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Small-airway obstruction and emphysema in chronic obstructive pulmonary disease

Authors: McDonough JE et al.
Comment: The major sites of obstruction in patients with COPD have been reported to be the small airways (<2 mm in diameter), but it is unclear what changes lead to increased peripheral airway resistance in patients with COPD. Furthermore, the relationship between small airways obstruction and emphysematous destruction has also not been determined. In this study, the number of airways measuring 2.0 to 2.5 mm in diameter was counted by multidetector CT (MDCT) in patients at different GOLD stages of COPD, as well as in lungs removed from patients with very severe COPD (GOLD stage 4). Furthermore, microCT (spatial resolution 16.24 µm) was applied to the isolated COPD lungs, to measure the extent of emphysema, the number of terminal bronchioles, and the dimensions of the terminal bronchioles. The MDCT study showed that the number of airways measuring 2.0 to 2.5 mm in diameter was reduced, even in patients with GOLD stage 1 COPD ($P = 0.001$), as well as in patients with more severe disease. The microCT study showed a reduction of 81 to 99.7% in the total cross-sectional area of terminal bronchioles, and a reduction of 72 to 89% in the number of terminal bronchioles ($P <0.001$), in lungs removed from patients with GOLD stage 4 COPD. Importantly, there was a sharp reduction in the number of terminal bronchioles in diseased regions of the lungs, in patients with the centrilobular emphysematous phenotype of COPD, in which the mean linear intercept (indicating the extent of emphysema) remained below the upper limit for control lungs ($P <0.001$). The investigators concluded that narrowing and disappearance of small airways preceded the onset of emphysematous destruction in patients with COPD. These findings provide a better understanding of the pathophysiology of COPD. However, the precise mechanism underlying these structural changes remains unclear, and the clinical translation of these findings should be exploited, in order to improve treatment of COPD.
**Changes in forced expiratory volume in 1 second over time in COPD**

Authors: Vestbo J et al.


Comment: COPD is characterized by an accelerated decline in FEV₁; however, there have been few longitudinal cohort studies that provide detailed data regarding the rate of decline in FEV₁. This study analyzed data on changes in FEV₁ over a 3-year period, in 2,163 patients with GOLD stage 2 to 4 COPD, which was collected during the Evaluation of COPD Longitudinally To Identify Predictive Surrogate Endpoints (ECLIPSE) observational study. In this cohort, FEV₁ declined by 33 mL/year with a standard deviation of 59 mL. Over the 3-year period, 38% of patients had an estimated decline in FEV₁ of more than 40 mL/year, 31% had a decline of 21 to 40 mL/year, 23% had a decrease of 20 mL/year to an increase of 20 mL/year, and 8% had an increase of more than 20 mL/year, indicating that there was significant variation among the patients studied. Patients with GOLD stage 2 or 3 disease showed a faster decline in FEV₁ than those with stage 4 disease. Current smoking, exacerbations during follow-up, presence of bronchodilator reversibility, and clinically significant emphysema on CT were associated with a faster decline in FEV₁. Among the biomarkers analyzed in a subset of 1,793 patients, only CC-16 levels were associated with the rate of decline in FEV₁ ($P = 0.04$ without correction for multiple testing). Limitations of the study included the fact that effects of pharmacotherapy during the study period were not considered and that it was unclear whether the patients’ respiratory medications were withdrawn before spirometry and/or when spirometry was performed. Nevertheless, the investigators concluded that COPD is not invariably progressive, and their findings may influence management decisions.

**Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease**

Authors: Nishimura M et al.


URL: [http://ajrccm.atsjournals.org/content/185/1/44.full](http://ajrccm.atsjournals.org/content/185/1/44.full)

Comment: This was another longitudinal observational cohort study (Hokkaido COPD cohort study), measuring the annual rate of decline in FEV₁. The investigators focused on clinical phenotypes of COPD, particularly on severity of emphysema as measured by CT and carbon monoxide transfer coefficient (Kco). They assessed the annual decline in pre-bronchodilator and post-bronchodilator FEV₁ over a 5-year period, in 279 Japanese patients with GOLD stage 1 to stage 4 COPD. Withdrawal of any respiratory medication before pulmonary function testing was confirmed at each visit. The authors identified three groups: those with a rapid decline in lung function (-63 ± 2 mL/year), those with a slow decline (-31 ± 1 mL/year), and those with sustained lung function (-2 ± 1 mL/year). Although there was no difference in either FEV₁/FVC or FEV₁% at enrolment, severity of emphysema, as evaluated by either method, differed significantly among the three groups. Multiple logistic regression analysis demonstrated that a rapid decline in lung function was independently associated with severity of emphysema. Although the sample size in this study was not large compared with that in the ECLIPSE study, it more clearly demonstrated that severity of emphysema was associated with a rapid annual decline in FEV₁ in patients with COPD, and also confirmed that there were “sustainers” (non-decliners), who maintained their pulmonary function over a period of 5 years, with appropriate therapy. What remains to be elucidated is the mechanism behind this association. Nevertheless, these clinical features, which have not been well recognized, should be considered in daily clinical practice and in future clinical trials.
Azithromycin for prevention of exacerbations of COPD

Authors: Albert RK et al.

Comment: Macrolide antibiotics have immunomodulatory, anti-inflammatory, and antibacterial effects. The investigators performed a randomized, placebo-controlled trial to determine whether azithromycin, at 250 mg per day, decreased the frequency of exacerbations in patients with COPD. A total of 1,142 subjects were randomly assigned to receive azithromycin or placebo for one year, in addition to their usual care. The median time to the first acute exacerbation (primary outcome) was 266 days in the azithromycin group as compared with 174 days in the placebo group ($P < 0.001$). The frequency of exacerbations was reduced in the azithromycin group compared with the placebo group (1.48 vs. 1.83 per patient-year, $P = 0.01$) and the hazard ratio for having an acute exacerbation in the azithromycin group was 0.73 per patient-year ($P < 0.001$). Quality of life scores on the St. George's Respiratory Questionnaire improved more in the azithromycin group than in the placebo group. Hearing decrement, as an adverse event, was more frequent in the azithromycin group than in the placebo group (25% vs. 20%, $P = 0.04$). The incidence of resistance to macrolides on nasopharyngeal swab culture was higher in patients in the azithromycin group than those in the placebo group, who were not colonized with selected respiratory pathogens at the time of enrolment, but who became colonized during the course of the study (81% vs. 41%, $P = 0.04$). The investigators concluded that azithromycin decreases the frequency of exacerbations and improves quality of life, although it causes hearing decrements in a small percentage of subjects, and the long-term effects of this treatment on microbial resistance in the community are unknown. Further investigations using lower doses and less frequent administration of azithromycin or other macrolides would be required, to evaluate better treatment options for the prevention of acute exacerbations of COPD.

Lung volumes and emphysema in smokers with interstitial lung abnormalities

Authors: Washko GR et al.

Comment: There is increasing awareness that smoking of cigarettes is associated not only with emphysematous destruction but also with interstitial abnormalities. In this study, the relationship between radiographic interstitial lung abnormalities and high-resolution computed tomography (HRCT) measures of total lung capacity (TLC) and emphysema were investigated in a cohort of 2,416 smokers recruited for the COPDGene study. Interstitial lung abnormalities were observed in 194 (8%) of the 2,416 HRCT scans. Interstitial lung abnormalities were associated with reduced TLC ($P < 0.001$) and a lower percentage of emphysema, as defined by lung-attenuation thresholds of either -950 or -910 Hounsfield units ($P < 0.001$). Subjects with interstitial lung abnormalities were more likely to have a restrictive lung deficit ($< 80\%$ of predicted TLC; odds ratio 2.3; $P < 0.001$), and were less likely to be diagnosed as having COPD (odds ratio 0.53; $P < 0.001$). Both the extent of exposure to cigarette smoke and current smoking were associated with interstitial lung abnormalities. The investigators concluded that interstitial lung abnormalities are associated with reduced TLC and less emphysema among smokers. Longitudinal studies would definitely be needed, to determine the clinical significance of these interstitial lung abnormalities.
Identification of chronic obstructive pulmonary disease in lung cancer screening computed tomographic scans

Authors: Mets OM et al.
URL: [http://jama.ama-assn.org/content/306/16/1775.abstract](http://jama.ama-assn.org/content/306/16/1775.abstract)
Comment: Cigarette smoking is a major risk factor for both lung cancer and COPD, and COPD is substantially under-diagnosed. The investigators hypothesized that low-dose CT scans for lung cancer screening in heavy smokers could provide an opportunity to acquire information on the incidence of COPD. A total of 1,140 male participants were recruited from the Dutch and Belgian Lung Cancer Screening Trial, and inspiratory and expiratory CT scans, as well as pre-bronchodilator pulmonary function tests, were performed on the same day. A total of 437 participants (38%) had COPD, as assessed by pulmonary function testing (FEV1/FVC <70%). A diagnostic model that included emphysema on CT (% of voxels < -950 Hounsfield units), air trapping on CT (expiratory:inspiratory ratio of mean lung density), body mass index, pack-years, and smoking status, yielded an area under the receiver operating characteristic (ROC) curve of 0.83. Using the point of optimum accuracy, the model identified 274 participants with COPD, with 85 false positive results, a sensitivity of 63%, specificity of 88%, positive predictive value of 76%, and negative predictive value of 79%. This diagnostic model showed a higher area under the ROC curve of 0.87 for participants with symptoms and 0.78 for those without symptoms. The investigators concluded that quantitative low-dose CT parameters may be useful in a lung cancer screening setting for identifying heavy smokers with COPD. Smokers are susceptible not only to lung cancer but also to other pulmonary diseases such as COPD; therefore, it may be important to evaluate low-dose lung CT screening scans for additional information. External validation of this approach would appear to be warranted, in order to achieve this goal.

Comparison of inhaled long-acting β-agonist and anticholinergic effectiveness in older patients with chronic obstructive pulmonary disease: a cohort study

Authors: Gershon A et al.
URL: [http://www.annals.org/content/154/9/583.full](http://www.annals.org/content/154/9/583.full)
Comment: Long-acting inhaled β2-agonists and anticholinergics are recommended for the management of moderate to severe COPD. However, little is known about their comparative effectiveness in actual clinical practice. The investigators compared survival in older patients with COPD (66 years or older), who initially received inhaled long-acting β2-agonists (n = 17,840) with that of patients who received anticholinergics (n = 28,563), using health administration data from Ontario, Canada (population-based, retrospective cohort study). Mortality was higher in patients who were initially prescribed a long-acting anticholinergic than in those initially prescribed a long-acting inhaled β2-agonist (adjusted hazard ratio 1.14). Rates of hospitalization and emergency department visits were also higher in those initially prescribed a long-acting anticholinergic. These findings suggest that long-acting β2-agonists may be a better initial therapy for patients with COPD. However, considering the potential bias in the study design, further research would definitely be needed, in order to confirm these findings in prospective randomized controlled trials, and preferably in younger patients.
Clinical and radiographic predictors of GOLD-unclassified smokers in the COPDGene study

Authors: Wan ES et al.
URL: http://ajrccm.atsjournals.org/cgi/content/full/184/1/57

Comment: This report focuses on the characterization of “GOLD-Unclassified (GOLD-U)” or “lower limits of normal (LLN)-Unclassified” smokers with impaired lung function, as characterized by a reduced FEV1 (<80% of predicted or <LLN), and a preserved FEV1/FVC ratio (≥0.7 or ≥LLN). This is a poorly characterized group due to their systematic exclusion from COPD studies. The investigators analyzed data for the first 2,500 subjects enrolled in the COPDGene study, to determine the clinical and radiological variables associated with GOLD-U and LLN-Unclassified status. GOLD-U subjects represented 9.1% of smokers in the COPDGene study and had a higher BMI, reduced total lung capacity (TLC) and emphysema, and included a higher proportion of subjects with diabetes and non-white subjects, whereas African American subjects were not over-represented in the LLN-Unclassified group. GOLD-U subjects exhibited increased airway wall thickness compared with smoking control subjects, and decreased gas trapping and bronchodilator responsiveness compared with COPD patients. Both GOLD-U and LLN-Unclassified subjects demonstrated a wide range of lung function impairment, BMI, and percentages of total lung emphysema. The investigators concluded that subjects with reduced FEV1 and a preserved FEV1/FVC ratio were a heterogeneous group with significant symptoms and functional limitation. Further longitudinal analyses would be needed, to define the pathophysiological significance of data from this under-characterized group of subjects.

Roflumilast in Asian patients with COPD: A randomized placebo-controlled trial

Authors: Lee SD et al.

Comment: Roflumilast, an oral, selective phosphodiesterase 4 inhibitor, has been shown to improve lung function and quality of life, and reduce the frequency of exacerbations in patients with COPD. This placebo-controlled study investigated the efficacy, safety, and tolerability of roflumilast, 500 µg once daily, in Asian patients with COPD. Of 551 patients recruited, 410 were randomized 1:1 to a 12-week treatment period, and received at least one dose of either oral roflumilast (n = 203) or placebo (n = 207), following a single-blind, 4-week baseline period, during which all patients received placebo. The primary end point was mean change in FEV1 from baseline, at each post-randomization visit during the treatment period. Compared with placebo, roflumilast significantly increased post-bronchodilator FEV1 in patients with COPD (between-treatment difference 79 mL, P <0.0001). Other spirometry end points, including pre-bronchodilator FEV1, pre- and post-bronchodilator FEV6, forced vital capacity, and peak expiratory flow were significantly increased with roflumilast, as compared with placebo. The results of safety assessments were in line with those reported in previous studies. This study demonstrates that roflumilast effectively improves lung function in Asian patients with COPD, and its safety and tolerability profile does not suggest any effects specific to the Asian patient population. Therefore, roflumilast may be a useful treatment option for patients with COPD.
Efficacy of tiotropium in COPD patients from Asia: a subgroup analysis from the UPLIFT trial

Authors: Fukuchi Y et al.


Comment: Differences in clinical phenotypes and practice patterns for COPD patients have been noted and/or suggested when comparing Western and Asian populations. This study reports on a subgroup analysis from a randomized, double-blind, placebo-controlled trial of tiotropium, 18 µg daily, (UPLIFT trial), in patients with COPD recruited at Asian centres. The primary end point was rate of decline in FEV₁. Of 5,992 patients, 362 were from Asian centres (100 from Japan). No significant treatment effect was observed for the rate of decline in FEV₁, although the annual decline was less in Asian patients (P <0.05) compared with other subjects. Tiotropium reduced the number of exacerbations (rate ratio 0.73). The St. George’s Respiratory Questionnaire total score improved by 1.5-6.1 units (P <0.05) with tiotropium. Fatal events occurred in 34 patients receiving tiotropium (18.5%) and 42 patients receiving placebo (23.6%). In conclusion, tiotropium improved lung function and health-related quality of life and reduced exacerbations over four years of treatment, in Asian patients with COPD. These results confirm that Asian patients with COPD benefit to a similar degree from treatment with tiotropium, although some regional differences were identified in the prevalence of exacerbations, the annual decline in FEV₁, as well as in the baseline characteristics of the patients.