

APSR Respiratory Research Review

Making Education Easy

Issue 19 - 2008

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Welcome to the latest edition of APSR Respiratory Research Review. Thank you for the feedback and interest in last month's edition.

This month's focus is on airways disease in particular 'looking beyond the smoke'. Several articles reflect on published COPD studies including statistical methods used. Several other authors comment on causes for COPD other than cigarette smoking.

Kind regards,

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Dyspnoea and airway responsiveness to methacholine in obese nonasthmatics

Authors: Salome CM et al

Summary: In order to better understand the mechanisms behind the increased prevalence and incidence of asthma among obese patients, subjects in this study underwent tests to determine if there are increases in dyspnoea intensity (due to airway narrowing) or airway responsiveness in nonasthmatic obese subjects. Sensitivity and maximal response to high-dose methacholine challenge, respiratory system resistance, perceptions of dyspnoea and static lung volumes were measured in 49 nonasthmatic subjects aged 18–70 years. Twenty-three subjects with a body mass index ≥ 30 kg/m² were classified as obese and the remaining 26 subjects with body mass index < 30 kg/m² were classified as nonobese. The obese subjects had lower static lung volumes and significantly greater dyspnoea intensity than nonobese subjects. There were no significant between-group differences in the methacholine challenge findings. Although the magnitude of respiratory system resistance changes were similar between the two groups, the negative resistance after challenge was significantly greater in the obese subjects, signifying a higher elastic load. The investigators commented that because obese individuals appear to have enhanced perception of dyspnoea associated with increased respiratory system stiffness, they may be at greater risk of symptoms of asthma.

Comment: Obesity is often associated with wheeze and increased prescribing of asthma medication but is not normally associated with airway hyper-responsiveness. The Australian/NZ group has designed an attractive study, which warrants closer reading. With up to 15% of the adult population having asymptomatic airway hyper-responsiveness, the authors concluded that subjects who develop obesity do not have increased airway hyper-responsiveness, but experience more dyspnoea for the same degree of airway hyper-responsiveness. The bottom line: obesity does not alter airway responsiveness, but it does lead to greater respiratory system stiffness and more severe dyspnoea.

<http://dx.doi.org/10.1038/sj.ijo.0803752>

Reference: *Int J Obes (Lond)* 2008; 32:502-9



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Single versus bilateral lung transplantation in end-stage COPD

Authors: Thabut G et al

Summary: This retrospective analysis of registry data was conducted to compare survival time between single and bilateral lung transplantation. The analysis included 9,883 patients with COPD who had undergone single (64.3%) or bilateral (35.7%) lung transplantation. Bilateral lung transplantation was associated with significantly longer median survival than single lung transplantation (6.41 versus 4.59 years; $p < 0.0001$). This association between bilateral transplantation and longer survival persisted in analyses for covariance, propensity-score risk adjustment and propensity-based matching with hazard ratios between 0.83 (95% CI 0.78 to 0.92) and 0.89 (0.80 to 0.97). However, when the analysis was limited to patients aged ≥ 60 years, little benefit of bilateral over single lung transplantation was seen (hazard ratio 0.95; 95% CI 0.81 to 1.13).

Comment: More than 20,000 lung transplantations have been performed internationally since 1987. Approximately half of these transplants were for COPD. Single lung transplantation is technically easier, can be performed in advanced disease and allows for some economy of organs. Data from an international registry suggests that relief of dyspnoea is equally effective in single or bilateral lung transplantation, but the survival in patients under the age of 60 is increased from 4.59 to 6.41 years in those who received bilateral lung transplantation.

[http://dx.doi.org/10.1016/S0140-6736\(08\)60344-X](http://dx.doi.org/10.1016/S0140-6736(08)60344-X)

Reference: Lancet 2008; 371:744-51

Effects of chronic cotton dust exposure on lung function

Authors: Wang X et al

Summary: In order to assess the impact of occupational cotton dust exposure on lung function the association between cross-shift FEV_1 changes and chronic loss of FEV_1 was investigated in 408 cotton workers and 417 silk workers in this 20-year observational study. Assessments approximately every 5 years showed that cotton dust exposure resulted in a 10 mL/year decrement in 5-year annualised decline in FEV_1 . There was also a 1.5 mL/year loss in annualised FEV_1 decline with every 10mL decrease in cross-shift change in FEV_1 . Cotton workers exhibited a stronger association between the frequency of reductions and annualised FEV_1 decline than silk workers over the entire study period.

Comment: In this study from Shanghai, researchers investigated the effect of cotton dust exposure on the decline in FEV_1 over 20 years. When compared with silk workers, cotton textile workers experienced a higher degree of cross shift drops in FEV_1 , a greater fall in the FEV_1 and most importantly a chronic decline in FEV_1 . The authors concluded that the occurrence of cross shift FEV_1 drop is a predictor for the development of COPD in cotton textile workers.

<http://dx.doi.org/10.1164/rccm.200702-318OC>

Reference: Am J Respir Crit Care Med 2008; 177:316-20

Effect of wood dust on lung function

Authors: Jacobsen G et al

Summary: Changes in lung function among 1,112 individuals with occupational exposure to wood dust and 235 reference workers were analysed in this 6-year longitudinal Danish study. Females were found to have a dose-dependent relationship between cumulative wood dust exposure and percent annual decrease in FEV_1 . Among them, those exposed to 3.75–4.71 mg/yr/m³ and >4.71 mg/yr/m³ had additional changes in FEV_1 of –14.50 mL/yr and –27.97 mL/yr, respectively, compared with females with no or low exposure. There was also evidence of a positive trend between wood dust exposure and a cumulative incidence proportion of $FEV_1/FVC < 70\%$ in the female subjects.

Comment: Wood dust has been recognised as a cause of occupational asthma, chronic bronchitis and rhinoconjunctivitis. This Danish group extends our thinking about wood dust as a possible cause for loss of lung function in addition to smoking. The authors found that in females, there was a dose relationship between the amount of wood dust exposure and reduction in FEV_1 , which is expected to reach clinical relevance over the working life. However, this study may underestimate the effect of wood dust on the development of lung disease because the Danish furniture industry has very low levels of wood dust.

<http://dx.doi.org/10.1183/09031936.00146806>

Reference: Eur Respir J 2008; 31:334-42



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Variability of methods used for determining and analysing COPD exacerbations

Authors: Aaron SD et al

Summary: The consistency of methods used to measure exacerbations of COPD was investigated in this analysis of 22 clinical trials of long-acting bronchodilators with or without corticosteroids published between 2000 and 2006. Failure to analyse outcome data from participants who terminated study treatments early was a potential source of selection bias in 64% of the studies. Mean number of exacerbations per patient-year was calculated in only 31% of trials, and between-subject variation was accounted for in only 15% of trials. Using data from the Canadian Optimal Therapy of COPD Trial, the investigators demonstrated that exclusion of data from participants who stopped study treatment prematurely resulted in an overestimation of the time-weighted rate ratio for exacerbations per patient-year from 0.85 to 0.79. Failure to perform a time-weighted analysis resulted in an additional overestimation to 0.46. Furthermore, p values varied between 0.03 and 0.24 for different methods of determining and analysing COPD exacerbations.

Comment: If you were to read only one paper on COPD this year this might be the most important one. The authors use one of their own studies as an example to explore the effect of different definitions of exacerbation of COPD on the study outcome. The paper is written for clinicians and the authors carefully explain the impact of different statistical/analytical models on study results. Bottom line: different methods to define and analyse COPD exacerbations can lead to biased estimates of treatment effects.

<http://dx.doi.org/10.1136/thx.2007.082636>

Reference: *Thorax* 2008; 63:122-8

The relationship between snoring and chronic bronchitis

Authors: Baik I et al

Summary: The association between snoring and chronic bronchitis was investigated a study cohort of 5,015 participants aged 40–69 years. During a 4-year follow-up period, 314 cases of new-onset chronic bronchitis were identified. A multivariate analysis that took age, smoking status and other risk factors for chronic bronchitis into account revealed that the relative risks for chronic bronchitis associated with snoring ≤ 5 and 6–7 days per week were 1.25 (95% CI 0.95 to 1.64) and 1.68 (1.17 to 2.42), respectively; p value for trend = 0.049. Stratification by risk factors showed that the association was stronger in never smokers, house workers and overweight individuals. When the joint effects of smoking and snoring were analysed, the relative risks for chronic bronchitis compared with never snoring and nonsmoking were 1.39 (95% CI 1.01 to 1.90) for snoring and non-smoking, 2.31 (1.38 to 3.87) for never snoring and smoking and 2.86 (1.91 to 4.27) for snoring and smoking.

Comment: Patients with obstructive sleep apnoea and chronic bronchitis share common risk factors. This Korean prospective study followed 5,015 snorers for four years. The authors found that after correcting for age, smoking and other risk factors snorers were 1.68 times more likely to develop chronic bronchitis. The authors speculate that causes may include obesity, hypoxia and mechanical stress in enhancing inflammation. We will need to wait for conformational studies, but we may have to add snoring to our list of risk factors for the development of COPD.

<http://archinte.ama-assn.org/cgi/content/abstract/168/2/167>

Reference: *Arch Intern Med* 2008; 168(2): 167-73

Effects of roxithromycin on LPS-induced airway mucus hypersecretion

Authors: Ou XM et al

Summary: This study investigated the mechanisms behind the effects of roxithromycin, a 14-membered ring macrolide, on lipopolysaccharide (LPS)-induced mucus hypersecretion in rat airways. Oral roxithromycin 1–10 mg/kg, josamycin 10 mg/kg and amoxicillin 40 mg/kg were administered to rats for 4 days with or without LPS administration. LPS resulted in significant induction of bronchial epithelial Muc5ac mRNA and protein expression, increased release of mucins, interleukins 1b and 8 and tumour necrosis factor- α , and increased neutrophils in bronchoalveolar lavage (BAL) fluid. Increased cytoplasmic staining for nuclear factor (NF)- κ B with nuclear translocation of this transcription factor in airway epithelial cells was also evident, and there was a positive correlation between NF- κ B activation and cytokine levels. LPS-induced expression of Muc5ac and NF- κ B nuclear translocation were significantly inhibited by roxithromycin 5 and 10 mg/kg, and BAL neutrophils, mucins and inflammatory cytokines were decreased ($p < 0.05$). Roxithromycin had no effect on LPS-induced p38 or ERK1/2 expression in airway epithelium, and no effects were seen with josamycin or amoxicillin.

Comment: This is an elegantly designed paper by a Chinese group who investigated the molecular basis for the anti-inflammatory effect of 14-ring macrolide antibiotics (e.g. erythromycin, roxithromycin, clarithromycin) on inflammatory airway disease. This paper provides some *in vivo* rationale for the anti-inflammatory and anti-hypersecretory effect of macrolide antibiotics in patients with chronic airway inflammation.

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1440-1843.2007.01213.x>

Reference: *Respirology* 2008; 13:63-72

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Mortality risk with β -blockers for CV disease in hospitalised COPD patients

Authors: Dransfield MT et al

Summary: Due to concerns about pulmonary effects, patients with COPD often do not receive treatment with β -blockers if they develop cardiovascular (CV) disease, which is associated with increased hospitalisation for acute COPD exacerbations and in-hospital and post-discharge mortality rates. This study of 825 patients admitted with a primary diagnosis of acute COPD exacerbation, or a secondary diagnosis of this condition along with a primary diagnosis of acute respiratory failure, was conducted to identify factors associated with β -blocker use in this setting and also to see if they can help prevent in-hospital deaths. After adjusting for potential confounders, including propensity, β -blockers were associated with fewer deaths (OR 0.39; 95% CI 0.14 to 0.99). Other predictors of mortality included age, number of previous exacerbations, length of hospital stay and presence of congestive heart failure, respiratory failure, liver disease or cerebrovascular disease.

Comment: Most patients with COPD do not actually die of COPD but rather of CV disease or lung cancer. β -blockers have been shown to improve survival in patients with CV disease, but patients with COPD have been systematically excluded from most clinical trials. This retrospective, single centre study has several limitations, but it did find an almost 60% decrease of mortality in patients with COPD on β -blockers. We will need to await prospective studies, but can take reassurance from the fact that β -blockers seem to be well tolerated by patients with COPD.

<http://dx.doi.org/10.1136/thx.2007.081893>

Reference: *Thorax* 2008; 63:301-5

Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

FEV₆ and FVC for predicting reduced total lung capacity

Authors: Vandevoorde J et al

Summary: The reliability of forced expiratory volume in 6 seconds (FEV₆) and forced vital capacity (FVC) for predicting reduced total lung capacity was evaluated in this study of 12,693 lung function tests in subjects of Caucasian descent aged 18–70 years. A two-by-two table analysis showed that FEV₆ and FVC were generally low positive and high negative predictors of reduced total lung capacity beyond lower limits of normal (LLN). A logistic regression analysis revealed that in subjects without lung obstruction, an FEV₆ or an FVC that was <55% of predicted in males or <40% of predicted in females positively predicted restriction. An FEV₆ or FVC that was >100% of predicted in males or >85% of predicted in females ruled out restriction. While spirometry could not reliably diagnose a concomitant restrictive defect in patients with obstruction (defined as FEV₁/FVC or FEV₁/FEV₆ <LLN), it was able to exclude restriction in subjects with an FVC or FEV₆ >85% and >70% of predicted for males and females, respectively.

Comment: Most quality infringements that occur during the performance of spirometry are due to inaccurate measurements of the FVC. In addition, the manoeuvre is both inconvenient and difficult for many patients. Measurement of FEV₆ has been put forward as a candidate to replace the FVC. Modern reference values have FEV₆ included in their parameters. This article confirms the useful role of FEV₆ and concludes that it can be substituted for FVC when excluding pulmonary restriction. Bottom line: a normal FEV₆ excludes restrictive lung disease; however, a reduced FEV₆ only predicts restriction 60% of the time.

<http://dx.doi.org/10.1183/09031936.00032307>

Reference: *Eur Respir J* 2008; 31:391-5

Efficacy of rhDNase for treating acute asthma in children

Authors: Boogaard R et al

Summary: This RCT investigated the efficacy of recombinant human deoxyribonuclease (rhDNase; a mucolytic agent) for the treatment of asthma in children. The study subjects consisted of 121 children who presented at an emergency department with a moderate-to-severe exacerbation of asthma. They were randomised to receive nebulised rhDNase 5mg or placebo following 2 doses of standard bronchodilator treatment. Adjusted mean decreases in baseline asthma score one hour post-treatment were 1.0 (95% CI 0.5 to 1.6) and 0.7 (0.3 to 1.2) in the rhDNase and placebo groups, respectively, with a mean between-group difference of 0.4 points (p=0.23). The mean between-group difference over the study's full observation period of 24 hours was also nonsignificant at 0.2 points (p=0.40). The number of bronchodilator treatments administered and oxygen requirements over 24 hours also did not differ significantly between rhDNase and placebo recipients.

Comment: Negative trials are rarely published and often not reported. This RCT of the use of rhDNase in children with asthma presenting to the emergency department did not reach its primary endpoint of improving asthma scores after one hour. In addition, the authors did not find a difference in the subgroup analysis of children with severe asthma or in any of the secondary endpoints of need for hospitalisation, time until discharge or duration of oxygen therapy. Bottom line: currently there is no role for the use of rhDNase in children with acute asthma.

<http://dx.doi.org/10.1136/thx.2007.081703>

Reference: *Thorax* 2008; 63:141-6.

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