REVIEW

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Chronic Obstructive Pulmonary Disease: Respiratory Review of 2013

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Chronic obstructive pulmonary disease (COPD) is a common airway disease that has considerable impact on disease burdens and mortality rates. A large number of articles on COPD are published within the last few years. Many aspects on COPD ranging from risk factors to management have continued to be fertile fields of investigation. This review summarizes 6 clinical articles with regards to the risk factors, phenotype, assessment, exacerbation, management and prognosis of patients with COPD which were being published last year in major medical journals.

Keywords: Pulmonary Disease, Chronic Obstructive; Airway Obstruction; Review

Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disorder that is more prevalent in the elderly. It would have more considerable impact on disease burden and mortality as the nation is rapidly moving toward an aged society with the elderly population rising in Korea. It is predicted to rank fifth worldwide in terms of burden of disease and third in terms of mortality in 2020[1,2]. Many papers on COPD were published within last year. Among them, this article reviews 6 clinical articles that were published in major medical journals; one of each article regarding risk factors, phenotype, assessment, exacerbation, management and prognosis of patients with COPD, respectively.

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Risk Factors

Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. Mehta et al.[3] Am J Respir Crit Care Med 2012;185:1292-300.

Rationale: There is limited evidence from population-based studies demonstrating incidence of spirometric-defined chronic obstructive pulmonary disease (COPD) in association with occupational exposures.
Objectives: We evaluated the association between occupational exposures and incidence of COPD in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA).
Measurements and Main Results: Prebronchodilator ratio of forced expiratory volume in 1 second over forced vital capacity (FEV_1/FVC) was measured in 4,267 nonasthmatic SAPALDIA participants ages 18–62 at baseline in 1991 and at follow-up in 2001–2003. COPD was defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criterion (FEV_1/FVC,0.70) and Quanjer reference equation (FEV_1/FVC, lower limit of normal [LLN]), and categorized by severity (>80% and 80%predicted FEV_1 for stage I and stage II+, respectively). Using a job-exposure matrix, self-reported occupations at baseline

were assigned exposures to biological dusts, mineral dusts, gases/fumes, and vapors, gases, dusts, or fumes (VGDF) (high, low, or unexposed as reference). Adjusted incident rate ratios (IRRs) of stage I and stage II+ COPD were estimated in mixed Poisson regression models. Statistically significant ($P < 0.05$) IRRs of stage II+ GOLD and LLN-COPD, indicating risks between two- and fivefold, were observed for all occupational exposures at high levels. Occupational exposure associated risk of stage II+ COPD was observed mainly in males and ages >40 years, and remained elevated when restricted to nonsmokers.
Conclusions: In a Swiss working adult population, occupational exposures to biological dusts, mineral dusts, gases/fumes, and VGDF were associated with incidence of COPD of at least moderate severity. *(Mehta et al.[3], 2012, p. 1292; Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society. Official Journal of the American Thoracic Society.)*

1. Comments and learning points

The key message of this study is that occupational hazards can be risk factors for developing COPD. A recent statement from the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1] and Korean COPD guidelines[4] suggested that there was epidemiologic evidence of occupational exposures for developing COPD. However, little is known about incidence of COPD in association with occupational exposures to general population. This study can be one of important evidences supporting the meaningful relationships between occupational risk factors and development of COPD. A recent study by Gan et al.[5] also showed that ambient air pollution, including traffic-related fine particulate pollution and woodsmoke pollution, was associated with COPD.

This study has a number of strengths, including prospective study design with large sample size. However, one of limitations was that the authors used prebronchodilator spirometric measurements to define COPD.

Phenotypes of COPD

Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease. Nishimura et al.[6] Am J Respir Crit Care Med 2012;185:44-52.

Rationale: Although the rate of annual decline in FEV1 is one of the most important outcome measures in chronic obstructive pulmonary disease (COPD), little is known about intersubject variability based on clinical phenotypes.
Objectives: To examine the intersubject variability in a 5-year observational cohort study, particularly focusing on emphysema severity.
Methods: A total of 279 eligible patients with COPD (stages I-IV: 26, 45, 24, and 5%) participated. We conducted a detailed assessment of pulmonary function and computed tomography (CT) at baseline, and performed spirometry every 6 months before and after inhalation of bronchodilator. Smoking status, exacerbation, and pharmacotherapy were carefully monitored. Emphysema severity was evaluated by CT and annual measurements of carbon monoxide transfer coefficient.
Measurement and Main Results: Using mixed effects model analysis, the annual decline in post-bronchodilator FEV_1 was -32±24 (SD) ml/yr (n=261). We classified the subjects of less than the 25th percentile as Rapid decliners, the 25th to 75th percentile as Slow decliners, and greater than the 75th percentile as Sustainers (-63±2, -31±1, and -2±1 [SE] ml/yr). Emphysema severity, but not $\%FEV_1$, showed significant differences among the three groups. Multiple logistic regression analysis demonstrated that the Rapid decliners were independently associated with emphysema severity assessed either by CT or carbon monoxide transfer coefficient. The Sustainers displayed less emphysema and higher levels of circulating eosinophils.
Conclusions: Emphysema severity is independently associated with a rapid annual decline in FEV_1 in COPD. Sustainers and Rapid decliners warrant specific attention in clinical practice. *(Nishimura et al.[6], 2012, p. 44; Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society. Official Journal of the American Thoracic Society.)*

1. Comments and learning points

The key message of this study is that clinical phenotype in COPD is related to a decline in pulmonary function, forced expiratory volume in 1 second (FEV_1). The annual decline of FEV_1 was larger in subjects with high emphysema score compared to the subjects with no or mild emphysema.

Annual change in FEV_1 can be affected by many factors such as smoking status[7,8], frequency of exacerbation[9] and bronchodilator response[8]. The airflow limitation in COPD is caused by an inflammatory airway change and emphysema[10]. This study has several strengths. It was a well designed, prospective study. Assessment of annual change in FEV_1 was based on measurements over a long duration, 5 years. However, there are several limitations. Emphysema severity on computed tomography (CT) was visually assessed and it was not measured by automated software. The sample size in this study was not so large compared to the previous similar study such as Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study[11]. Thus, the lack of adequate power as a result of the small sample size may well explain some of the failures in detecting the factors, such as exacerbation and chronic bronchitis syndrome.

Assessment

GOLD 2011 disease severity classification in COPDGene: a prospective cohort study. Han et al.[12] Lancet Respir Med 2013;1:43-50.

Background: The 2011 GOLD (Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [COPD]) consensus report uses symptoms, exacerbation history, and forced expiratory volume (FEV_1)% to categorise patients according to disease severity and guide treatment. We aimed to assess both the influence of symptom instrument choice on patient category assignment and prospective exacerbation risk by category.

Methods: Patients were recruited from 21 centres in the USA, as part of the COPDGene study. Eligible patients were aged 45–80 years, had smoked for 10 pack-years or more, and had an FEV_1/forced vital capacity (FVC) <0.7. Categories were defined with the modified Medical Research Council (mMRC) dyspnoea scale (score 0–1 *vs* ≥2) and the St George's Respiratory Questionnaire (SGRQ; ≥25 *vs* <25 as a surrogate for the COPD Assessment Test [CAT] ≥10 *vs* <10) in addition to COPD exacerbations in the previous year (<2 *vs* ≥ 2), and lung function (FEV_1% predicted ≥50 *vs* <50). Statistical comparisons were done with *k*-sample permutation tests. This study cohort is registered with ClinicalTrials.gov, number NCT00608764.

Findings: 4484 patients with COPD were included in this analysis. Category assignment using the mMRC scale versus SGRQ were similar but not identical. On the basis of the mMRC scale, 1507 (33.6%) patients were assigned to category A, 919 (20.5%) to category B, 355 (7.9%) to category C, and 1703 (38.0%) to category D; on the basis of the SGRQ, 1317 (29.4%) patients were assigned to category A, 1109 (24.7%) to category B, 221 (4.9%) to category C, and 1837 (41.0%) to category D (κ coefficient for agreement, 0.77). Significant heterogeneity in prospective exacerbation rates (exacerbations/person-years) were seen, especially in the D subcategories, depending on the risk factor that determined category assignment (lung function only [0.89, 95% CI 0.78–1.00]), previous exacerbation history only [1.34, 1.0–1.6], or both [1.86, 1.6–2.1; p<0.0001]).

Interpretation: The GOLD classification emphasises the importance of symptoms and exacerbation risk when assessing COPD severity. The choice of symptom measure influences category assignment. The relative number of patients with low symptoms and high risk for exacerbations (category C) is low. Differences in exacerbation rates for patients in the highest risk category D were seen depending on whether risk was based on lung function, exacerbation history, or both. *(Han et al.[12], 2013, p. 43; Reprinted with permission of Elsevier Ltd.)*

1. Comments and learning points

The key message of this study is that the choice of symptom measurements and exacerbation risk factors influences category assignment of COPD; 1) classification of COPD group produced by the modified Medical Research Council (mMRC) or COPD Assessment Test (CAT) score can be different, and 2) exacerbation risk for COPD patients can be changed whether risk was based on lung function or exacerbation history. The other recent reports also showed that the classification of COPD produced by the mMRC or CAT score was not identical[13,14]. The 2011 Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) document proposed a new classification system for COPD[1]. This report is the first study to evaluate the prevalence of COPD group according to new GOLD document. Also, this result suggests that refinement for differentiating symptom and exacerbation risk groups would be needed in the future. The limitation of this study is that the COPDGene cohort is not a true population-based sample. It might not represent the true distribution of COPD severity in the general population. The authors used St George's Respiratory Questionnaire (SGRQ) scores instead of CAT scores for symptom measurements. However, patients were recruited from multiple centres in the United States; the participating clinical centres and general community advertising. The COPDGene study is also one of the largest COPD cohorts and this study examined prospective outcomes. SGRQ scores can be comparable to CAT scores.

Exacerbation of COPD

Pulmonary arterial enlargement and acute exacerbations of COPD. Wells et al.[15] N Engl J Med 2012;367:913-21.

Background: Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with accelerated loss of lung function and death. Identification of patients at risk for these events, particularly those requiring hospitalization, is of major importance. Severe pulmonary hypertension is an important complication of advanced COPD and predicts acute exacerbations, though pulmonary vascular abnormalities also occur early in the course of the disease. We hypothesized that a computed tomographic (CT) metric of pulmonary vascular disease (pulmonary artery enlargement, as determined by a ratio of the diameter of the pulmonary artery to the diameter of the aorta [PA:A ratio] of >1) would be associated with severe COPD exacerbations.

Methods: We conducted a multicenter, observational trial that enrolled current and former smokers with COPD. We determined the association between a PA:A ratio of more than 1 and a history at enrollment of severe exacerbations requiring hospitalization and then examined the usefulness of the ratio as a predictor of these events in a longitudinal follow-up of this

cohort, as well as in an external validation cohort. We used logistic-regression and zero-inflated negative binomial regression analyses and adjusted for known risk factors for exacerbation.
Results: Multivariate logistic-regression analysis showed a significant association between a PA:A ratio of more than 1 and a history of severe exacerbations at the time of enrollment in the trial (odds ratio, 4.78; 95% confidence interval [CI], 3.43 to 6.65; P<0.001). A PA:A ratio of more than 1 was also independently associated with an increased risk of future severe exacerbations in both the trial cohort (odds ratio, 3.44; 95% CI, 2.78 to 4.25; P<0.001) and the external validation cohort (odds ratio, 2.80; 95% CI, 2.11 to 3.71; P<0.001). In both cohorts, among all the variables analyzed, a PA:A ratio of more than 1 had the strongest association with severe exacerbations.
Conclusions: Pulmonary artery enlargement (a PA:A ratio of >1), as detected by CT, was associated with severe exacerbations of COPD. *(Wells et al.[15], 2012, p. 913; Reprinted with permission of Massachusetts Medical Society)*

1. Comments and learning points

The key message of this study is that pulmonary artery enlargement can be a risk factor for exacerbation of COPD. Acute exacerbations of COPD are very important clinical issues because it can accelerate loss of lung function and it is a cause of death in patients with COPD[16]. Therefore, many studies have reported the risk factors such as previous exacerbation history or pulmonary hypertension[17] for exacerbation of COPD. This study suggests a more powerful risk factor (pulmonary artery enlargement, as determined by a PA:A ratio of >1) for severe exacerbation compared to the previous exacerbation history. Measurements of PA diameter were performed by using CT images. This method can be easily applicable in clinical settings. However, a limitation of this result is that the study was observational design, and therefore it cannot definitively conclude that elevations in the PA:A ratio cause acute exacerbations of COPD.

Management

Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison. Mahler et al.[18] Thorax 2012;67:781-8.

Background Current guidelines recommend treatment with one or more long-acting bronchodilators for patients with moderate or more severe chronic obstructive pulmonary disease (COPD). The authors investigated the approach of dual bronchodilation using indacaterol, a once-daily long-acting β_2 agonist, and the long-acting muscarinic antagonist tiotropium, compared with tiotropium alone.
Methods In two identically designed, double-blind, 12-week studies, patients with moderate to severe COPD were randomised to indacaterol 150 μg once daily or matching placebo. All patients concurrently received open-label tiotropium 18 μg once daily. The primary outcome was standardised area under the curve of forced expiratory volume in 1 s (FEV_1) from 5 min to 8 h post dose at week 12. The key secondary outcome was 24 h post-dose ('trough') FEV_1 at week 12. Resting inspiratory capacity (IC) was measured in a subgroup.
Results 1134 and 1142 patients were randomised in studies 1 and 2; 94% and 94% completed. Compared with monotherapy, concurrent therapy increased FEV_1 (area under the curve by 130 and 120 ml, trough by 80 and 70 ml; all p<0.001) and trough IC (by 130 and 100 ml, p<0.01). Cough was more common with indacaterol plus tiotropium (10% and 9%) than with tiotropium alone (4% and 4%). Most cases (~90%) of cough were mild. Other adverse events were similar for the treatment groups.
Conclusions Compared with tiotropium monotherapy, indacaterol plus tiotropium provided greater bronchodilation and lung deflation (reflected by increased resting IC). Adverse events were similar between treatments apart from mild cough being more common with indacaterol plus tiotropium. These results support COPD guideline recommendations to combine bronchodilators with different mechanisms of action. *(Mahler et al.[18], 2012, p. 781; Reprinted with permission of BMJ Publishing Group Ltd.)*

1. Comments and learning points

The key message of this study is that more powerful bronchodilation can be obtained by combination treatment using bronchodilators with different mechanisms; indacaterol and tiotropium. Combination treatment using long-acting bronchodilators was recommended for patients with moderate or severe COPD[1,4]. The long-acting bronchodilators are tiotropium (the long-acting muscarinic antagonist [LAMA])[11], and formoterol, salmeterol, or indacaterol (long-acting b2 agonists [LABAs]). In general, combination therapy using a different pharmacological class has been shown to improve lung function, symptoms and health status compared with a single bronchodilator[19-21]. However, there are very limited data for the combination of once-daily bronchodilators. This is the first report of dual bronchodilation effect using indacaterol and tiotropium, compared with tiotropium alone. It also supports new GOLD 2012 document to combine bronchodilators with different mechanisms. It has not proven, however, whether combination therapy using LABA and LAMA is more effective for the prevention of acute exacerbation of COPD. Further study will be needed for a synergistic effect for prevention of exacerbation using combination therapy.

Prognosis

Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Suissa et al.[22] Thorax 2012;67:957-63

Background The long-term natural history of chronic obstructive pulmonary disease (COPD) in terms of successive severe exacerbations and mortality is unknown.
Methods The authors formed an inception cohort of patients from their first ever hospitalisation for COPD during 1990–2005, using the healthcare databases from the province of Quebec, Canada. Patients were followed until death or 31 March 2007, and all COPD hospitalisations occurring during follow-up were identified. The hazard functions of successive hospitalised COPD exacerbations and all-cause mortality over time were estimated, and HRs adjusted for age, sex, calendar time and comorbidity.
Results The cohort included 73,106 patients hospitalised for the first time for COPD, of whom 50,580 died during the 17-year follow-up, with 50% and 75% mortality at 3.6 and 7.7 years, respectively. The median time from the first to the second hospitalised exacerbation was around 5 years and decreased to <4 months from the 9th to the 10th. The risk of the subsequent severe exacerbation was increased threefold after the second severe exacerbation and 24-fold after the 10th, relative to the first. Mortality after a severe exacerbation peaked to 40 deaths per 10,000 per day in the first week after admission, dropping gradually to 5 after 3 months.
Conclusions The course of COPD involves a rapid decline in health status after the second severe exacerbation and high mortality in the weeks following every severe exacerbation. Two strategic targets for COPD management should include delaying the second severe exacerbation and improving treatment of severe exacerbations to reduce their excessive early mortality. *(Suissa et al.[22], 2012, p. 957; Reprinted with permission of BMJ Publishing Group Ltd.)*

1. Comments and learning points

The key messages of this study are that 1) after the 2nd severe exacerbation of COPD, the subsequent severe exacerbation developed earlier and there is a rapid decline in health status, and 2) mortality was high in the early period (first week) after admission due to severe exacerbation. Many other studies have also suggested that exacerbations of COPD are related to a decline in lung function and mortality[9,23]. Therefore, preventive strategies delaying the second severe exacerbation should be considered for the subjects with severe exacerbation of COPD. A limitation of this study was that the diagnosis of COPD was not verified by spirometric data and it was based only on the primary discharge diagnosis.

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