Making Education Easy

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Welcome to the first issue of Chronic Obstructive Pulmonary Disease Research Review.

Every month 10,000 scientific publications are printed worldwide containing a multitude of new studies. In short, keeping up is hard and requires significant time to screen out what is irrelevant to your practice or country. We aim to save you time by identifying what's important so you can spend more time doing what you're best at.

The Review is a summary of some of the most significant new papers, plus my thoughts on why they are important and how they can potentially affect practice. Selection and review of the trials is carried out independently. Website links to the abstracts or fully published papers have been included so you can make your own judgements.

This review focuses on causes, stratification, diagnosis and treatment of COPD. Even for physicians without significant exposure or interest, COPD will become more important in daily practice as it soon becomes the third most common cause of death. Controversy still surrounds its diagnosis, new aetiologies continue to be elucidated, at-risk groups are described and pleasingly new treatments are researched in this burgeoning field. Hopefully new light will be shed on this previously somewhat mundane disease.

We hope you find this issue interesting and welcome any feedback you may have.

Kind Regards,

Dr Andrew Ng

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Effect of β blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study

Authors: Short PM et al

Summary: This Scottish study investigated the use of β-blockers in the management of COPD when added to established inhaled stepwise treatment. A cohort of 5977 patients aged >50 years with COPD was selected from a disease-specific database of COPD patients (TARDIS). Patients (mean age 69.1 years) were followed for a mean 4.35 years. Compared with controls (treated with inhaled short-acting β-agonists or short-acting antimuscarinics), the adjusted hazard ratio for all cause mortality in patients taking an inhaled corticosteroid, long acting β-agonist, and long acting antimuscarinic was 0.28 (95% CI 0.21–0.39) when they also took a β-blocker, and 0.43 (95% CI 0.38–0.48) when they did not. Add-on β-blockers reduced oral corticosteroid use and hospital admissions due to respiratory disease and had no adverse effects on lung function when given with either a long-acting β-agonist or antimuscarinic agent. In conclusion, β-blockers may reduce mortality and COPD exacerbations when added to established therapy for COPD, without adversely affecting lung function.

Comment: The use of β-blockers in COPD is often avoided because of concerns regarding possible bronchospasm and the potential to block the bronchodilating effects of β-agonist inhalers. This retrospective observational study from Scotland has reassuringly shown a reduction in mortality and COPD exacerbations when β-blockers (88% of which were cardioselective) were added to stepwise inhaled therapy for COPD. These benefits were independent of other cardiovascular drugs and history of overt cardiovascular disease (ischaemic heart disease, heart failure, peripheral vascular disease). This suggests that the benefits were in addition to that gained by reducing cardiovascular risk as has been suggested with asthma. One hypothesis is that chronic β blockade (even with cardioselective agents) up-regulates β2 receptors. In this respect, no worsening of lung function was observed.

Reference: BMJ 2011;342:D2549
http://dx.doi.org/10.1136/BMJ.D2549

COPD in never smokers: results from the population-based Burden of Obstructive Lung Disease study

Authors: Lamprecht B et al for the BOLD Collaborative Research Group

Summary: This study analysed data from the international, population-based Burden of Obstructive Lung Disease (BOLD) study to evaluate the characteristics and possible risk factors for `never smokers' with COPD. 4,291 never smokers participated in BOLD. 6.6% of never smokers met criteria for mild COPD and 5.6% met criteria for moderate to very severe COPD. They were less likely to have COPD and had less severe COPD than ever smokers, but still comprised 23.3% of those classified with GOLD stage II+ (moderate to very severe) COPD. Predictors of COPD in never smokers included age, education, occupational exposure, childhood respiratory diseases, and changes in BMI. In conclusion, increased age, a prior diagnosis of asthma and lower education levels are associated with increased risk for COPD among never smokers, who comprise a substantial proportion of COPD patients.

Comment: Although smoking is the most common cause of COPD, there is growing evidence that other causes may account for up to one-third of cases. This study analysed BOLD data of 10,000 patients, 4291 of whom never smoked. Using questionnaires and spirometry, it was found that 12.2% of never smokers met the criteria for COPD, 81% of whom were undiagnosed. In the age group 40–98 years, 28% of COPD occurred in never smokers. Predictors of COPD included severe childhood respiratory disease, occupational organic dust exposure, age, education, and BMI alterations. In addition, two-thirds of never smokers with moderate to severe disease were women, suggesting an increased susceptibility to harmful exposures. This study highlights the importance of screening for COPD in symptomatic never smokers.

Reference: Chest 2011;139(4):752-63
http://dx.doi.org/10.1378/chest.10-1253

Overdiagnosing subjects with COPD using the 0.7 fixed ratio: correlation with a poor health-related quality of life

Authors: García-Rio F et al

Summary: This study evaluated the clinical impact of the different criteria for COPD diagnosis. 3,802 patients aged 40–80 years were selected from the Epidemiologic Study of COPD in Spain. Health-related quality of life, exacerbations, exercise tolerance, physical activity, comorbidity, and systemic biomarkers in patients with FEV1/FVC < 0.7 but > lower limit of normal (LLN; ratio-only group) were compared with those in non-COPD individuals and in patients with mild or moderate-to-severe COPD. After adjustment for confounding factors, the ratio-only group had a worse health-related quality of life than the non-COPD group ($p<0.05$) but there were no between-group differences in respiratory exacerbations, 6-min walk distance, physical activity, or systemic biomarkers. Compared with the non-COPD group, ratio-only patients were not at greater risk for cardiovascular disease but patients with mild COPD were (adjusted relative OR 2.32; 95% CI 1.11–4.84). In conclusion, patients diagnosed with COPD using the fixed ratio had worse self-reported quality of life than subjects without COPD but there were no between-group differences for respiratory exacerbations or physical activity.

Comment: This study continues the debate between the two definitions of COPD. As people age, their FEV1/FVC ratio naturally declines, meaning that many elderly patients may be incorrectly diagnosed as having COPD (4.6% in this study which is significant, being about half of the COPD prevalence usually reported). Using the LLN definition (advocated by the ATS/ERS guidelines) these patients would be classified as no COPD. For example, if an elderly patient has a ratio of 0.69, with the LLN being 0.68, he/she has no COPD according to the LLN definition, but does have COPD according to the ratio definition. This exact population was examined in this study and found to have poorer HRQL compared to the non-COPD group. Some of these patients also had higher inspiratory capacities, suggesting hyperinflation, which has previously been linked to higher all cause and respiratory mortality. Therefore this subgroup of patients may actually have a poorer prognosis … and the debate continues.

Reference: Chest 2011;139(5):1072-1080
http://dx.doi.org/10.1378/chest.10-1721

COPD Research Review

Independent commentary by *Dr Andrew Ng MBBS FRACP PhD. Dr Ng is Director, Centre for Sleep Disorders & Respiratory Failure St George Hospital and has honorary appointments at both Sydney University and NSW University. His research interests include respiratory failure and sleep breathing disorders.*

The acute effects of water-pipe smoking on the cardiorespiratory system

Authors: Hakim F et al

Summary: This study examined the acute effects of water-pipe smoking (WPS) on cardiopulmonary function in healthy volunteers. Carboxyhemoglobin (COHb) levels, pulmonary function, vital signs, fractional exhaled nitric oxide (FENO) levels, and exhaled breath condensate (EBC) cytokine levels were assessed before and after a single 30-min session of WPS in 45 volunteers. COHb levels increased from 1.47% at baseline to 9.47% after the WPS session ($p<0.001$). Systolic and diastolic BP, heart rate and respiratory rate also increased significantly after smoking (all $p<0.001$). Forced expiratory flow between 25–75% of FVC, peak expiratory flow rate, FENO levels, percentage of eosinophils in peripheral blood, and 8-isoprostane levels in EBC all decreased after WPS. In conclusion, WPS causes acute biological changes that might result in marked health problems.

Comment: WPS has been around for 400 years, and is making a resurgence particularly in Western countries. It is erroneously believed to be less harmful and less addictive than cigarette smoking. Despite having small numbers, this prospective study is important because it demonstrates that one 30-minute session increases COHb, systolic and diastolic BP, heart rate and respiratory rate. Peak flow, eosinophils, FEF 25%–75%, FENO and 8-isoprostane are also reduced. These changes are at least equal to those that occur with cigarette smoking. Whilst WPS contains 70% honey, it also contains nicotine, CO, carcinogens, tar and heavy metals. Further studies are needed in order to deter the 40 or so percent of youths that have already experienced WPS.

Reference: Chest 2011;139(4):775-781
http://dx.doi.org/10.1378/chest.10-1833

Effects of water-pipe smoking on lung function: a systematic review and meta-analysis

Authors: Raad D et al

Summary: This study reviewed evidence of the effects of WPS on lung function, and compared its effects with those of cigarette smoking. Analysis of data from 6 cross-sectional studies revealed that WPS was associated with a reduction in FEV1 (–4.04%), a trend toward lower FVC (–1.38%), and lower FEV1/ FVC (–3.08%) compared with no smoking. There were no significant differences in FEV1, FVC, and FEV1/ FVC between WPS and cigarette smoking. In conclusion, WPS may be as harmful to lung function as cigarette smoking and is likely to be a cause of COPD.

Comment: WPS has recently been dubbed 'an emerging deadly trend' by the American Lung Association. These meta-analyses add to the growing evidence that hookah is harmful and that the water jar is unlikely to filter out the deadly chemicals. FEV1 is significantly reduced and there is a trend towards lower FVC and FEV1/FVC. The decrement in FEV1 would be around 173ml for a 40-year-old Caucasian male, making it clinically relevant, and a possible risk factor for obstructive disease. Causality of course cannot be determined from cross-sectional studies. Nevertheless, combined with other studies linking WPS with lung cancer, oesophageal cancer, low birthweight and periodontal disease – 'hubble-bubble' spells trouble.

Reference: Chest 2011;139(4):764-774
http://dx.doi.org/10.1378/chest.10-0991

Exhaled breath condensate pH as a biomarker of COPD severity in ex-smokers

Authors: Papaioannou A et al

Summary: This study measured pH levels of exhaled breath condensate (EBC) in a large cohort of COPD patients, and examined the associations between these levels and functional parameters. 161 patients with stable COPD and 112 controls (current and ex-smokers) had EBC pH measured and underwent pulmonary function testing. EBC pH was lower in COPD patients than in controls (7.21 vs 7.50; $p<0.001$), and ex-smokers with COPD had lower EBC pH than current smokers (7.16 vs 7.24; $p=0.03$). In ex-smokers with COPD, EBC pH was lower in patients with GOLD stage III ($p=0.026$) and IV ($p=0.004$) COPD than in patients with stage I disease. However no differences were observed among current smokers with different disease severity. EBC pH levels in ex-smokers were associated with static hyperinflation, air trapping and diffusing capacity for carbon monoxide, but no associations were seen in current smokers. In conclusion, airway acidification is related to disease severity, hyperinflation and air trapping in ex-smokers with COPD.

Comment: Spirometry remains the gold standard in COPD diagnosis. However, various biomarkers have been investigated, particularly to stratify disease severity. Acidification of exhaled air may be a surrogate marker of airway inflammation. In this study, COPD patients had lower EBC pH levels than controls, and in ex-smokers it was associated with disease severity, static hyperinflation, air trapping and DLCO. The reason ex-smokers had lower EBC pH levels than current smokers could be more severe disease and/or ongoing inflammation following smoking cessation. Airway inflammation reportedly causes bronchoconstriction, impaired ciliary motility, increased mucous production and viscosity, and airway epithelial damage and may contribute to airway damage. Further studies are warranted to investigate whether EBC pH levels could be used in evaluating therapeutic interventions.

Reference: Respir Res 2011;12:67
http://dx.doi.org/10.1186/1465-9921-12-67

Transcutaneous carbon dioxide in severe COPD patients during bronchoscopic lung volume reduction

Authors: Fruchter O et al

Summary: This study measured transcutaneous carbon dioxide tension (TcPCO2) with a noninvasive digital sensor to examine the occurrence of hypoventilation during bronchoscopic lung volume reduction (BLVR). Combined TcPCO2 and SpO2 saturation and arterial blood gases (ABG) were measured in 15 patients with severe COPD (mean FEV1 29%) undergoing BLVR. There was a highly significant correlation between simultaneous ABG PCO2 samplings and TcPCO2 ($r=0.85$, $p<0.001$). Mean TcPCO2 increased from 41.7mm Hg at baseline to a peak of 61mm Hg during the procedure. Significant hypercapnea (TcPCO2 >55 mmHg) was observed in 7 (46%) patients, for a mean 9 minutes. In conclusion, patients with severe COPD undergoing bronchoscopy frequently have significant hypoventilation that can only be detected by TcPCO2 monitoring.

Comment: Bronchoscopy complications are generally rare events. However, more complicated bronchoscopic procedures are being performed and on sicker patients. Hypoventilation is especially important in lung disease patients and oximetry alone, in the presence of supplemental oxygen, can be misleading. Capnography, used in anaesthetics, is difficult under conscious sedation and unreliable in severe COPD. This study from Boston and Israel used TcPCO2 to monitor hypoventilation. Finding significant hypoventilation is important so that appropriate and timely treatment can then be instituted such as limiting further sedation, reversing sedation and/or delivering upper airway support. A rise of >15 mmHg has been suggested as significant and occurred in 9 patients, only 3 of whom had baseline hypercapnea. This small study has shown the utility of TcPCO2 particularly as baseline characteristics and drug dosage probably don't predict hypoventilation.

Reference: Respir Med 2011;105(4):602-7
http://dx.doi.org/10.1016/j.rmed.2010.11.005

CD8 positive T cells express IL-17 in patients with chronic obstructive pulmonary disease

Authors: Chang Y et al

Summary: This study investigated the role of the cytokines IL-17A and IL-17F in the pathogenesis of COPD. Bronchial biopsies from 16 patients with COPD (GOLD stages II-IV) and 15 controls were examined. IL-17F immunoreactivity was significantly higher in the bronchial biopsies from COPD patients compared with controls ($p<0.0001$), as was the absolute number of both IL-17A and IL-17F positive cells in the submucosa (even after adjustment for the total number of cells; both $p<0.0001$). The expression of IL-17A and IL-17F was co-localised with not only CD4 but also CD8 positive T cells. In conclusion, Th17 cytokines may play an important role in the pathogenesis of COPD.

Comment: COPD is characterised by marked accumulation of both CD8+ and CD4+ T cells in the alveolar walls with CD8+ cells predominating. Expression of IL-17A and F was co-localised with both cell types in the 16 patients compared to 15 controls suggesting that IL-17 plays a significant role in COPD pathogenesis. By triggering production of numerous chemokines, resulting in neutrophil and macrophage recruitment and subsequent pathogen clearance, IL-17 may mediate interaction between both the innate and acquired immune systems. They have been suggested to contribute to autoimmune diseases such as rheumatoid arthritis and psoriasis. This finding could lead to novel therapeutic approaches for COPD.

Reference: Respir Res 2011;12:43
http://dx.doi.org/10.1186/1465-9921-12-43

Identification and prospective validation of clinically relevant chronic obstructive pulmonary disease (COPD) subtypes

Authors: Garcia-Aymerich J et al on behalf of the PAC-COPD Study Group

Summary: This study identified and validated 3 different clinically relevant COPD subtypes. 342 patients who had been hospitalised for the first time because of a COPD exacerbation underwent clinical assessment 3 months after discharge. COPD groups were identified then validated prospectively against cause-specific hospitalisations and all-cause mortality during a 4-year follow-up. Three COPD groups were identified: group 1 had severe airflow limitation (FEV1 38% predicted) and worse performance in most of the respiratory domains of COPD; group 2 showed milder airflow limitation (FEV1 63% predicted); and group 3 showed a similarly milder airflow limitation (FEV1 58% predicted) combined with a high proportion of obesity, cardiovascular disorders, diabetes and systemic inflammation. Patients in group 1 were hospitalised more often for COPD during follow-up (HR 3.28, p<0.001) and had higher all-cause mortality (HR 2.36, p=0.018) than the other two groups. Patients in group 3 were hospitalised more often for cardiovascular disease (HR 2.87, p=0.014). In conclusion, three subtypes of COPD were identified and validated: severe respiratory COPD, moderate respiratory COPD, and systemic COPD.

Comment: Lung function is only weakly correlated in COPD and may be due to COPD heterogeneity. Previous studies have used factor analysis to identify various independent factors such as exercise capacity, dyspnoea, hyperinflation and airway inflammation but none have included extrapulmonary manifestations of COPD nor have any been prospectively validated. This study examined 342 patients hospitalised for the first time with COPD. Three subtypes were identified and then prospectively validated. Subtyping of this sort may improve patient management, improve prognostic tools and prevent discarding potentially useful treatments on the basis of trials that mix various types of COPD. For example, subtype 3 had similar airflow limitation to subtype 2, but had more dyspnoea, poorer health related quality of life, poorer exercise capacity and higher cardiovascular disorders. This group may respond more poorly to interventions targeting airflow limitation, and may respond better to an integrated cardiorespiratory assessment and therapeutic plan.

Reference: Thorax 2011;66:430-437
http://thorax.bmj.com/content/66/5/430.abstract

Cardio- and cerebrovascular safety of indacaterol vs formoterol, salmeterol, tiotropium and placebo in COPD

Authors: Worth H et al

Summary: This study reviewed data from the indacaterol clinical trials database to compare the cardio- and cerebrovascular (CCV) effects of indacaterol with those of other inhaled bronchodilators (formoterol, salmeterol, tiotropium) in patients with COPD. Data for 4635 patients with moderate-to-severe COPD who had participated in studies of ≥6 months' duration and were treated with indacaterol, placebo or other bronchodilators were reviewed. Indacaterol did not increase the risk of adverse CCV events compared with placebo, and relative risks for indacaterol were not significantly different from those of the other bronchodilators. Overall, most adverse CCV events occurred in patients with pre-existing cardiovascular risk factors. The risk of APTC events (MI, stroke or cardiovascular-related death) was not significantly increased with indacaterol vs placebo, nor was the risk of arrhythmia. In conclusion, the CCV safety profile of indacaterol was similar to that of placebo and other long-acting bronchodilators.

Comment: The safety of LABAs in COPD remains somewhat controversial. Certainly, in asthma LABAs alone have been associated with increased hospitalisation, intubation and sudden death. β2-receptor stimulation may increase heart rate and the risk of arrhythmias in COPD patients who commonly have CCV co-morbidities. Given that 15% of COPD patients have concomitant asthma and the lack of long-term safety of LABA without ICS in COPD, the PBAC rejected the recent submission of indacaterol for Restricted Benefit listing. Although this study had significant input from industry and only medium term data, it does provide some reassuring data on safety with respect to cardio- and cerebrovascular effects.

Reference: Respir Med 2011;105(4):571-579
http://dx.doi.org/10.1016/j.rmed.2010.11.027

