

Clinical physiology of chronic obstructive pulmonary disease

A variety of methods can be used to assess disturbances and dysfunctions common in COPD, including pulse oximetry and exercise testing.

ABSTRACT: The symptoms and functional limitations of chronic obstructive pulmonary disease (COPD) are a direct result of airway and lung parenchymal processes. These processes lead to airflow obstruction, increased work of breathing, and gas exchange abnormalities. When advanced, these can in turn cause pulmonary hypertension, cor pulmonale, and left heart dysfunction. Cataloguing of symptoms, physical examination, and routine radiology are of limited utility in the early diagnosis and assessment of response to therapy for COPD. Patients can benefit from the use of laboratory measurements to manage this disorder. Spirometry and oximetry have the broadest application, while arterial blood gas and exercise testing have selected utility.

Although many different factors may be involved in the development of COPD, smoking is the most significant. Exposure to tobacco smoke provokes a series of inflammatory processes involving the small as well as the large airways and can also impair host defence mechanisms. In predisposed individuals this leads to pathological processes that we have come to recognize as chronic bronchitis and emphysema. It is important to note that bronchial inflammation can be detected long before the disease is evident clinically¹ and persists long after the cessation of smoking,² and that the inflammatory processes of COPD are readily distinguishable from those of asthma.^{3,4}

Physiological defects Airflow limitation and hyperinflation

Expiratory airflow limitation is the principal physiological defect in COPD. Intrinsic airway factors relate to bronchial wall inflammation and include mucosal inflammation/edema, bronchial wall remodeling/fibrosis, and increased mucosal secretions. Extrinsic factors involve the loss of elastic tissue support for small airways and the dynamic expiratory

compression of these airways.^{5,6} Other factors such as respiratory muscle dysfunction can further limit airflow in some patients.

Hyperinflation can also occur in COPD, leading to an increase in functional residual capacity (FRC)—the amount of air that remains in the lungs at the end of tidal exhalation. This can lead to gas trapping and an increase in residual volume (RV). As a consequence, there is an augmentation of the inspiratory work of breathing, which is an important factor in producing dyspnea. As the expiratory time is essential for lung emptying, factors that decrease this time, such as an increasing respiratory rate during exercise, result in a progressive increase in FRC (**Figure 1**).⁷ This phenomenon is called dynamic hyperinflation, and is largely responsible for exercise limitation in COPD.⁷⁻¹¹

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Gas exchange disturbances

Perturbations in gas exchange are caused primarily by regional inequalities of ventilation and perfusion (VQ mismatching).¹² This process commonly produces hypoxemia, but in

more advanced disease can also contribute to hypercapnia and chronic respiratory acidosis. Other contributing factors to gas exchange disturbances in advanced COPD are pulmonary hypertension and impaired cardiac

function, which can lead to reduced mixed venous oxygenation.

Ventilatory muscle dysfunction

A number of factors contribute to ventilatory muscle dysfunction in COPD. A major factor is a consequence of hyperinflation, which limits force generation and endurance,¹³ and places the inspiratory muscles at a mechanical disadvantage. Other factors include nutritional alterations, a sustained inflammatory response that affects the contractile apparatus, tissue hypoxia, and loss of muscle mass.^{14,15} These factors also affect other skeletal muscles, which may further contribute to exercise limitation.^{16,17}

Cardiovascular disturbances

Cardiovascular disturbances are common in COPD and may represent a complication of COPD itself or may be triggered by the same factor, that is, smoking. Recently it has been proposed that lung inflammation may directly affect atherogenesis by driving systemic inflammation.

Pulmonary hypertension is a late complication of COPD and indepen-

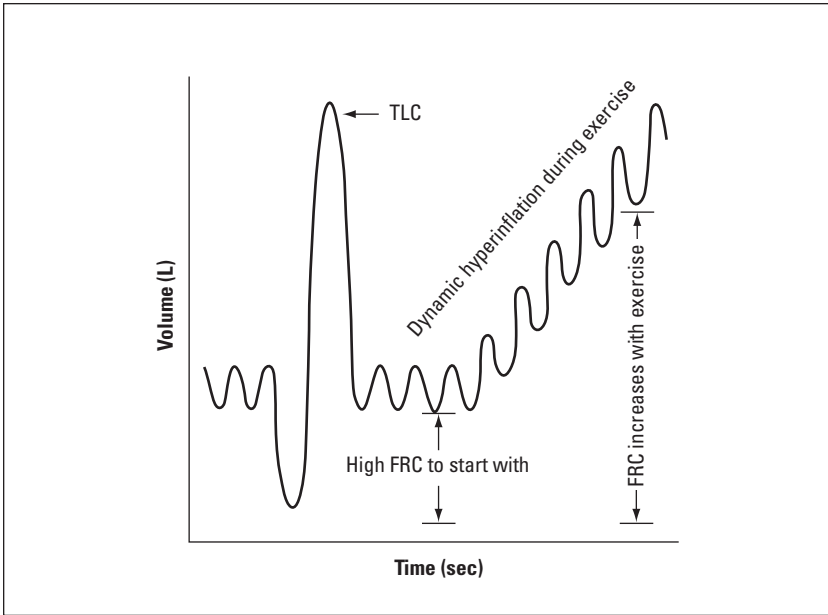


Figure 1. Dynamic hyperinflation in patients with emphysema during exercise.

FRC: functional residual capacity TLC: total lung capacity

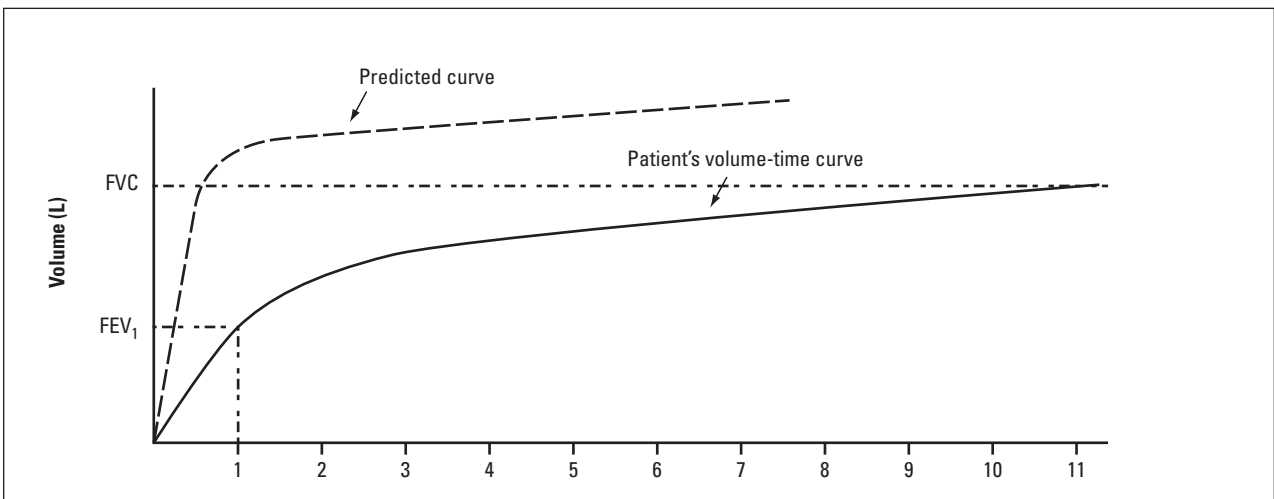


Figure 2. Volume-time curve of a patient with COPD. Airway obstruction is indicated by the significant straightening of the patient's curve compared with the predicted curve.

FEV₁: forced expiratory volume in 1 second FVC: forced vital capacity

dently worsens its prognosis.¹⁸⁻²⁴ A major factor is chronic hypoxia, which can result in pulmonary vasoconstriction. Other factors include endothelial dysfunction, remodeling of pulmonary arteries, and pulmonary capillary bed destruction. Right ventricular dysfunction and failure (cor pulmonale) may eventually develop and add to the morbidity and mortality of this disease.

Reduced exercise capacity

Deconditioning may result from lack of physical activity and can be an independent factor in exercise limitation. Fortunately, this is amenable to a pulmonary rehabilitation program. Management of deconditioning, like the management of other physiological defects of COPD, begins with assessment of function.

Assessment of airflow limitation and hyperinflation

Spirometry with measurements derived from a maximal forced expiratory maneuver is the most clinically relevant test in assessing COPD. Airway obstruction is diagnosed when the FEV₁/FVC (forced expiratory volume in 1 second to forced vital capacity) ratio is less than 0.7 L, a situation usually accompanied by a reduction in FEV₁ to less than 80% of predicted (**Figure 2**). FEV₁ has traditionally been used to grade severity of COPD (see "Pharmacological management," **Table 2**, page 86).²⁵⁻²⁶ In COPD the expiratory flow-volume curve is characteristically concave (**Figure 3**). This appearance is typical for emphysema (but not specific) and implies the dynamic airway collapse with forced exhalation.²⁷ Significant response to bronchodilators, defined as an increase in FEV₁ by 12% and 180 mL, is common in asthma but uncommon in COPD.

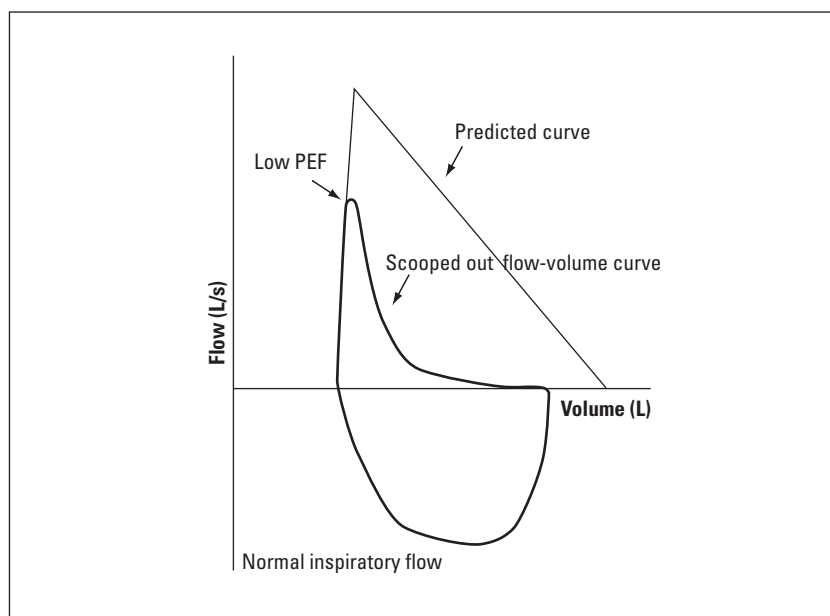


Figure 3. Maximal inspiratory and expiratory flow-volume curve. In emphysema, the loss of supportive tissues means the airways tend to collapse with forced exhalation, giving a characteristic concave appearance in the expiratory portion of the flow-volume curve. This can also be seen in other obstructive disorders such as asthma.

PEF: peak expiratory flow

New technology has allowed the development of portable hand-held spirometers that are robust, simple to use, and reasonable in cost (\$500 to \$1500), making spirometry a test that can be performed in the office setting. Accreditation can be obtained in BC through the Diagnostic Accreditation Program, and once you have the required pulmonary function test (PFT) credentials you may bill for performing this test. Spirometry should be routine in COPD for the following:

- Diagnosis (particularly of early disease or to differentiate from asthma).
- Establishing severity.
- Determining prognosis.
- Monitoring disease progression and response to therapy.

More detailed lung function tests are available in most PFT labs. These are utilized in select instances in COPD. Most commonly this occurs when

there is a reduction in FVC and a need to determine whether there is a concomitant restrictive disorder such as interstitial lung disease. In pure COPD, FVC is modestly decreased if there is air trapping and hyperinflation (RV increased). Diffusing capacity (DLCO) is very sensitive in detecting gas exchange abnormalities. It is usually reduced in emphysema (whereas it is normal or high in asthma) and correlates reasonably well with the pathological severity of emphysema.²⁸ Full pulmonary function tests should therefore be considered when spirometry indicates a reduced FVC to determine if there is a restrictive disorder present, and when spirometry is normal despite the presence of dyspnea to determine if there is an impairment in DLCO that might suggest another pulmonary parenchymal or vascular disorder.

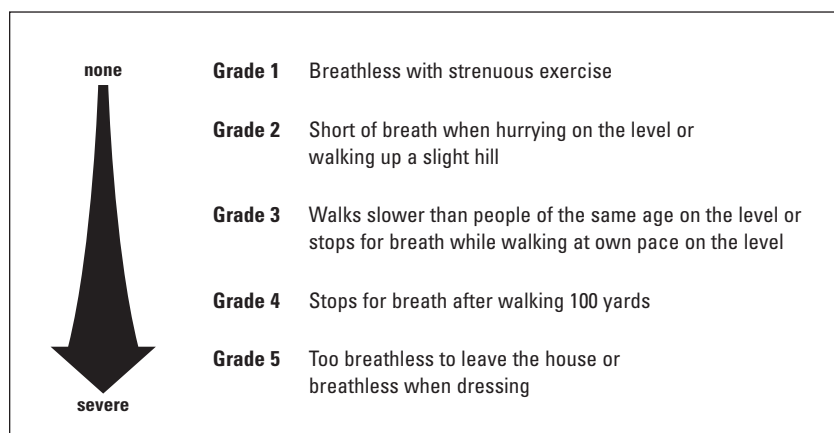


Figure 4. The Medical Research Council dyspnea scale.²⁶

The 6-minute walk test distance (degree of reduction) correlates well with functional disability and provides prognostic information.

Peak expiratory flow rate

Peak expiratory flow rate (PEFR) testing provides a simple, readily available measure of airflow. PEFR, however, may underestimate airflow obstruction in COPD as it is predominantly a measure for the large airways. Furthermore, the reproducibility and reliability of PEFR testing is inferior to spirometry. We therefore advise against its use for routine assessment of COPD (in contrast to asthma) although it may have some merit as a serial measurement for a given individual.²⁹⁻³⁰

Radiological tests

Chest radiography may show features of hyperinflation such as flattening of the diaphragms with increased anteroposterior diameter on a lateral film,

but this is not sensitive or specific for COPD. Although not routinely indicated, a CT chest scan may on occasion be of use in the characterization of COPD (emphysema).³¹

Assessment of gas exchange disturbances

Pulse oximetry can be done in the ambulatory setting to reliably quantify oxygen saturation. Arterial blood gas measurement can be considered in patients with SaO_2 of less than 92% (or FEV_1 of less than 40%) to more precisely assess the degree of hypoxemia and hypercapnia.³² Both tests can be used to determine the potential role of domiciliary oxygen. The portability of pulse oximetry makes it applicable in the quantitation of hypoxemia with exertion and during sleep.

Assessment of ventilatory muscle dysfunction

Tests for ventilatory muscle function may be considered in select cases, including those where ventilatory muscle involvement is suspected in a neuromuscular disorder, or where dyspnea or hypercapnia are out of proportion to the patient's FEV_1 .¹² Other assessment methods for muscle dysfunction may include measuring lung volumes (restrictive disorder), blood gases (elevated PCO_2), and maximal inspiratory and expiratory pressures. EMG and nerve conduction studies may also be considered.

Assessment of cardiovascular disturbances

Clinical evaluation, chest X-ray, EKG, and echocardiography with Echo-Doppler estimation can be used in patients with suspected cardiac disorders or pulmonary hypertension to assess the pulmonary artery systolic pressure and ventricular function.²⁷

Assessment of reduced exercise capacity Dyspnea scale

The Medical Research Council dyspnea scale is a simple clinical tool used to assess shortness of breath and disability during activity (Figure 4).²⁵ This scale has been found to correlate with the patient's quality of life and may be of use in predicting mortality.²⁵

6-minute walk test

The 6-minute walk test is a standardized lab test in which the patient walks unassisted for 6 minutes and the distance is measured. The normal distances walked are about 500 m for women and about 580 m for men, with a change of 40 m in a properly performed test considered significant. The 6-minute walk test distance

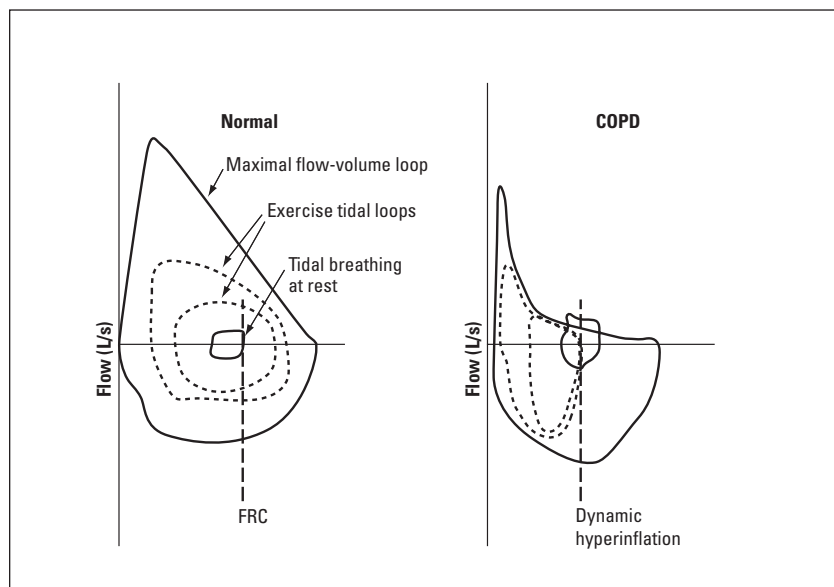


Figure 5. The relation between the exercise tidal flow-volume loops and the baseline maximal flow-volume loop. Normally (left), tidal flow-volume loops expand in both directions during exercise. In emphysema (right), the decreased expiratory time (because of increased respiratory rate during exercise) results in more air-trapping and increases the FRC, shifting the tidal flow-volume loop curves to the left, a phenomenon called dynamic hyperinflation.

FRC: functional residual capacity

(degree of reduction) correlates well with functional disability and provides prognostic information.³³⁻³⁴

Cardiopulmonary exercise testing

The cardiopulmonary exercise test (CPET) objectively measures maximum exercise capacity. When exercise capacity is reduced, CPET can assist in identifying the organ system responsible. The measure of peak oxygen uptake during incremental testing is an independent prognostic factor in COPD.²⁰ Dynamic hyperinflation can be demonstrated by performing repeated inspiratory capacity maneuvers and by comparing the exercise tidal flow-volume loops with the baseline maximal flow-volume loop (Figure 5). CPET can assist with patient selection for pulmonary rehabilitation, lung volume reduction

surgery, and suitability for pulmonary resection.

Conclusions

COPD is an inflammatory airway disease with a complex pathophysiology. This disorder leads to airway obstruction and often to hyperinflation, which along with gas exchange abnormalities interact to cause dyspnea and functional limitation. Spirometry is a widely available tool that quantifies the abnormalities in COPD and can be fundamental in diagnosing, monitoring, and establishing the prognosis of individuals with this condition. More detailed lung function testing may have utility, but is not generally required. Measures of oxygenation (oximetry and arterial blood gases) can be used to monitor disease severity and to determine the appropriateness of domiciliary oxygen. Such

measurements should play a fundamental role in the management of COPD as the monitoring of blood sugar does in diabetes.

Competing interests

None declared.

References

- Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2645-2653.
- Shapiro SD. End-stage chronic obstructive pulmonary disease. The cigarette is burned out but inflammation rages on. *Am J Respir Crit Care Med* 2001;164:339-340.
- Saetta M, Di Stefano A, Turato G, et al. CD8+ T-lymphocytes in peripheral airways of smokers with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:822-826.
- Fabbri LM, Romagnoli M, Corbetta L, et al. Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;167:418-424.
- Leopold JG, Geoff J. Centrilobular form of hypertrophic emphysema and its relation to chronic bronchitis. *Thorax* 1957;12:219-235.
- McLean KA. Pathogenesis of pulmonary emphysema. *Am J Med* 1958;25:62-74.
- O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. *Am Rev Respir Dis* 1993;48:1351-1357.
- O'Donnell DE, Revill S, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:770-777.
- Tantucci C, Duguet A, Similowski T, et al. Effect of salbutamol on dynamic hyperinflation in chronic obstructive pulmonary disease patients. *Eur Respir J* 1998;12:799-804.

10. Parker C, Voduc N, Aaron SD, et al. Physiological changes during symptom recovery from moderate exacerbations of COPD. *Eur Respir J* 2005;26:420-428.
11. Stevenson NJ, Walker PP, Costello RW, et al. Lung mechanics and dyspnea during exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172:1510-1516.
12. Rodriguez-Roisin R, MacNee W. Pathophysiology of chronic obstructive pulmonary disease. *Eur Respir Monograph* 1998;3:107-126.
13. Hughes RL, Katz H, Sahgal V, et al. Fiber size and energy metabolites in five separate muscles from patients with chronic obstructive pulmonary disease. *Respiration* 1983;44:321-328.
14. Satta A, Migliori GB, Spanevello A, et al. Fibre types in skeletal muscles of chronic obstructive pulmonary disease patients related to respiratory function and exercise tolerance. *Eur Respir J* 1997;10:2853-2860.
15. Wilson DO, Rogers RM, Wright EC, et al. Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. *Am Rev Respir Dis* 1989;139:1435-1438.
16. Schols AM, Slagen J, Volovics L, et al. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1791-1797.
17. Calverley PMA, Anderson JA, Celli B, et al. for the TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775-789.
18. Weitzenblum E, Hirth C, Ducolone A, et al. Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. *Thorax* 1981;36:752-758.
19. Bishop JM, Cross KW. Physiological variables and mortality in patients with various categories of chronic respiratory disease. *Bull Eur Physiopathol Respir* 1984;20:495-500.
20. Oga T, Nishimura K, Tsukino M, et al. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: Role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003;167:544-549.
21. Biernacki W, Flenley DC, Muir AL, et al. Pulmonary hypertension and right ventricular function in patients with COPD. *Chest* 1988;94:1169-1175.
22. MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part two. *Am J Respir Crit Care Med* 1994;150:1158-1168.
23. Soriano JB, Visick GT, Muellerova H, et al. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005;128:2099-2107.
24. Sidney S, Sorel M, Quesenberry CP Jr, et al. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 2005;128:2068-2075.
25. O'Donnell DE, Aaron S, Bourbeau J, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease—2003. *Can Respir J* 2003;10(suppl A):11A-65A.
26. Hancox R, Whyte K. *Pocket Guide to Lung Function Tests*. Sydney: McGraw-Hill; 2001. 157 pp.
27. Gibson GJ, MacNee W. Chronic obstructive pulmonary disease: Investigations and assessment of severity. *Eur Respir Monograph* 2006;11:24-40.
28. McLean A, Warren PM, Gillooly M, et al. Microscopic and macroscopic measurements of emphysema: Relation to carbon monoxide gas transfer. *Thorax* 1992;47:144-149.
29. BTS guidelines for the management of chronic obstructive pulmonary disease. The COPD Guidelines Group of the Standards of Care Committee of the BTS. *Thorax* 1997;52(suppl 5):S1-28.
30. Kelly CA, Gibson GJ. Relation between FEV and peak expiratory flow in patients with chronic airflow obstruction. *Thorax* 1988;43:335-336.
31. Pauwels RA, Buist AS, Ma P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): Executive summary. *Respir Care* 2001;46:798-825.
32. Roberts CM, Bugler JR, Melchor R, et al. Value of pulse oximetry in screening for long-term oxygen therapy requirement. *Eur Respir J* 1993;6:559-562.
33. Pinto-Plata VM, Cote C, Cabral H, et al. The 6-min walk distance: Change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004;23:28-33.
34. Casanova C, Cote CG, Marin JM, et al. The 6-min walking distance: Long-term follow up in patients with COPD. *Eur Respir J* 2007; 29:535-540. **BCMJ**