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Role of Respiratory Muscle Strength using MIP Testing Following COVID-19 Infection

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ABSTRACT

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are measures of respiratory muscle strength and may be more sensitive in detecting early respiratory muscle impairment compared with spirometry. Respiratory muscle strength is a proven conjecturer of many diseases like muscular dystrophy, neuromuscular disease, amyotrophic lateral sclerosis and spinal muscular atrophy. Maximal inspiratory pressure is gaining interest as a test to improvise impaired respiratory muscle strength of COVID-19 patients following infection.

The primary aim of this study is to discuss the potential role of respiratory muscle performance followed by coronavirus infection. The sensitivity and specificity of MIP and MEP was estimated on patients suffering with chronic lung disease. This study proposes a hypothesis that aims to screen for respiratory muscle impairment in patients with dyspnea or characteristics associated with increased risk of severe respiratory complaints.

This work was done at a Premier Medical Institute of Mumbai, which is a tertiary care centre catering to a large number of patients from all over Mumbai and also other parts of the state of Maharashtra. After proper diagnosis (examining X-Ray of Chest, spirometric data FEV_1, FVC and FEV_1/FVC pre and post bronchodilator) from the Chest Physician and labelled as COPD (Chronic Obstructive Lung Disease) patient, the involving examinations including MIP and MEP measurements were conducted. Spirometry was done during the routine procedure.

In total, 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 ±9.92 L were recruited. Average MIP and MEP was significantly higher in control group than COPD (p value< 0.05). The analysis of variance (ANOVA) showed significant difference for maximal inspiratory pressure (p=0.003) between different stages of COPD. A significant positive correlation among maximal static pressure and FEV_1 % (r= 0.5) was observed.

MIP and MEP showed good correlation with the spirometric data so these modalities can be used to assess pulmonary function in patients with COPD. In fact, conventional Spirometry tests can be considered insensitive measures of respiratory muscle function since a significant reduction in lung volume may not be observed until severe impairment of respiratory muscles has occurred. Respiratory muscle testing by especially measurement of the MIP in high-risks patients following COVID-19 infection would for sure be noteworthy.

Keywords: Maximal Inspiratory Pressure, Maximal Expiratory Pressure, Forced Vital Capacity, FEV_1

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1 Introduction

The respiratory muscle performance can be an important factor from the perspective of COVID-19 infection. It is a factor which is not appreciated much for contributing to poor outcomes during the coronavirus pandemic. In this paper, we have tried to use the outcome of our study on chronic lung disease on the respiratory muscle strength of COVID-19 patients following infection.

The symptoms exhibited by some patients suffering from chronic obstructive pulmonary disease (COPD) can be difficult to resolve with conclusions drawn from spirometry[1], indicating that additional quantitative tests might be necessary to complement spirometry when screening for disease related to respiration. Reduced respiratory function, as is seen in individuals with COPD or older adults, can often be attributed to many factors, one prominent factor being reduced respiratory muscle strength. [2] There are likely to be other means by which reduced respiratory function can be detected. Spirometry is an inexpensive tool and easily administered at the primary care level. But new methods of respiratory assessment should be developed to accompany spirometry. An additional means for quickly and effectively assessing respiratory function might also be necessary on the basis that spirometric measurements require individuals to perform specific respiratory maneuvers that can be uncomfortable or even distressing.

The use of MIP as a measure of respiratory muscle strength in clinical trials of targeting respiratory muscle, examine the correlation of MIP with survival, quality of life, and other measures of pulmonary function, and outline the role of MIP as a clinically significantly meaningful outcome measure. Respiratory muscle strength is a proven conjecturer of the long-term outcomes concerning neuromuscular disease. Furthermore, MIP and MEP may be more sensitive in detecting early respiratory muscle impairment compared with spirometry. [3]

MIP is a measure of global inspiratory muscle strength and therefore has a close relationship with diaphragmatic strength, since the diaphragm is the major inspiratory muscle; MEP is generated through the abdominal and intercostal muscles. [4]

Together, MIP and MEP measurements can accurately assess respiratory muscle weakness, and MIP may even predict diaphragm weakness before a significant change in spirometry endpoints (eg, forced vital capacity, FVC). [5] Results from Spirometry tests have utility but they can be considered insensitive measures of respiratory muscle function since a significant reduction in lung volume may not be observed until severe impairment of respiratory muscles has occurred. [6]

According to the current guidelines in the healthcare system, the pulmonary function testing should be limited to tests that are only essential for immediate treatment decisions. It is advised that the type of pulmonary function testing be limited to the most essential tests when possible, and that measures to protect both the staff and individuals being tested should be put in place.

The role of a type of pulmonary function test is Maximal Inspiratory Pressure (MIP) which depicts the Respiratory muscle strength is very well reviewed by Severin and coworkers recently, [7] wherein they have evaluated all aspects of the treatment based on respiratory muscle testing and training. Through their vast experience, they have reviewed and hypothesized a model following COVID-19 infection to improve outcomes and reduce the burden of future viral pandemics.

Another group[8] have recently published that grip strength is inversely associated with the most common global measures of maximal strength of respiratory muscles (i.e. maximal inspiratory pressure (MIP). Most pulmonary function tests including Respiratory muscle strength (MIP) were inversely associated with the diagnosis of sarcopenia and its indicators including grip strength.

Coronavirus (COVID-19) pandemic has shown how a single highly infectious virus can affect healthcare systems of developed as well as developing nations so drastically. [9-13] It is noticed that COVID-19 and other

viral infections can cause significant damage to the lungs and air ways potentially resulting in acute respiratory distress syndrome and, if severe enough, respiratory failure [14]. Many patients with comorbidities as well as elderly population is at higher risk to developing severe respiratory complications from COVID-19 and require intensive care unit admission and mechanical ventilation. [10-13,15] Not only older age it also includes smoking as well as cardio metabolic and lung disease.[10-13] Patients with these characteristics are at higher risk for serious complications from seasonal flu. [14, 16]

As such, there are other, less appreciated factors contributing to the risk for poor outcomes resulting from the COVID-19 pandemic observed in admitted patients beyond the risk factors.

We hypothesize that one of the ignored aspects of COVID-19 pandemic management is impaired respiratory muscle performance. While impaired respiratory muscle performance is considered to be rare, [17-18] it is more frequently seen in patients possessing poor health characteristics, in particular chronic lung diseases. Measures of respiratory muscle performance are also not routinely performed in clinical practice, even in patients presenting with dyspnea. [19]

Yang and coworkers [20] have investigated pulmonary rehabilitation for patients with COVID-19 having complications, such as chronic pulmonary disease, especially COPD patients. According to them, patients with COVID-19 having chronic pulmonary diseases often have excessive airway secretions, expiration exercises should be performed in addition to general airway clearance exercises to facilitate sputum excretion and reduce the exhaustion due to coughing. Chen and coworkers [21] have reported that due to chronic lung disease and reduced activity, the respiratory muscles of patients with COVID-19 are weakened. More studies are needed to indicate whether respiratory muscle performance influences outcomes following a viral infection of any kind. There is some preliminary work that does suggest this is a plausible hypothesis, and Severin and coworkers [7] are currently working on developing studies to test this. The purpose of this paper is to discuss the potential role of testing respiratory muscle performance. It can be utilised for large population following COVID-19 infection.

2 Research Methodology

The primary aim of this study was to evaluate Maximum Inspiratory Pressure (MIP) and Maximum Expiratory Pressure (MEP) 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% and its relation to MIP and MEP. We also used FEV_1% for assessing different stages of COPD and analyzed its correlation to various parameters obtained by other techniques and their use in treating high risk COPD patients. The final aim is to see if respiratory muscle performance influences outcomes following a viral infection of any kind.

We planned this cross-sectional study which included 90 COPD patients (age group 45-75 years) from PFT Lab of Chest Medicine Department, attending the outpatient department of chest medicine in a tertiary care institute and were diagnosed to have mild to very severe COPD (Forced Expiratory Volume in 1 sec.(FEV_1) /Forced Vital Capacity (FVC)<0.7) by a chest physician. Age matched healthy controls were also tested who denied any respiratory complaints. Other exclusion criteria were history of having any disease or meditation and inability to perform the tests. Participation in the study was voluntary. Oral and written information was given, and informed consent was obtained from all study subjects prior to enrolment. This study was done for duration of three years starting from March 2015 to April 2018. Required Ethics committee approval was taken before commencement of the study.

Statistics: SPSS version 23 and Microsoft Excel software were used for statistical analysis. Data is represented as mean+/-SD. Statistical analysis to calculate sensitivity and specificity was done using Receiver Operating Characteristic Curve (ROC Curve). p value <0.05 is kept as significant for all statistical

analysis. Confidence interval was calculated as 95%. To estimate the sample size, a pilot study in a group of 40 subjects (20 subjects with COPD and 20 controls) was conducted. Based on the results, the software MedCalc ® 8.2 (Medicalc Software Mariakerke, Belgium) was used to calculate the sample size based on the difference between means, assuming type I and type II errors of 5% and 20%respectively. Comparisons between the groups have been made by analysis of variance (ANOVA).

90 patients suffering from COPD were enrolled in this study. The appointments were previously scheduled by phone, and the subjects were informed to suspend the use of bronchodilators during the 12 hours that preceded the tests. On the scheduled date, the examination sequence was carried out as follows: the collection of anthropometric measurements (age, body weight and height) testing, MIP, MEP and, finally, gathering spirometric measurements (Table 1). Both males and females from the city of Mumbai were included.

All patients were in clinically stable condition and COPD patients showing obstructive pattern, that is FEV_1/Forced vital capacity (FVC) < 0.7 were recruited. Patients who have FEV_1 improvement after taking bronchodilator (≥12%) were excluded from the study. Patients suffering from Asthma, Interstitial Lung Disease, Lung Cancer, tuberculosis, neuromuscular disease, fibro thorax were also excluded. Some patients were excluded because of lack of cooperation during spirometry, MIP and MEP maneuvers.

Spirometry maneuvers (including flow volume loops) were performed according to ATS guidelines[22] using a spirometer that is a computerized machine MASTER SCREEN PFT by JAEGER. The best values for FEV_1, FEV_1% and FVC out of 3 acceptable maneuvers were reported.

Measurements of MIP and MEP were performed and carried out with a computerized machine SPIRO AIR by MEDISOFT (Germany). An onsite evaluation of acceptability was performed by the technician. The test subjects had at least three measurements meeting the acceptance criteria (varying by less than 5%). The patient is asked to maximally inspire during MIP at the level of RV (Residual Volume) and maximally expire during MEP at the level of TLC (Total Lung Capacity). The measurements were made in sitting position only. Subjects were encouraged continuously to achieve maximal strength. MIP and MEP measurements were repeated until three values varying by less than 5% were obtained.

MIP measurement is done at lung volumes progressively closer to residual volume, so that the patient can generate the greatest negative force while inspiring against the occluded airway and the measurement of maximal inspiratory muscle strength can be attained. This technique yields more reproducible, consecutive measurements and discloses values probably nearer the real MIP.

We divided COPD patients into four groups on the basis of airway obstruction: mild (FEV_1 < 80%), moderate (FEV_1 between 70 and 50%), severe (FEV_1 between 50 and 30%) and very severe (FEV_1 < 30%) with FEV_1/FVC <70% in all groups. The COPD patients in each group were mild group -13 patients, moderate group -39, severe group -26 and very severe -12 patients. The control group included 60 age matched normal subjects, free of any respiratory complaints and symptoms and with normal functional parameters.

3 Results and Discussion

The MIP and MEP values of healthy subjects were used as a control group for the comparison with patients with different stages of COPD (Table 1). In this study, there was no significant difference of proportion of patients in different age groups between both the study groups that is COPD patients and control (p value=0.118) using unpaired t-test. The mean age of COPD and control group was 60.32 ± 14.76 years and 59.54 ± 13.27 years respectively. Average age of both groups was comparable.

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%)	

BMI , body mass index; GOLD, Global Initiative for chronic Obstructive Lung Disease; SD, standard deviation

As expected, among the Spiro metric data, FEV_1 % and FEV_1/FVC was found higher in healthy subjects. Mean FEV_1 % of COPD and Control group was 55.86 ± 18.11 and 89.67 ± 9.87 respectively. There was significant difference of mean FEV_1 % values between both the study groups. (p value< 0.05). Mean FEV_1/FVC of COPD and Control group was 57.53 ± 10.55 and 80.38 ± 5.29 respectively. As expected, average FEV_1/FVC was significantly higher in control group than COPD. (p value < 0.05). Table 1 shows the demographic parameters of the COPD patients and control group.

The analysis of variance (ANOVA) showed statistically significant difference between the different groups (Table 2). 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 value< 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 value < 0.05)

Table 2: Characteristics of patients

Patients	Control group	Mild	Moderate	Severe	Very Severe	p value*	COPD
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
FEV1(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
FEV1 %	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

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, moderate and mild stage. A significant positive correlation among maximal static inspiratory pressure for stage 4 and FEV_1 % (r= 0.5) (Fig 1a-d) 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 value>0.5) (Fig.2a-d).

SPSS version 23 was used to plot Receiver operating curve to find out the sensitivity and specificity of MIP and MEP. Table 2 (Fig. 3a-c) shows ROC curves for both of these techniques.

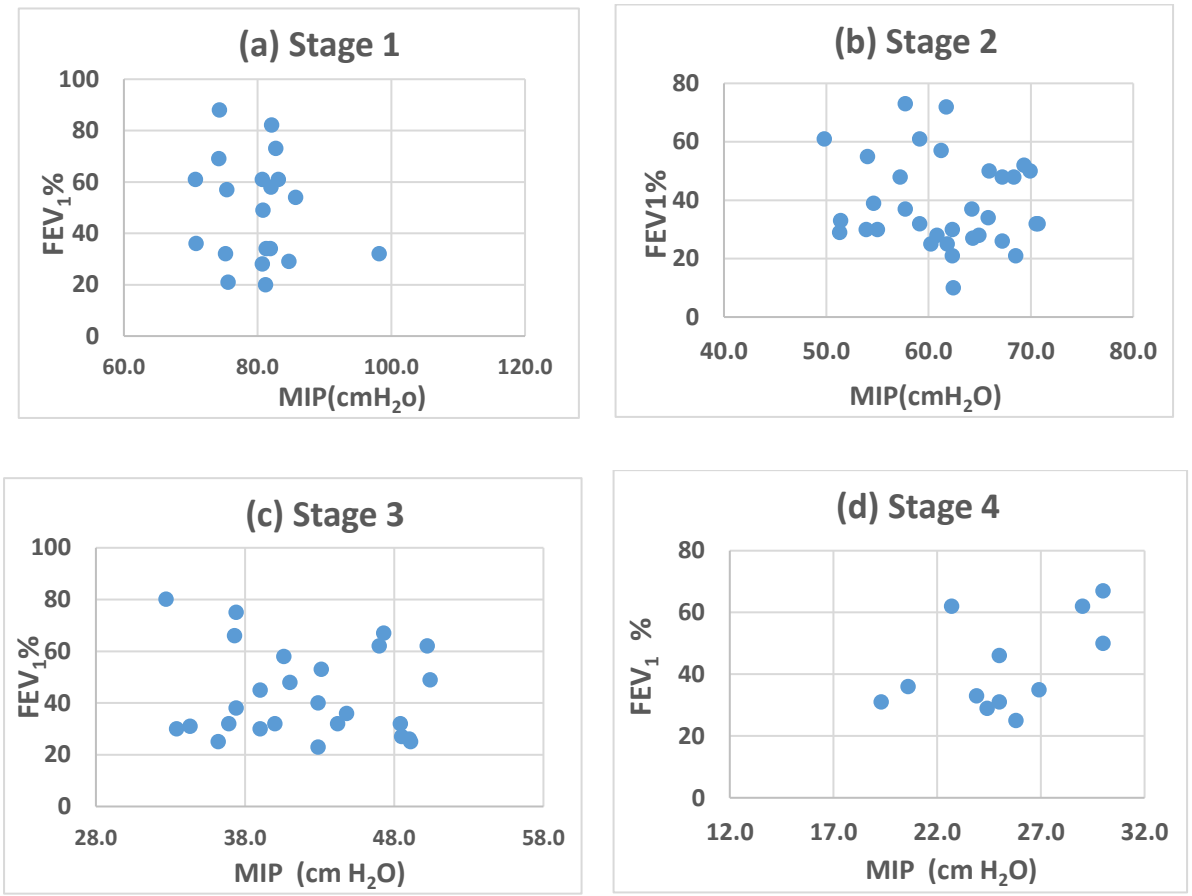

Figure 1 (a-d): Relationship between MIP and FEV_1%

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%)

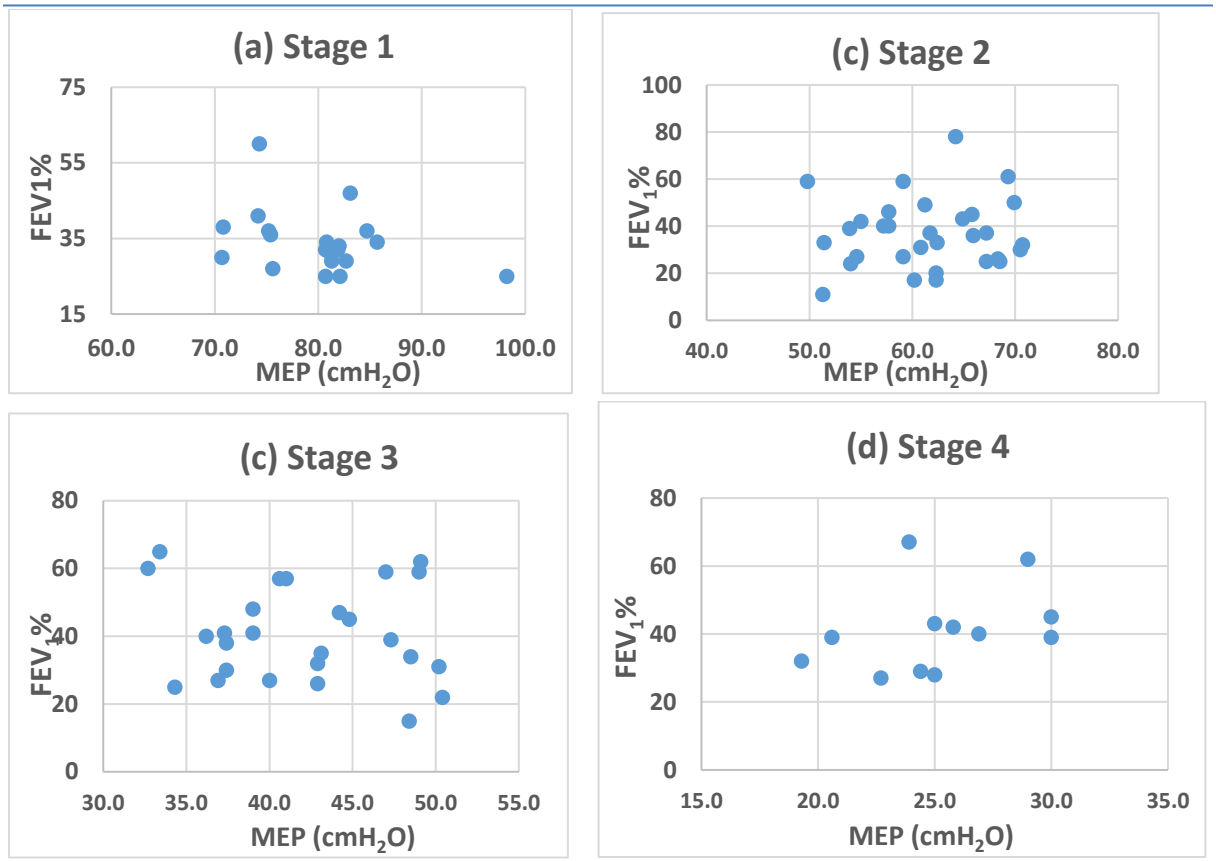

Figure 2 (a-d): Relationship between MEP and FEV_1%

(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%)

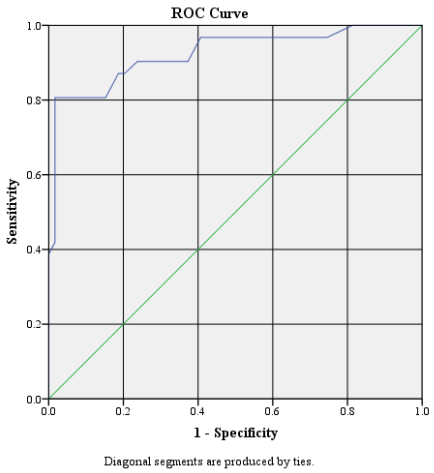

Figure 3a: ROC Curves for MIP parameters in COPD patients

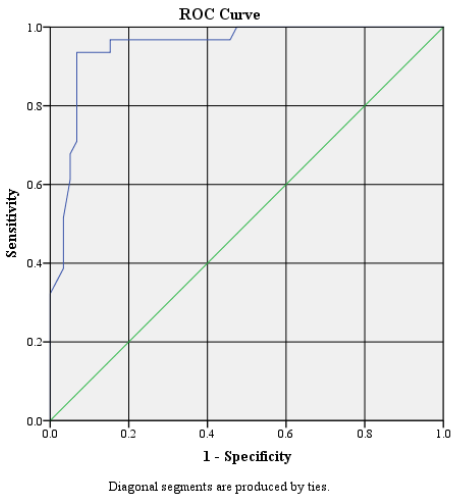

Figure 3b: ROC Curves for MEP parameters in COPD patients

4 Discussion

The 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.

Given that respiratory muscle impairment is common in most diseases, directly evaluating diaphragm muscle strength by measuring MIP could complement spirometric data in studies of these patients. MIP is clinically relevant outcome measure in chronic diseases when respiratory failure is secondary to respiratory muscle weakness.

However, there are some limitations. Diminished MIP does not always reliably confirm inspiratory muscle weakness. This is due to MIP measurement errors, including submaximal effort, poor transmission of intra thoracic pressure to the extra thoracic airways and patients have difficulty making a good lip seal. However, with proper training, MIP testing can be a reliable, accurate, and an early indicator of respiratory muscle weakness.

In COVID-19 patients, the respiratory muscle deterioration due to invasion of virus will lead to reduction in respiratory muscle strength. We propose to do MIP testing using a MIP measuring capsule after the recovery of the patient from COVID-19 infection. Also, if the respiratory muscle weakness is observed, such patients can be sent for respiratory muscle training programme. [7]

Several factors like aging, physical inactivity, smoking and chronic lung diseases decrease respiratory muscle performance. [23-26] In patients with chronic lung diseases, in addition to a reduction in respiratory muscle strength, the demand imposed on the respiratory muscle also increases due to changes in airway resistance and chest wall mechanics. [23-25] Quiet breathing accounts for 1-3% of total oxygen consumption in normal weight, healthy individuals. [23-27] In an acutely diseased lung (e.g., acute respiratory distress syndrome), the pressure required to breathe further increases. [28] Lou and coworkers have discussed recently [29] more about the pathogenesis of such diseased lungs.

The respiratory muscle weakness is normally not seen in the general population. [30] The threshold for respiratory muscle weakness in a younger healthy adult is also fairly low. However, respiratory muscle weakness is associated with dyspnoea, and there are certain populations where respiratory muscle weakness

is more likely. The maximal inspiratory pressure produced by the respiratory musculature decreases in healthy older individuals. [17] However, due to the normal age-related changes in lung compliance and muscle strength the threshold for respiratory muscle weakness with aging is also lower (i.e., >80 years: 42cmH_2O). [13] It is important to acknowledge that these age-related reductions are in reference to healthy individuals. As described earlier, in patients with multimorbidity, the risk of respiratory muscle weakness may increase or potentially compound these age-related reductions in respiratory muscle performance. [23-26]

While routinely screened measures of lung volume and flow rate are associated with respiratory muscle performance [24-25] changes in respiratory muscle performance may occur independently of these values and may be detected prior to changes in lung volume. [24-25]

The capsule-sensing pressure gauge (CSPG-V) is a new tool that measures the strength of inspiratory muscles; it is easy to use, non-invasive, inexpensive and lightweight. [31] It is a small, handheld, portable, without battery-powered, device with a mouth pressure manometer attached to a flexible tube with a plastic rigid flanged mouthpiece and a small monitor that displays the test results in cmH_2O.With this new type of tools it is very easy to measure MIP. We strongly recommend the use of newly developed tools so that it is not at all inconvenient to a patient who has spent 15 days already under hospitalization to recover from COVID-19 infection.

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. In fact, both tests can be performed in the PFT laboratory after the spirometry which will give a clear and a better picture of the lung machinery.

The results of these tests revealed that MIP and MEP are methods of choice to assess pulmonary function with better specificity. MIP and MEP as a supplementary tool may aid in the assessment of lung functions in this population. In fact, for geriatric population, it would be interesting to see how these techniques Spirometry, 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.

Use of newer type of MIP measuring capsule sensing measure gauge can be very handy. [31] More studies are needed to indicate whether respiratory muscle performance influences outcomes following a viral infection of any kind. There is some preliminary work that does suggest this is a plausible hypothesis, and Severin and coworkers [7] are currently working on developing studies to test this.

5 Conclusions

Our research work done on COPD patients using MIP strongly suggest the use of this technique in COVID -19 patients following infection. Use of relatively newer device may lead to better patient care and management pertaining to known and unknown causes of dyspnea requiring inspiratory muscle training.

With so many factors which may be behind the viral pandemic scene, we propose that screening for respiratory muscle impairment in patients with dyspnea or characteristics associated increased risk of severe respiratory complication due to viral infection may be advantageous.

6 Declarations

6.1 Acknowledgements

We are grateful to Dr. Amita Athavale, Professor and Head, Chest Medicine Department for permitting us to use PFT lab. We are grateful to the technical team of Pulmonary function laboratory of Department Of Chest Medicine for assisting us while collecting data. We are thankful to Dr. D.N. Shenvi, Professor and

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6.2 Competing Interests

There are no conflicts of interest.

6.3 Ethical Approval

Ethics approval was taken from the institute Ethics Committee letter no Ec/OA-44/2013

6.4 Informed Consent

Informed consent was taken from all the participants.

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