnostic tools by testing their sensitivity and specificity in COPD patients. In addition to this, the aim of this study was to find the correlation between two values i.e. decrease in FEV_1% measured by Spirometry and airway resistance measured by the FOT and also FEV_1% and its relation to respiratory muscle strength as measured by MIP and MEP. We also used FEV_1% for assessing different stages of COPD and analyzed its correlation to various parameters and their use in treating high risk COPD patients.

Material and Methods: The present study was conducted in the Department of Pulmonary medicine in Seth G. S .Medical College Medical College, Parel Mumbai. Before commencement of study, approval was taken from the Institutional Ethical Committee. The study design involved 150 individuals which can be divided in two groups. Group I –Diagnosed patients of COPD as per GOLD criteria, after applying inclusion and exclusion criteria were accepted for study (n=90) Group II – Age & sex matched normal healthy adults (n=60).

The evaluation was done in following stages –

1) A written informed consent was taken from all participants of this study.

2) A detailed history-taking and thorough clinical examination was done.

3) Spirometric test was performed in both groups and diagnosis of COPD was confirmed in cases.

4) MIP, MEP and FOT was performed.

Participation in the study was voluntary. Informed consent was obtained from all study subjects prior to enrolment. The subjects were informed to suspend the use of bronchodilators during the 12 hours that preceded the tests. Both males and females were included. Patients who have FEV_1 improvement after taking bronchodialator (≥12%) were excluded from the study. Patients suffering from Asthma, Interstitial Lung Disease, Lung Cancer, tuberculosis, neuromuscular disease, fibrothorax were also excluded.

Spirometry manoeuvres were performed according to ATS guidelines[10] on computerized machine MASTER SCREEN PFT by JAEGER. FOT measurements along with MIP and MEP were carried out with a computerized machine SPIRO AIR by MEDISOFT (Germany).

Statistical Analysis: The results were expressed as mean and standard deviation for each variable. Unpaired (independent) t- test was used for intergroup comparisons in the healthy volunteers group and the COPD group. Pearson's correlation coefficient test was applied to correlate between airway resistance and respiratory muscle strength and FEV_1% predicted. All statistical analyses were carried out with the help of SPSS version 23.0 software and Microsoft Excel. p value of 0.05 or less has been considered as statistically significant. Comparisons between the groups have been made by analysis of variance (ANOVA).

Results:

Table1

Table 1: Demographic data of the COPD patients and Control group

Demographics	Mean ± SD COPD Patients	Mean ± SD Control
Sex	Male = 64.4%, Female = 35.6%	Male = 60% , Females = 40%
Age (years)	60.3 ± 14.76	59.94 ± 13.27
Body weight (kg)	55.5 ± 10.83	58.6 ± 11.28
Height (cm)	156 ± 7.98	157 ± 9.66
BMI (kg/m2)	22.7 ± 4.53	24.8 ± 5.28
Gold Stage	Stage 1: 13/90 (14%) Stage 2: 39/90 (43%) Stage 3: 26/90 (28%) Stage 4: 12/90 (13%)	

Table2

Table 2: Characteristics of patients

	Control group	Mild	Moderate	Severe	Very Severe	p value*	COPD Patients
N	60	13	39	26	12		90
MIP (cm/H2O)	70±22	68±21	64±15	42±5	39±3	p=0.003	70±21
MEP (cm/H2O)	60±11	46±14	42±12	36±14	34±8	p=0.04	36±13
FEV$_1$(L)	2.8±0.3	2.4±0.3	1.8±0.6	1.7±0.2	1.6±0.5	p<0.001	1.7±0.8
FEV$_1$ %	89.6±9.9	79.6±6.2	60.6±6.1	41.8±4.7	25.8±3.6	p=0.000	55.9±18.1
FVC(L)	3.5±0.9	3.1±0.6	2.5±0.8	2.0±0.8	1.9±0.3	p<0.001	2.8±0.9
Ravr	0.69±0.33	1.5±0.7	1.6±0.3	1.9±0.2	2.4±0.34	p=0.005	1.67±.64
(cm/H2O/L/s)							

- Comparison between the five groups (control, mild, moderate, severe and very severe) have been made by ANOVA (analysis of variance)
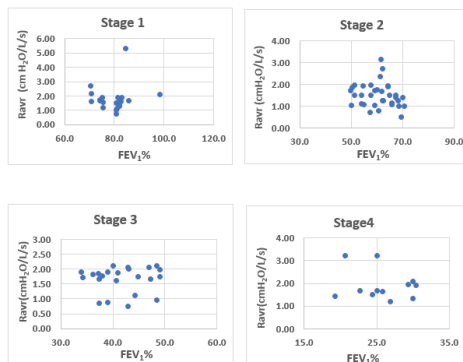
Table 3

Table 3: Values of area under the curve (AUC), sensitivity (Se) and specificity (Sp) for the optimal cutoff points for the FOT, MIP and MEP indices in COPD patients

Characteristics	FOT	MIP	MEP
Sensitivity (Se)	92.6	80.6	93.5
Specificity (Sp)	81	99.8	99.3
AUC	0.843	0.925	0.95
Cut off values	103	83	98.5

Figure 1(a-d)

Figure 1 (a-d): Relationship between Ravr and FEV$_1$% (p=0.005, r=0.2 in stage 4)

a) Stage 1-mild COPD (FEV$_1$ % <80%), b) Stage 2- moderate (FEV$_1$ 50%-70%), c) Stage 3 – severe (FEV$_1$ 30%-50%), d) Stage 4 – very severe (FEV$_1$<30%)

Statistical analysis were performed on the data obtained from COPD patients to find the possible correlation (Pearson correlation) between Ravr and FEV$_1$ %. The correlation between FOT parameters to FEV$_1$ % in various stages of COPD is depicted in Fig. 1(a-d). As seen in the Figure 1(a-d), correlation was observed between FEV$_1$ % and Stage 4 Ravr (r=0.2) as compare to other stages (r=0.09, 0.05,

0.17 for stages 1, 2 and 3 respectively). In stage 4, we observed that all COPD patients were of the age group 60 years and above. The correlation is seen best in stage 4 i.e. very severe with FEV$_1$.

The analysis of variance (ANOVA) showed statistically significant difference between the different groups (Table 2). A value of p=0.005 for Ravr was observed, which shows a significant difference between the different stages of COPD. As the severity of disease increases, the average resistance is significantly increased.

As regard the maximal mouth pressures, MIP was significantly lower at all stages of COPD than in the control group. Mean MIP of COPD and Control group was 41.43 ± 16.30 and 59.47 ± 14.94 respectively. Average MIP was significantly higher in control group than COPD. (p < 0.05). Mean MEP of COPD and Control group was 35.3 ± 13.22 and 58.4 ± 11.52 respectively, Average MEP was significantly higher in control group than COPD (p < 0.05).

Figure 2(a-c): ROC Curves for FOT, MIP and MEP parameters in COPD patients
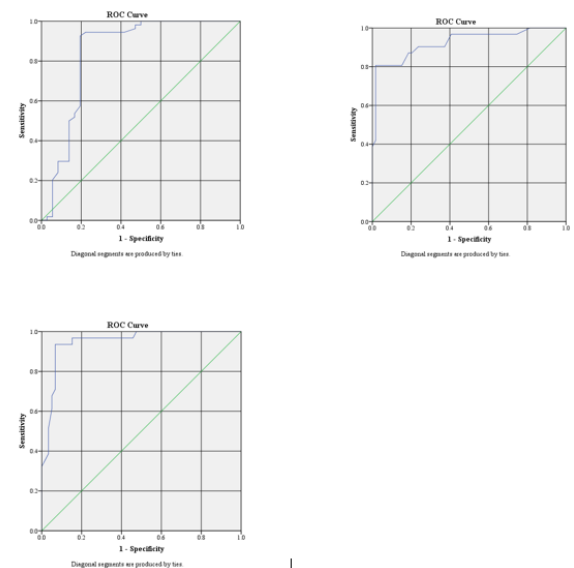
Moreover we evaluated whether there was a possible correlation between COPD stages and respiratory muscular strength. The analysis of variance (ANOVA) showed significant difference for maximal inspiratory pressure (p=0.003) between severe (very severe) patients and moderate (mild) stage.

A significant positive correlation among maximal static inspiratory pressure for stage 4 and FEV_1 % (r= 0.5) was observed. As regard the MEP, it was lower in severe airway obstruction than in the control group (r=0.35), no difference was observed in the mild and moderate patients (p>0.5).

SPSS version 23 was used to plot Receiver operating curve to find out the sensitivity and specificity of FOT, MIP and MEP. Fig. 2a-c shows ROC curves for all three of these techniques and the sensitivity and specificity are tabulated in Table 3.

Discussion:
Previous studies have shown a good correlation between FOT and spirometric data.[13-14] Our study have further highlighted that such a good correlation can be maintained even at an advanced stage among COPD patients.

FEV_1 is generally regarded as marker to reflect central airway function, was shown to be correlated to Ravr especially in the stage 4 of COPD (r=0.2). The assessment of severity of airflow obstruction was further highlighted by the fact that the correlation was less in stage 1 and 2 (r=0.09, 0.05) as compare to stage 3-4 (r=0.17, 0.2) in the current study. These results are comparable with earlier studies[21] and are of importance since the current COPD guideline recommends combined assessment approach in the management of patients with COPD with severe airflow obstruction (FEV_1% <50%) are regarded as high risk group.

Many previous studies have suggested that FOT may detect subtle changes in distal airway function earlier than conventional spirometry [28]. Other studies [29] have suggested that small airway oscillometry (a type of FOT) its index was better than FEV_1 and $FEF_{25-75\%}$. Besides, Frantz et al.[30] have reported that COPD was associated with high impulse oscillometry pulmonary resistance, even in patients with normal spirometry.

Our study is consistent with the study of Van Noord[31] which showed that the total respiratory resistance is more in emphysema than asthma. Tse and coworkers[32] have calculated the AUC for Ravr and found it to be 0.4 to 0.6. In the present analysis, we considered 0.8 to be the minimum value of the AUC (Area Under Curve) for adequate diagnostic accuracy. Among all the studied parameters, FOT showed a high diagnostic accuracy (AUC=0.843) with a Sensitivity (Se) of 92.6% and a Specificity (Sp) of 81% (Table 3, Fig. 2a). This indicates that FOT can be used as good diagnostic tool as both sensitivity and specificity are above 80%. Same is true for MIP and MEP.

Another objective of this study was to determine whether the decrease in Maximal inspiratory and expiratory pressure is closely associated with different stages of airway obstruction. Both MIP and MEP values were lower in patients with different severity in obstruction than in normal patients. In fact, MIP and MEP decreased in patients with mild and moderate obstruction; this could suggest that even in early stage of COPD, there is deterioration of respiratory muscles.

Similar results were reported by Kabitz and coworkers[32] but they have evaluated only the strength of inspiratory muscles and not expiratory muscles. A reduction in the dynamic parameters like FEV_1, & FVC in severe COPD is seen, we have also observed similar decrease in the MIP and MEP (Table 2). Our study strongly correlates the reduction in the functional parameters (FEV_1) and MIP and MEP reduction in COPD patients. Nishimura and colleagues[33] have shown a similar relationship between respiratory muscle strength and FEV_1. Thus using MIP and MEP, periodical evaluation of respiratory muscle strength seems to be a helpful tool in monitoring the disease severity. MIP can also be used to test respiratory muscle strength in COVID 19 patients following infection. Severin and coworkers[34] recently published the use of MIP for COVID patients following infection.

FOT shows high diagnostic accuracy (AUC= 0.843) so it can be considered a diagnostic test whenever patient is unable to perform spirometry. Also it is less time consuming and easier to perform.

As regard the MIP, the cut off value (as obtained along with ROC curve from SPSS Version 23) of MIP of 83 gives sensitivity of 80.6 % and specificity of 93.5%. The cut off value of MEP of 98 gives sensitivity of 93.5 % and specificity of 99.3%. As both sensitivity and specificity are above 80%, both MIP and MEP can be used as a diagnostic tool for assessing the respiratory muscle weakness in COPD patients. All three tests can be performed in the

PFT laboratory after the spirometry which will give a clear and a better picture of the lung machinery.

For geriatric population, it would be interesting to see how these techniques Spirometry, FOT and MIP/MEP can be performed in one session so as to derive the exact nature of the COPD stage and it will definitely help in the treatment of the high risk patients.

This is one of its kind of study in Indian population. There is scantiness of similar studies in Indian subcontinent. Only few laboratories have forced oscillation instrument. On the other hand lot of data is available in the western world. [21,23,24] Salvi and coworkers [35] published heterogeneity of COPD in Indian states. They have stated that age-specific prevalence of COPD increased rapidly after the age of 30 years, greater increase in men than women, reaching highest prevalence among men in 80 years or older age group. There is a lack of established baseline values according to age in healthy patients. Establishment of normal values of the mechanical parameters for old age population is needed. We did pilot studies on the COPD patients and published earlier.[36] More studies are required with a larger population to confirm our findings.

Conclusion: The results of this study revealed that FOT along with MIP and MEP are good modalities to assess pulmonary function in patients with COPD as they showed significantly more sensitivity and specificity as obtained by the ROC curves. Good correlation between functional spirometric parameters and Ravr and respiratory muscle strength can be helpful for treating high risk COPD patient. It will be helpful in prognosis in geriatric population.

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