Respiratory muscle assessment in acute exacerbation of chronic obstructive pulmonary disease and its role as a potential biomarker

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Background. AECOPD is a life threatening condition for patients with chronic obstructive pulmonary disease (COPD) and lack of specific biomarker hinders effective management. Sputum, blood, breath and urinary biomarkers have all been investigated. We measured maximum respiratory pressure post exacerbation once the patient was compliant with the test and after 6 weeks, to assess any correlations.

Methods and Results. The maximum pressures were measured using a closed circuit spirometer with a clean rubber mouthpiece properly placed with the patients lips sealed around it. Patients were properly instructed to exhale slowly and completely, then inspire with maximum possible effort and advised to keep it for nearly 1.5 s for maximum inspiratory pressure (MIP). For maximum expiratory pressures (MEP) patients were instructed to inspire slowly and completely, then expire forcefully with maximum effort. With the recorded values TTI (time tension index) was calculated. This was repeated again after 6 weeks. Using Pearsons correlation coefficient we found that MIP had a negative correlation with TTI and a positive correlation with FEV1. FEV1 had a positive correlation with FVC. MEP showed no significant correlation with TTI, but a positive correlation with FEV1.

Conclusion. Acute exacerbations of COPD has a profound effect on the respiratory musculature especially the expiratory muscles but the maximum pressures are not specific enough to be prognostic markers. It might be worthwhile studying transformations of the respiratory musculature at the molecular level. More studies must be conducted to find a specific marker to aid in the management of the condition.

Key words: acute exacerbation of COPD, respiratory muscle assessment, respiratory muscle pressures, biomarkers

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INTRODUCTION

COPD is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal response of the lungs to noxious particles or gases. It is primarily caused by cigarette smoking. Although COPD affects the lungs it also produces systemic effects[1-3]

Acute exacerbation of COPD (AECOPD) has not yet been fully defined as it would require a very broad definition to cover the spectrum from a mild episode that requires a brief hospitalization to a severe one that require intensive care unit admission and life saving ventilatory support .Thus worsening of symptoms in a patient with COPD beyond day to day variation is the common denominator of the condition. However, the agreed definition is a sustained worsening of patient's condition from stable state and beyond normal day to day variations, that is acute in onset and necessitates a change in regular medication, which would be either the need for oral/parenteral corticosteroid, antibiotic or both[4]. AECOPD can be classified as mild moderate, severe and life threatening.

On average, an exacerbation takes about 7-14 days to recover from. However a much longer period lasting into months are needed to recover health as measured by health related quality of life. This longer duration of worsened health status compared with the lung function suggests that AECOPD has a lasting impact. Mortality rates of patients admitted with an exacerbation range from 4%-30% (ref.[1]). Variability is due to the different subgroups of patients. These numbers are alarming enough to warrant a rigorous study and search into biomarkers or other surrogate marker that could aid in the proper assessment and thereby better management of the underlying condition.

There is scarcity of well-validated biomarkers for COPD. Several studies have been and are conducted to look for the ideal marker for the disease. An ideal biomarker includes a molecule for which there is a noninvasive test that may be performed even in patients with the severe form of disease and the test can be taken repeatedly in the same individual. The test should be specific, have good reproducibility and be sensitive to small and early changes in disease state. It is now widely accepted that COPD is an inflammatory disease in which there is luminal, bronchial wall, and interstitial inflammatory cell activity[5-8] and resultant tissue damage[9].

Measurement of respiratory muscle strength is no novelty in the lung function laboratory[10]. Clinically, respiratory muscle force is indirectly measured through the pressure generated during inspiration or expiration. These

pressures reflect changes against atmospheric pressure generated by all muscles under investigation (both inspiratory and expiratory) and hence it is not muscle specific. In addition, reduced respiratory force may result from cerebral, spinal cord, anterior horn, peripheral (phrenic) nerve, neuromuscular junction or muscle fiber dysfunction and hence warrants a thorough clinical examination. The pressures measured also depend on the geometry of the thorax. This is based on laplace's law (radius is inversely proportional to pressure), the relative degree to which it is apposed to the rib cage and the muscle's length - force properties[11]. Another variable influencing the outcome of inspiratory and expiratory pressure measurement is the relative lung volume at which it is measured. Like all skeletal muscles, respiratory muscles have a well-defined length tension relationship. If the diaphragm is shortened below its optimal length, it can generate less tension[12]. This has repercussions during acute hyperinflation where the mechanism of reduced tension generating capacity seems to be more important than the geometric changes[13]. The length tension relationship has important consequences for the techniques of measuring inspiratory and expiratory muscle force. Indeed, changes in the lung volume at which the measurement is performed may alter the outcome of the measurement and hence lung volumes are properly standardized. A final factor influencing the pressure measured is the elastic recoil of the lungs inward and the chest wall outward. However, these recorded pressures though not the actual muscle pressure, are a very good reflection of the functional reserve of the respiratory pump since the net pressure is needed to drive ventilation.

The environment in which the muscles have to contract (hypoxic, hypercapnic, steroid treatment) along with mechanical disadvantage (hyperinflation), reduced pulmonary dynamic compliance and increased airway resistance, all of which increase the work and can lead to overuse. By looking further into the inherent muscle functions we could possibly derive markers for the assessment of damage following an exacerbation and hence could help in the further management of the patient.

BIOMARKERS

The most widely used marker of disease severity and progression is FEV1 (Forced Expiratory Volume in 1st second). However, FEV1 correlates poorly with both symptoms and other measures of disease progression[14]. Moreover, it does not differentiate between the causes of airflow obstruction or identify extra pulmonary manifestations of COPD. There is very clearly a need to find a biomarker that can aid in the diagnosis, risk stratification and assessment of therapeutic intervention. Search has been varied and centered around proteins and other molecules in exhaled breath condensate, sputum, urine, broncho alveolar lavage and blood that have been implicated in the pathogenesis of COPD. There are numerous potential candidates for biomarkers like exhaled breath molecules nitrous oxide, hydrogen peroxide (NO, H_2O_2), markers of oxidative stress (plasma TEAC {Trolox equivalent antioxidant capacity} TBA-MDA {thiobarbituric acid-malonialdehyde}) urinary isoprostane, PF2 derivatives, Interleukins (IL) such as IL6, IL8, IL2, TNF-alpha (Tumor Necrosis Factor alpha), Interferons (IFN) and other sputum parameters. NO is probably the most studied exhaled biomarker of airway inflammation but most emphasis has been directed towards asthmatic patients. Patients with stable COPD have relatively low levels of exhaled NO production[15,16]. This could be related to current cigarette smoking which downregulates NO production[16,17], high previous cigarette consumption[18,19]. In contrast, patients with severe or unstable form have high levels but no difference was found between them and acute exacerbations. Inflammatory cell activation results in an increased production of O_2-(oxygen free radicals) which ultimately leads to the production of H_2O_2. This molecule is less reactive than other oxygen species[20] and its solubility ensures that airway epithelial H_2O_2 equilibrates with air and thus expired H_2O_2 provides a potential marker of oxidative stress[21]. These concentrations are increased in stable COPD and even more increased in an exacerbation[22]. Arachidonic acid derivatives include the prostaglandins, isoprostanes, and leukotrienes. Prostaglandins are detectable in exhaled breath in COPD (ref.[23]) but there is no published literature on the changes occurring during AECOPD. A wide variety of inflammatory derivatives have been measured in sputum samples in stable state and AECOPD and some provide useful markers of exacerbation. Purulent outpatient exacerbations of COPD are associated with increases in spontaneous sputum myeloperoxidase (MPO), neutrophil elastase (NE), protein leakage (sputum, serum albumin ratios) (ref.[24]). More severe exacerbations are shown to have increased levels of IL-8 and sputum:serum alpha1 antitrypsin ratios[25]. However it is not known whether the increases precede the onset of exacerbation or rise simultaneously with it. Nevertheless, these are useful in purulent exacerbations and may direct therapy. Certain markers like Endothelin-1 (ET-1) and IL-6 from induced sputum have been reported to have increased levels in stable form[26,27] and even more increased during AECOPD (ref.[28]). Raised plasma fibrinogen concentrations have been noted during exacerbations, particularly when there is purulent sputum or symptoms of cold or cough[29]. Bacterial exacerbations with purulent sputum requiring admission are also associated with high serum C-reactive protein (CRP) concentrations indicating a significant systemic acute phase response[25]. Even outpatient exacerbation with purulent sputum shows an increase in CRP but to a smaller degree, whereas mucoid exacerbations are associated with low normal concentrations. This protein may therefore provide some guidance to the nature of the episode and hence its treatment but at the moment it adds little to the observation of sputum color[24]. Absolute concentrations of ET-1 rise significantly in AECOPD. The concentrations of serum Granulocyte Monocyte Colony Stimulating Factor (GM-CSF), Myeloperoxidase (MPO) and Extracellular protein (ECP) are shown to be high in AECOPD suggesting in-

creased activation of neutrophils and eosinophils[30]. Sahin et al.[31] demonstrated that erythrocyte glutathione peroxidase activity (a marker of antioxidant activity) is decreased during AECOPD compared with tenth day of treatment and an increased level of malonialdehyde at the onset which returns to normal after tenth day of treatment. Rahman et al.[32] measured TEAC and TBA-MDA as markers of overall plasma antioxidant-oxidant balance. It was found out that during AECOPD patients had lower TEAC and higher TBA-MDA while compared to the stable state confirming increased oxidant stress. Bronchoscopy with bronchial lavage and bronchoalveolar lavage (BAL) can be used to obtain samples from smaller airways and alveoli respectively. BAL studies have revealed higher number of cells, including eosinophils and neutrophils in samples from patients with non purulent exacerbations compared with patients in a stable state[33]. However this is an invasive technique and cannot be readily applied in such patients and hence is unacceptable in routine clinical practice. Therefore it will always be a research tool and cannot provide useful biomarkers of AECOPD. Recent studies on biomarkers aim to find associations between these molecules and prognostic index (BODE index, dyspnea and exercise capacity). Fat-Free Mass Index (FFMI) reflects the skeletal muscle mass and has been shown to be associated with dyspnea and exercise capacity. Further associations between FFMI and systemic inflammation were evaluated. Biomarkers for systemic inflammation were lepitin, adiponectin, CRP, IL-6 and TNF-alpha. Both BODE index and FFMI are related to the circulating levels of lepitin in patients with COPD, suggesting a possible role for lepitin in the systemic component of COPD. The additional association of FFMI with TNF-alpha further supports the role of systemic inflammation in muscle wasting in COPD (ref.[34]). Biomarkers that are elastin degradation products such as desmosine (DES) and its isomer isodesmosine (IDES) are more accurately measured in the urine. These products form highly stable cross links unique to elastin. During lung repair processes these molecules are liberated from the extracellular matrix. The presence of DES/IDES in the human body is independent of diet and its elimination route is specific to urine[35]. These factors making them potentially good biomarkers are assessed using Ultra Performance Liquid Chromatography-Ion Mobility-Mass Spectrometry (UPLC-IM-MS). Results have shown a higher concentration in COPD affected individuals when compared to healthy ones[36]. One study suggest that impulse oscillometry can assess the within breath behaviour of the oscillatory mechanics with high temporal resolution, which may be helpful for evaluating the severity of COPD (ref.[37]). Further studies are needed to reveal which biomarkers obtained with this approach would be suitable for evaluating the airway obstruction. Circulating levels of Clara Cell secretory protein-16 (CC-16) have been linked to Clara Cell toxicity. It has therefore been suggested that this protein may be a useful marker of COPD. A study concluded that serum CC-16 levels are reduced in individuals with COPD and there is a weak correlation with disease severity in former smokers[38]. There is a need for biomarkers to better characterize individuals with COPD and for this purpose a study was conducted to evaluate the repeatability of blood biomarkers assessed through Bland-Altman Plots and correlation between biomarkers and clinical characteristics were assessed using Spearman Correlation Coefficient. From the range of biomarkers tested, fibrinogen was the most repeatable and exhibited a weak correlation with a 6-minute walk distance, exacerbation rate, BODE index and MRC dyspnea score in COPD subjects[39]. CRP, fibrinogen, IL-6 and surfactant protein D were significantly elevated and repeatable on COPD subjects with an exacerbation within 30 days of their 3 month visits[39]. Recent studies are centered around Proteomics, which is the large scale study of proteins, particularly their structure and function. This can give us a clearer insight as proteins are main components of the physiological metabolic pathways of cells. As far as COPD is concerned, the application of proteomics has been limited compared to other fields such as cancer. The complexity of the disease combined with the inaccessibility and invasiveness of disease relevant samples have provided a hurdle to the progress of respiratory proteomics. Advances in proteomic instrumentation and methodology have led to the possibility of identifying proteomes in much smaller quantities of biologic material[40]. This is likely to contribute to the increased understanding of the disease mechanism, establishment of biomarkers for these endotypes and improved patient care. Similar to proteomics, metabolomics refers to the entire metabolic profile of the cell. Nuclear Magnetic Resonance (NMR) spectroscopy based metabolic analysis is currently preferred. NMR based metabolomics characterized COPD patients based on systemic effects and lung function parameters. Open profiling metabolomics identified reduced lipoproteins (VLDL/Chylomicrons; LDL) and N-dimethylglycine and increased glutamine, phenylalanine, 3-methylhistidine, ketone bodies in COPD patients with reduced branch chain amino acids (BCAA) in GOLD4 patients[41]. BCAA and its degradation products 3-methylhistidine, ketone bodies and triglyceride correlated negatively with cachexia and positively with systemic inflammation. Increased protein turnover occurred in all COPD patients with increased protein degradation in individuals with emphysema and cachexia[41]. A future challenge, however is to describe the cellular metabolome for purposes of understanding cellular function. This, together with proteomics and genomics can be used to construct a computer network model which could describe the cellular function. This could be an aid in identifying patterns and also in the establishment of biomarkers.

However at present, despite these discussed biomarkers being able to confirm the clinical diagnosis, they are not able to predict an impending exacerbation and thus not quite able to play a role in the clinical setting of patient management. The absence of proper classification of exacerbations and the multi-component nature of the condition makes the possibility of a single ideal biomarker

very difficult but study of different molecules and other surrogate markers are ongoing.

ASSESMENT OF RESPIRATORY MUSCLE STRENGTH

There are a number of tests that are currently performed to assess respiratory muscle strength. Measurements of respiratory muscle function are generally obtained from measuring pressure achieved by volitional activation or electrical or magnetic stimulation of the phrenic nerve or motor roots. Pressure can be measured in the nose, mouth, in the esophagus or across the diaphragm. Lung function impairment (static and dynamic volumes) does not correlate with respiratory muscle dysfunction except for patients with advanced neuromuscular disease. Techniques used in the laboratory are described below:

MAXIMUM VOLUNTARY PRESSURES MEASURED AT THE MOUTH

Maximum voluntary inspiratory (PImax) and expiratory (PEmax) pressures are the most frequently used noninvasive measures of respiratory muscle force. Ever since Black and Hyatt[10] reported this noninvasive technique in the late 1960s, it has been widely used in patients, healthy control subjects across all ages, and athletes. Pressure is recorded at the mouth during a quasi-static short (few seconds) maximal inspiration (Muller maneuver) or expiration (Valsalva maneuver). No airflow is allowed during the maneuver and pressure can build up to greater than 30 kPa in extremely fit and healthy subjects. The maneuver is generally performed at RV for PImax, and at TLC for PEmax. Although functional residual capacity would theoretically be more appropriate, for reasons explained earlier, patients find it easier and more straightforward to perform the maneuvers from RV and TLC. Only a few contraindications exist for these measurements and these can be due to aneurysm, uncontrolled hypertension or urinary incontinence. The coefficient of variation is reported to be acceptable for clinical testing[42-44]. Although the technique appears simple and with the advanced software making measurements easily accessible in the laboratory, there are some technical pitfalls. Quality control of the measurements can only be obtained from inspection of the pressuretime curves. The peak pressure should be obtained in the very beginning of the maneuver. The pressure maintained for at least 1 s is generally reported as the PImax or PEmax (plateau pressure) (ref.[45]). A recent study however, challenged the use of the plateau pressure, concluding that the peak pressure may be easier to obtain and equally reliable when subjects are well instructed[46]. Measurements are obtained preferably in the sitting position. Although body posture has no significant influence on the result of the measurement in healthy subjects[47], and even in convalescent neonates[48], in COPD patients changes in body posture may significantly impact the result. Leaning forward for example may result in higher inspiratory pressures[49] while measurements obtained in the recumbent position may lead to lower pressures[50]. To avoid pressure generation by the muscles of the cheeks and buccal muscles, a small leak should be present in the equipment. The leak described by Black is 15 mm long and has an internal diameter of 2 mm. Using this leak, the glottis should be opened to generate pressures for 1 s, and the pressure obtained reflects the pressure generated by the respiratory muscles. When a leak is absent, the recorded pressures may erroneously reflect the pressure generated in the mouth by the cheeks and buccal muscles. Flanged mouthpieces (as the ones generally used for lung function testing) have been reported to result in pressures inferior to those obtained when a rigid mouthpiece is sealed against the mouth. Especially for expiratory pressures, flanged mouthpieces may result in underestimated pressures due to additional leaks that appear with the increased pressure in the mouth[51]. Sometimes tests can be more successfully performed using a face mask (especially in patients with neuromuscular diseases characterised by facial or bulbar muscle weakness). On average there is no significant difference in PImax, but PEmax may be higher using a tube or non flanged mouthpiece[52]. Practice Tests should be performed by an experienced technician. Since the Valsalva and Muller maneuvers are unfamiliar to patients, the maneuvers should be carefully explained. There has been debate on the number of repetitions that need to be carried out before a result can be considered valid[53-56]. Most authors[57] suggest that a minimum of five maneuvers should be performed, and reproducibility should be within 510%. Increasing the number of measurements is time consuming and tedious. In case of questionable effort, a sniff nasal pressure maneuver (see below) may give additional information.

Interpretation and normal values

In absolute numbers, the PEmax is roughly the double of PImax when the Black and Hyatt technique is used, with a rigid mouthpiece. It has to be noted that in all models of maximal in-and expiratory pressures the explained variance is low, reflecting large inter-individual differences even when age, sex and anthropometric values are taken into account. Hence, a low PImax should always be interpreted with caution. A normal PImax however, generally excludes clinically relevant inspiratory muscle pathology.

INSPIRATORY PRESSURES MEASURED AT THE NOSE

PImax measured at the nostril Psniff during a sniff maneuver is a relatively newly developed technique[58] to measure inspiratory muscle function. One of the main advantages is that it is a technique that involves a natural maneuver (sniff), which is "easy to understand" by the patient[59]. Pressure is measured in an occluded nostril during a forced sniff. The unoccluded nostril serves as a variable resistance, prohibiting flow greater than 30 L/min and the pressures measured at the nose reflect those

obtained in the esophagus during sniff maneuver[59]. Since there is more airflow compared with the PImax maneuver, these sniff maneuvers are not static. Generally the sniff nasal pressures are as high as PImax (or even slightly higher) (ref.[60]). Maillard[42] reported a Psniff/PI, max ratio of 1.03/0.17, and reported equal and good within session reproducibility. Although less common in routine clinical practice this technique showed to be extremely useful in the diagnosis and follow-up of respiratory muscle weakness in children[61,62] and patients with neuromuscular disease[63,64] where sniff nasal pressures were reported to be superior to PImax. It should be acknowledged that some investigators reported sniff nasal pressures to be inferior to PImax in severe neuromuscular disease[65]. Hence, in patients with low PImax, the addition of sniff nasal pressures further improved the diagnostic process and some patients were consequently classified with normal respiratory muscle force[66]. The two techniques should hence be considered complementary, rather than interchangeable. Normal values for sniff nasal pressure are available[60]. Sniff measurements may be problematic in patients with significant upper airway disease. Since the sniff is a very short maneuver, damping of the pressure from the esophagus to the mouth and nose may occur in patients with obstructive lung disease, such as cystic fibrosis[64]. Much like the PImax, the sniff nasal pressure reflects a global measure of inspiratory muscle strength and not of diaphragm strength[59].

Essentially the equipment can consist of the same pressure transducer as the one used in the assessment of the PImax. A perforated plug with a tube is used to occlude the nostril. The tube is connected to the pressure transducer and the pressuretime curve is recorded for inspection and quality control. The peak pressure is reported after a series of maximal sniffs separated by normal breathing. A plateau is generally obtained after 510 sniffs. As the sniff pressure is a very brisk maneuver, the recording of the trace should be done with high resolution to allow detection of the peak pressure. Currently these devices and accompanying software, are commercially available.

MEASUREMENT IN ESOPHAGUS OR STOMACH

In rare clinical cases, and to answer specific research questions, it may be useful to measure the pressure in the oesophagus or in the gastric area. In the oesophagus the pressure (Pes) is a reflection of the pleural pressure (Ppl); the gastric pressure reflects the abdominal pressure (Pabd). The difference between both pressures is the "transdiaphragmatic pressure" (Pdi), which is a more specific measure of diaphragmatic function. To obtain these pressures a latex balloon catheter is put in place. Generally this is done by swallowing a balloon catheter introduced in the nose, after application of a local anaesthetic spray to the nasal mucosa and pharynx. Double lumen catheters are available for simultaneous measurements of pressure above and below the diaphragm (Pdi). Balloons placed over the catheters are 510 cm long, have thin walls and are filled with 0.5 mL of air to allow proper transmission of the pressure into the catheter. Catheter mounted micro transducers are an alternative to the "classical" balloon catheters. These transducers are accurate, but measure pressure only at one spot. Hence the measurement obtained may be a less precise reflection of the overall Pes. In addition, these catheters are much more expensive[45].

These tests are perceived by many patients as rather uncomfortable, but the results give probably the best estimate of the pressures generated by the respiratory muscles during normal breathing, during exercise, or during static manoeuvres or sniffs. When the balloon is positioned in the stomach, gastric pressure can also be recorded during cough. Hence "cough" pressure is recorded (Pcough) (ref.[67]). In healthy subjects, Pcough was reported to be superior to PEmax, and the lower limit of normal is set at 12.9 kPa (132 cmH_2O) male and 9.5 kPa (97 cmH_2O) for female subjects. Recently, Pcough were found to be a useful addition in the diagnosis of expiratory muscle weakness. In a significant number of patients with low PEmax, Pcough was reported normal. By contrast only a few patients with normal PEmax exhibited low Pcough. As a noninvasive variant of Pcough Chetta[68] recently introduced the "whistle" pressures, measured at the mouth. Subjects were asked to perform a short, sharp blow as hard as possible from TLC through a reversed paediatric inhaler whistle.

NON-VOLITIONAL TESTS OF RESPIRATORY MUSCLE FUNCTION

Measurements of maximal voluntary inspiratory or expiratory pressures at the mouth, nose, or even using balloon catheters to measure esophagus or gastric pressures are biased by the motivation of the patient to collaborate with the tests. Maximal effort is sometimes difficult to ascertain because of lack of patient motivation, anxiety, pain or discomfort, sub maximal central activation, poor mental status or difficulties in understanding the maneuvers.

To overcome the issue of sub maximal (voluntary) activation, investigation of the diaphragmatic function can be done through electrical[69] or magnetic stimulation[70] of the phrenic nerve. This nerve passes superficially in the neck and can be stimulated relatively easily. In addition, electromyography of the costal diaphragm can be carried out. When the latter is done, the phrenic nerve latency can be studied[71,72] which allows lesions of the phrenic nerve to be detected. Pressures developed after twitch stimulation of the phrenic nerve can be measured trans-diaphragmatically, or at the mouth. Although this technique is not often used in clinical routine, there are specific situations in which it may provide useful and unique information[73].

MEASUREMENTS DURING SLEEP

Patients with moderate or severe respiratory muscle weakness characteristically show dip in oxygen saturation related to periods of REM sleep[74,75]. The episodic

desaturation is usually due to hypopnea and less often to apnea and is associated particularly with phasic REM sleep, when brief periods of rapid irregular eye movements are accompanied by reduced activity of skeletal muscles[75]. The hypopnea and\or apnea may appear to be either central or obstructive cause or a mixture of both. The precise pattern of such events depends on relative activation of the respiratory pump and upper airway dilator muscles[75].Obstructive apnea occurs normally in weal and overweight people[76]. In patients with severe respiratory muscle weakness a central looking lesion may be obstructive and this is due to the failure of external sensors to detect chest wall movements of reduced amplitude[77]. Hypercapnia in patients with slow progressive weakness, develops first probably during sleep. Continuous monitoring during sleep (eg; with a transcutaneous pCO_2 detector) shows a gradual rise in partial pressure of carbondioxide (pCO_2) during REM sleep[74]. Consequently pCO_2 measured shortly after waking is more likely to be elevated than values obtained later in the day. The timescale of progression from nocturnal to persistent diurnal hypercapnia in patients with chronic respiratory muscle weakness is not known.

To assess whether upper airway narrowing is a contributing cause of apnea/hypopnea may require use of a supra-glottic or esophageal pressure sensor. Interpretation of recordings obtained by inductance plethysmography or other devices that measure rib cage and abdominal expansion is problematic in patients with quadriplegia or diaphragmatic paralysis. It is essential to check the polarity of the tracings and to compare phase relationships awake and asleep. Reliability of the devices for monitoring p CO_2 in sleep is currently doubtful and needs more study.

Overnight oximetry is simple to perform. Nocturnal measurements are more sensitive for detection of abnormal pulmonary gas exchange than daytime blood gases. It is labor -intensive and relatively expensive. Current evidence suggests that nocturnal hypoxemia is a less good prognostic indicator than either VC or pCO_2 (ref.[70,79]).

The role of sleep measurements in patients with respiratory muscle weakness is currently uncertain. Marked REM, relative de-saturation is seen occasionally in patients with relatively normal daytime SaO_2. More typically however the severity of nocturnal de-saturations is predictable from daytime measurements with more marked de-saturation in patients with lower daytime pO_2, higher pCO_2 and lower VC (ref.[74]). Sleep studies should be performed in all patients for whom nocturnal ventilatory support is being considered. As there is no evidence that treatment of abnormalities of gas exchange per se during sleep is beneficial, currently there is no indication for widespread application of poly-somnography in the absence of symptoms.

RESPIRATORY MUSCLE ENDURANCE

Although maximal in- and expiratory muscle strength gives important information on respiratory muscle function, the respiratory muscles (especially the inspiratory muscles) should be able to cope with endurance tasks. Measurements of respiratory muscle endurance, therefore, give clinicians further insight into the function of the respiratory pump, and may unmask early task failure. In the clinic, respiratory muscle endurance is generally assessed using one of the following techniques:

MAXIMUM SUSTAINABLE VOLUNTARY VENTILATION

The maximal sustainable voluntary ventilation (MSVV) is measured, or estimated from protocols with incremental ventilation[80]. The achieved sustainable ventilation is then reported as a fraction of the actually measured 1215 s maximum voluntary ventilation (MVV), and/or as a fraction of the predicted MVV. MSVV should be 6080% of the 12 s MVV. This test can be considered as a test of in- and expiratory muscles, but it is relatively sensitive to changes in airway obstruction, and needs careful control and adjustment of CO_2 tension in arterial blood, by adding or removing dead space or CO_2 to the inspired air. In patients with severe airflow obstruction, MVV may be low due to important dynamic compression of the airways during the vigorous 12 s maneuver. Therefore, MSVV/MVV may seem relatively high in these patients, whereas other measurements of endurance showed reduced respiratory muscle endurance in COPD (ref.[81]). In a variant of this test proposed for COPD patients, patients are asked to sustain a ventilation of 6675% of their MVV (ref.[82]). This test allows comparison within one subject, but normal values are not available.

INCREMENTAL THRESHOLD LOADING

Patients are asked to breathe against increasing inspiratory loads. The inspiratory threshold load is increased every 2 min[83]. The test can be compared with an incremental exercise test. The highest pressure that patients can sustain for 2 min in the incremental protocol is called maximum threshold pressure (Pthmax). Generally patients should be able to reach a pressure equivalent to 7580% of PImax. It[84] is reported that the Pthmax/PImax is dependent on age. Important learning curves are reported for this test, and the test should be repeated at least two to three times[85,86]. One study, conducted in COPD patients confirms the learning curve for the Pthmax at which patients could continue breathing but since PImax showed a similar learning curves, the Pthmax/PImax ratio remained constant (61% in test 1 and 67% in test 4) (ref.[87]). Due to the incremental nature of the test, however, it can be criticised as a straightforward measure of endurance. Alternatively, the maximum sustainable threshold load can be determined. The sustainable load is the load that can be sustained for 10 min. This technique reflects better the concept of "endurance", but it is time consuming. Recently, an expiratory incremental threshold loading test was developed, and used in healthy subjects and patients with COPD (ref.[88]). It was reported that the

expiratory pressure that was achieved following an incremental protocol was only 44% of PEmax in COPD. In healthy subjects 87% of PEmax was reached. The clinical consequences of these findings may be illustrated by the recent finding that expiratory muscle training in COPD may be a successful training strategy to improve exercise capacity and dyspnoea in patients with COPD (ref.[89]). Further studies, however, should be conducted to assess the usefulness of such an intervention on a larger scale.

ENDURANCE LOAD A INCREASING INTENSITY

From the work of Nickerson and Keens[90] and others[83,91] it can be deduced that an inspiratory load of 60% of the PImax can generally be sustained for 10 min. As a simple test of respiratory muscle endurance, hence, patients can be asked to breathe at a fixed inspiratory load equal to 60% of PImax. When subjects fail to continue breathing against this resistance at any time point earlier than 10 min, respiratory muscle endurance can be assumed impaired. Although easy to apply in clinical routine, this test has many methodological problems that impair the use of this test in clinical studies. The most important problem is probably the fact that the time to fatigue is related to the breathing pattern (i.e. the inspiratory time (TI)/total respiratory time (Ttot) ratio). The higher this ratio, the sooner fatigue will occur. Hence TI/Ttot should be carefully controlled and maintained at around 0.4 during the test[92]. Despite these methodological shortcomings this test is a useful addition to a measurement of PImax in patients presenting with muscle weakness. In this case, the test may give clinicians information on the susceptibility to inspiratory muscle fatigue.

DISCUSSION

Suitable biomarkers of acute exacerbation will allow the onset of impending exacerbations to be detected and\ or will provide laboratory confirmation of the clinical impression of a significant exacerbation. The different patterns of markers may help determine the pathogenic nature of the episode and hence help in the management. At present, although these tests may have clear applications in clinical research, their role in patient management is far from certain. The indefinite way of classifying the different types of an exacerbation and the multi-component nature of the underlying condition makes the finding of an ideal noninvasive biomarker of AECOPD very difficult, however with recent research methods and advanced instrumentations we could certainly look to see the condition and understand it at every level of functioning and thereby hope to devise a set of markers and indices that would help in the management of the patient.. However at present, none of these is able to predict an impending exacerbation. As the nature of the subtypes of exacerbation becomes clearer it may be possible, through the use of biomarkers, to target management for each patient and episode more specifically.

In order to compensate for airflow limitation, attempts can be made to increase inspiratory flow, allowing more time for exhalation or over-inflation can occur which will increase the end expiratory volume and functional residual capacity, but takes advantage of higher expiratory flows at higher lung volumes due to both decreased airway resistance and increased elastic recoil. Eventually, a new equilibrium is reached at some end expiratory volume above functional residual capacity. This results in an inability to return to passive FRC before the next breath occurs, a process called dynamic hyperinflation. Both these compensatory mechanisms result in increased work on breathing and therefore place the inspiratory muscles especially the diaphragm at a mechanical disadvantage due to length tension effects. In addition when the respiratory system rests above functional residual capacity at end-expiration, this creates a residual lung elastic recoil pressure, producing a positive alveolar pressure. Thus a proportion of the inspiratory muscle pressure generated with each breath is wasted in overcoming the residual recoil pressure of the respiratory system. In addition, because breathing takes place at a higher lung volume it takes place in a less compliant portion of the lung pressure- volume cycle and thus increase the work of breathing. This dynamic hyperinflation is probably the major contributor to the sensation of dyspnea in stable COPD and the increased dyspnea in AECOPD. In patients with exacerbations there is a further reduction in the forced expiratory flow - volume loop and the ability to compensate may be impossible. Respiratory failure will occur against this background as a result of changes in the characteristics of the respiratory system either an increase in the overall load beyond the possible compensatory mechanisms or changes that impair the function or effectiveness of the respiratory muscles and the central nervous system to compensate. In severe exacerbations, the primary physiological change is worsening of gas exchange due to ventilation perfusion mismatch. As the v/q relationships worsen, increased effort of the respiratory muscles produces greater oxygen consumption and hence decreased oxygen tensions, which further amplifies the gas exchange abnormalities. The measurement of respiratory muscle force evolved from a technique used in clinical physiology studies to a measurement that has gained importance in the clinical routine. Assessment of respiratory muscle force is extremely useful to understand the etiology of dyspnea, and the detection of respiratory muscle weakness has consequences in the treatment of patients. The most obvious example is the introduction of respiratory muscle training in patients with respiratory muscle weakness. Since respiratory muscle weakness can be treated in many cases by respiratory muscle training, or tapering of treatment with drugs inducing the weakness or may help clinicians decide on mechanical ventilation strategies, knowledge of respiratory muscle dysfunction opens a window of clinical treatment opportunities.

Therefore by looking at different indices and markers of respiratory muscle function would give us an insight into the patho-mechanism of the condition and hence could play an important role in the management of the condition.

CONCLUSION

COPD and its exacerbations continue to pose a serious health, economic and social burden. It is ranked as the fourth leading cause of death and with its increasing numbers, it has become absolutely essential that we have better and more effective management plan for the condition. To achieve this, a suitable biomarker, other surrogate marker or a set of these that can help us understand the nature of the episode, assess the severity and can play a role in therapeutic management is important. Current studies and the potential in the future with advanced methodology and instrumentation can realistically hope to achieve it and thereby manage the patients more favourably and effectively.

ABBREVIATIONS

AECOPD, Acute exacerbation of chronic obstructive pulmonary disease; BAL, Bronchoalveolar lavage; BCAA, Branch chain amino acids; BODE - BMI, Obstruction dyspnea exercise tolerance index; CC-16, Clara Cell secretory protein-16; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; DES, Ddesmosine; ECP, Extracellular protein; ET-1, Endothelin-1; FEV1, Forced expiratory volume in 1st second; FFMI, Fat - free mass index; FRC, Functional residual capacity; GM-CSF, Granulocyte monocyte colony stimulating factor; GOLD4, Global initiative for chronic obstructive lung disease; IDES, Isodesmosine; IFN, Interferons; IL, Interleukins; LDL, Low density lipoproteins; MPO, Myeloperoxidase; MRC, Modified research council dyspnea scale; MSVV, Ma ximal sustainable voluntary ventilation; MVV, Maximum voluntary ventilation; NE, Neutrophil elastase; NMR, Nuclear magnetic resonance; pCO2, partial pressure of carbondioxide; Pcough, cough pressure; Pdi, transdiaphragmatic pressure; PEmax, Maximum voluntary expiratory pressure; Pes, oesophagus pressure; PImax, Maximum voluntary inspiratory pressure; pO2, partial pressure of oxygen; Ppl, pleural pressure; REM, Rapid eye movement; RV, Residual volume; SaO2, Arterial saturation percentage of Oxygen; TBA-MDA, Thiobarbituric acid-malonialdehyde; TEAC, Trolox equivalent antioxidant capacity; TI, Inspiratory time; TLC, Total lung capacity; TNF-alpha, Tumor Necrosis Factor alpha; Ttot, total respiratory time; UPLC-IM-MS, Ultra performance liquid chromatography - Ion mobility - Mass spectrometry; VLDL, Very low density lipoproteins; VC, Vital capacity.

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