



APSR Respiratory Research Review

Making Education Easy

Issue 27 - 2008

In this issue:

- *LLN of FEV₁/FVC ratio reduces airway obstruction misclassification*
- *FEV₁/FVC <70% underestimates airflow obstruction*
- *Driving performance not improved by O₂ therapy in hypoxaemia*
- *Modified BODE: validation with mortality in COPD*
- *6MWD as a predictor of mortality in stable COPD*
- *Language differentiates between adults with and without COPD*
- *A cell phone-based exercise programme for COPD*
- *SaO₂ during sex in COPD*
- *Medications for recently diagnosed COPD and risk for death*
- *Long-term erythromycin decreases COPD exacerbations*
- *β-blockers and mortality in COPD patients with atherosclerosis*
- *P. aeruginosa transmission: infrequent in NZ CF clinics*

Welcome to the last edition of Research Review for 2008.

It is a good opportunity to thank all readers for their feedback and suggestions. It is an honour to be involved with the Research Reviews.

This edition is focussed on COPD. For an outsider it will be surprising how much the definitions of COPD vary. Two papers warn against using fixed cut-offs to make a diagnosis, which may underestimate the prevalence of airway obstruction in a younger population by about 50%. Maureen Swanney from Christchurch, New Zealand and her colleagues have produced a landmark paper arguing that COPD may be overestimated by up to 60% when one doesn't use the lower limits of normal to make a diagnosis.

Only Australian researchers will know how to predict a patient's lung disease, if they state that they "feel like a cow in a paddock ...". American researchers found a significant survival advantage for COPD patients with vascular disease on β-blockers and researchers from Taiwan deliver a very successful rehabilitation course via cell phone. However, it could only be an Italian group who published that oxygen saturation improves during sexual intercourse.

Kind regards,
Dr Lutz Beckert
lutzbeckert@researchreview.co.nz



Using the lower limit of normal for the FEV₁/FVC ratio reduces the misclassification of airway obstruction

Authors: Swanney MP et al

Summary: Variations in prevalences of airway obstruction using regression equations from four different international guidelines were explored in three population samples of 40,646 adults, including a healthy subgroup of 13,136 never smokers. The lower limit of normal (LLN) for FEV₁/FVC was found to vary between equations and the median ages at which the LLN fell below 0.70 were 42 and 48 years for healthy men and women, respectively. Application of reference equations from the guidelines revealed the following variances in the prevalence of airway obstruction in healthy adults aged >60 years: 1) 17–45% (males) and 7–26% (females) for Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2) 0–18% (M) and 0–16% (F) for American Thoracic Society/European Respiratory Society (ATS/ERS); and 3) 0–9% (M) and 0–11% (F) for British Thoracic Society (BTS). When applied to the entire study population, use of the GOLD guidelines resulted in a false positive rate of 60%.

Comment: This paper by international experts in respiratory physiology systematically examines published reference values and applies different definitions of COPD. Surprisingly, they showed that if one were to apply a fixed cut off value to define COPD, up to 68% of healthy male volunteers above the age of 50 years would be classified as having COPD. In order to correctly identify patients with COPD, the authors argue to 1) test only people with symptoms, 2) use the LLN of the FEV₁/FVC ratio, 3) use an FEV₁ of less than LLN as a cut-off, and 4) confirm that airflow obstruction persists after bronchodilator administration.

Reference: *Thorax* 2008; 63(12): 1046-51

<http://thorax.bmj.com/cgi/content/abstract/63/12/1046>



Educational Seminar of the Asian Pacific Society of Respiriologists

Lung Cancer and Bronchology Symposium

19 - 20 February 2009



Tel: (65) 63214700/ 4685 Fax: (65)62271736 Email: pynglee16@gmail.com

Course description

A State of the Art Review on Imaging, Diagnosis, Staging and Treatment of Lung Cancer. New technologies aimed at imaging for early lung cancer detection, precision targeting of pulmonary nodules, endoscopic ultrasound for mediastinal staging as well as therapeutic bronchoscopic and pleuroscopic techniques for palliation will be discussed. The course features live demonstration by the experts and allows participants to have "hands-on" experience. In addition there are sessions on lung pathology and its precursors, new international classification for lung cancer as well as research into biomarkers for targeted therapy in the future.

Who should attend

Specialists, trainees in Pulmonary Medicine, Oncology, Thoracic Surgery, Pathology and researchers with interest in lung cancer. CME points will be awarded.

Underestimation of airflow obstruction among young adults using FEV₁/FVC <70% as a fixed cut-off

Authors: Cerveri I et al

Summary: This study investigated airway obstruction in 6249 participants divided into three groups: 1) no airway obstruction identified using the lower limit of normal (LLN) and the fixed FEV₁/FVC ratio <0.70; 2) airway obstruction identified only by LLN; and 3) airway obstruction identified by both LLN and the fixed FEV₁/FVC ratio. The fixed cut off method identified only 45% of participants with airway obstruction identified by LLN. There was a progressive decrease in FEV₁ and a progressive increase in bronchial hyper-responsiveness across the three groups at baseline. During follow-up, participants in whom airway obstruction was misidentified were at a significantly greater risk of developing COPD than participants without airway obstruction, and they also used significantly more health resources due to respiratory issues.

Comment: This paper is published in the same issue of Thorax as the study on page 1. This group investigated the impact of using a fixed cut off in identifying young patients with obstructive airways disease. While a fixed cut off significantly over-diagnoses airways disease in an older population, it potentially underdiagnoses airway obstruction in a younger cohort. The results indicated that misidentified subjects had increased health needs as measured by increased hospital utilisation and/or respiratory symptoms. The authors also argue that the LLN of the FEV₁/FVC ratio and a FEV₁ of less than the LLN should be used to identify airway obstruction.

Reference: *Thorax* 2008; 63(12): 1040-5

<http://tinyurl.com/thorax-63-1040>

Acute oxygen therapy does not improve cognitive and driving performance in hypoxaemic COPD

Authors: Pretto JJ et al

Summary: The impact of hypoxaemia on cognition and driving performance was investigated in 30 participants with hypoxaemic COPD during a computer-simulated 20-minute driving challenge and a 10-minute psychomotor vigilance task. These tests were performed at baseline, and again with intranasal air and intranasal oxygen in a randomised crossover manner. Breathing oxygen resulted in a significantly greater PaO₂ than room air (70.7 vs. 50.5 mm Hg), but there were no significant between-group differences for any of the driving performance measures or reaction time measurements.

Comment: Since the experiments in hot air balloons early last century, it has been known that hypoxaemia impairs cognitive function and reduces neuropsychological performance. However, a large number of hypoxic COPD patients still continue to drive. This group of researchers from Newcastle investigated the important question on whether oxygen supplementation improves simulated driving performance. In this well-designed study of 30 hypoxaemic COPD subjects, the researchers discovered that they can correct the hypoxaemia with oxygen supplementation, but not the simulated driving performance. **Bottom line: at this stage we have no evidence to recommend that hypoxaemic COPD patients should use supplemental oxygen while driving.**

Reference: *Respirology* 2008; 13(7): 1039-44

<http://www3.interscience.wiley.com/journal/121389771/abstract>

The modified BODE index: validation with mortality in COPD

Authors: Cote CG et al

Summary: The capacity of a modified BMI, airflow obstruction, dyspnoea, exercise capacity (mBODE) index (in which the 6-minute walk distance [6MWD] test is replaced with percentage predicted VO₂) to predict mortality was compared with that of the conventional BODE index in 444 patients with COPD. The mean mBODE and BODE indices were 4.1 and 5.5, respectively, and there were significant correlations between both indices and mortality. The BODE index, Charlson's and exercise capacity (in W) were associated with this outcome in a logistic regression analysis. The investigators concluded that the use of the simpler conventional BODE index is supported.

Comment: Only four years ago the Boston group published the BODE index. It combines BMI, airflow obstruction, dyspnoea and exercise capacity, and predicts outcomes in patients with COPD. A scientific debate persists on whether exercise capacity should be measured with peak oxygen uptake or 6MWD. In this study, the authors compared both measurements of exercise capacity to predict mortality as part of the BODE index in patients with COPD. They found an excellent correlation between both measures of exercise capacity, and that both measurements predicted mortality as well as each other. **Bottom line: the original BODE index encompassing the 6MWD test predicts mortality well and is easier to use.**

Reference: *Eur Respir J* 2008; 32(5): 1269-74

<http://erj.ersjournals.com/cgi/content/abstract/32/5/1269>



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Distance and oxygen desaturation during the 6-min walk test as predictors of long-term mortality in patients with COPD

Authors: Casanova C et al

Summary: The ability of the 6-minute walk distance (6MWD) test to predict outcomes in 576 patients with stable COPD over a 3-year observation period was investigated in this study. After adjusting for covariates, the 6MWD test was found to be a significant predictor of mortality due to all causes and respiratory causes in patients with FEV₁ <50% of predicted. The mortality rate associated with desaturation during 6MWD tests was 67%, compared with 38% for 6MWD tests without desaturation (p<0.001). Oxygen desaturation was associated with a greater risk of mortality (relative risk 2.63; 95% CI 1.53, 4.51; p<0.001), but not to the same extent as PaO₂ at rest.

Comment: Another group also working with Bart Celli from Boston is examining the data of the 6MWD test of 576 patients with stable COPD to answer the question whether, in addition to the number of metres walked, the degree of desaturation has a predictive value in the assessment of patients with COPD. They found that in patients with severe COPD and a FEV₁ <50%, the 6MWD test is an important prognostic factor. They confirmed that the oxygen desaturation during the test may give some additional information, but it is not as useful as the baseline PaO₂. **Bottom line: the 6MWD test has established itself as an important clinical parameter to assess patients with severe COPD.**

Reference: *Chest* 2008; 134(4): 746-53

<http://www.chestjournal.org/cgi/content/abstract/134/4/746>

The language of breathlessness differentiates between patients with COPD and age-matched adults

Authors: Williams M et al

Summary: The role that the language patients use to describe breathlessness in accurately categorising older patients with or without a prior COPD diagnosis was explored in this parallel-group study. The participants were clustered based on their choice of words/phrases volunteered to describe their breathlessness, and they also endorsed up to three statements that described the sensation associated with their breathlessness. Cluster membership corresponded well with the participants' original group classifications, but classification based on a single best descriptor did not correspond as well to group membership.

Comment: This is a fascinating study from the Adelaide group exploring the language of subjects describing episodes of breathlessness. They compared asymptomatic subjects with subjects with COPD. They found that older subjects without COPD used the following terms to describe their breathlessness: "out of breath", "rapid", and "cannot get enough air". Subjects with COPD, however, used terms like "frightening", "annoying" and "awful". The authors felt that they could identify subjects with COPD based on the language used. However, they couldn't classify the subject who chose to describe their symptoms as "like a cow in a paddock ...".

Reference: *Chest* 2008; 134(3): 489-96

<http://www.chestjournal.org/cgi/content/abstract/134/3/489>

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.

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Efficacy of a cell phone-based exercise programme for COPD

Authors: Liu W-T et al

Summary: This study investigated an endurance exercise programme in which 24 participants walked to the tempo of music preprogrammed into a cell phone; 24 control participants who walked daily were also included. The music tempo required to exercise at 80% of maximal capacity was determined for each participant with incremental shuttle walk tests (ISWTs), and this was re-evaluated monthly. At 8 weeks, participants in the cell phone group had significantly increased their ISWT distance and duration of endurance walking. By 12 weeks, improvements in inspiratory capacity and quality of life (QOL) scores were also evident. Participants in the cell phone group also had fewer acute COPD exacerbations and hospitalisations.

Comment: Pulmonary rehabilitation programmes improve QOL and decrease hospitalisations and emergency department and unscheduled doctor visits. Exercise training is a cornerstone of these programs. This group of researchers from Taiwan is publishing astonishing results offering a community-based programme via a cell phone. The researchers determined the walking speed at 80% of the maximal exercise programme and programmed the cell phone with music with a beat encouraging the patient to walk at this speed. This programme improved exercise capacity, respiratory symptoms and QOL at a cost of <\$10 per month.

Reference: *Eur Respir J* 2008; 32(3): 651-9

<http://erj.ersjournals.com/cgi/content/abstract/32/3/651>

Sexual intercourse and respiratory failure

Authors: Polverino F et al

Summary: Oxygen saturation was measured during three sexual performances, divided into four periods (presex baseline, sex, 10 minutes after sex and a 'relax' period), in a 63-year-old patient receiving long-term oxygen therapy for COPD. Heart rate or SaO₂ increased significantly during each sexual performance, with SaO₂ peaking during the 10 minutes after sex and returning to baseline by the end of the 'relax' period.

Comment: This Italian study is worth reading just for the detail provided. These researchers first demonstrated that this patient with oxygen-dependent COPD desaturated during a 6-minute walk test. Later they presented data during sexual activity and showed that the same patient does not desaturate during sexual intercourse, but rather has improved oxygenation. The authors postulate that this may be due to an improved VQ mismatch during a period of hyperventilation without significant muscle expenditure!

Reference: *Respir Med* 2008; 102(6): 927-31

<http://tinyurl.com/RespMed-102-927>



*Independent commentary
by Dr Lutz Beckert,
Respiratory Physician at
Christchurch Hospital,
New Zealand.*

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Medical Professionals**

**APSR Respiratory Research Review is an initiative
of the APSR education committee**

Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease

Authors: Lee TA et al

Summary: The relationships between various respiratory medications and mortality were explored in 32,130 patients with COPD who had died and 320,501 matched controls. Inhaled corticosteroids and long-acting β -agonists were associated with reduced risks of death from all-cause mortality (adjusted ORs 0.80; 95% CI 0.78, 0.83 and 0.92; 0.88, 0.96, respectively), with inhaled corticosteroids also associated with a reduced risk of death from cardiovascular causes (0.80; 0.72, 0.88). Ipratropium bromide use was associated with an increased risk of death from all causes (adjusted OR 1.11; 95% CI 1.08, 1.15) and cardiovascular causes (1.34; 1.22, 1.47), and the adjusted OR for death from all causes associated with theophylline was 1.05 (95% CI 0.99, 1.10).

Comment: This nested case-controlled study has caused some controversy and is probably worth reading. The authors used the large US Veteran Health Administration database to identify 145,020 patients with COPD of whom 32,130 died. They then selected up to 10 controls for each patient. In the past, long acting β -agonists had been shown to increase deaths in this group. This was not confirmed in this study, but the authors found an increased mortality in patients treated with ipratropium and theophylline.

Bottom line: we will need to await further studies, but need to keep an open mind for potential adverse affects.

Reference: *Ann Intern Med* 2008; 149(6): 380-90

<http://www.annals.org/cgi/content/full/149/6/380>

Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations

Authors: Seemungal TAR et al

Summary: This RCT investigated the anti-inflammatory effects of macrolides on COPD exacerbations in 109 patients randomised to receive erythromycin 250mg twice daily or placebo over a 12-month period. Erythromycin recipients had a lower incidence of moderate or severe COPD exacerbations (primary outcome) than placebo recipients (rate ratio 0.648; 95% CI 0.489, 0.859; $p=0.003$), and their exacerbations were of a shorter duration.

Comment: This powerful study performed randomised, double-blind, placebo-controlled trial of erythromycin in patients with COPD showed that low-dose erythromycin reduced exacerbations by 35% and increased the time to first exacerbation from 89 to 271 days. The authors could not confirm that this was due to an anti-inflammatory action and could not demonstrate an improvement in lung function. The editorial warns about the possible harm through bacterial resistance emergences when offering antibiotics to 10% of that adult population.

Reference: *Am J Respir Crit Care Med* 2008; 178(11): 1139-47

<http://ajrccm.atsjournals.org/cgi/content/abstract/178/11/1139>

Impact of cardioselective β -blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis

Authors: van Gestel YRBM et al

Summary: This study explored the effect of cardioselective β -blockers on mortality in COPD in 3371 consecutive patients who underwent major vascular surgery. The study population included 1205 patients with COPD, among whom 462 received cardioselective β -blocker therapy. The 30-day and long-term mortality rates were significantly lower among the β -blocker recipients (OR 0.37; 95% CI 0.19, 0.72 and 0.73; 0.60, 0.88, respectively). Moreover, β -blocker doses $\geq 25\%$ of maximum therapeutic dose were associated with lower long-term and 30-day mortality rates, while doses $< 25\%$ of maximum therapeutic dose were not.

Comment: This is a fascinating retrospective study on the mortality of patients with COPD who underwent vascular surgeries such as aortic aneurism repair. The authors identified that 37% of patients with COPD continued to use their β -blocker. These patients seemed to tolerate cardioselective β -blockers well, had reduced 30-day mortality with high-dose β -blockade and reduced 5-year mortality with all β -blocker doses. This study is a reminder that most patients with COPD die of cardiovascular disease and that these patients should not be deprived of the protective benefits of β -blockade.

Reference: *Am J Respir Crit Care Med* 2008; 178(7): 695-700

<http://ajrccm.atsjournals.org/cgi/content/abstract/178/7/695>

Pseudomonas aeruginosa transmission is infrequent in New Zealand cystic fibrosis clinics

Authors: Schmid J et al

Summary: Transmission of *Pseudomonas aeruginosa* in NZ's seven main cystic fibrosis (CF) clinics was investigated by combining DNA fingerprint data from 496 isolates (102 patients) with epidemiological data. The largest CF clinic had a cluster of an unexpectedly high prevalence of related isolates, which involved seven patients who had regular contact with each other. There was no convincing evidence for *P. aeruginosa* transmission at any of the other clinics, nor was there evidence that three strains present in NZ that are thought to be transmissible between Australia and the UK had spread.

Comment: This is an excellent NZ-wide study investigating the prevalence of cross infection of patients with CF with *P. aeruginosa* in CF clinics. Once *P. aeruginosa* is established, it leads to an accelerated decline in pulmonary function, quality of life and life expectancy. Segregation of CF patients is only practiced in three CF clinics (two paediatric). Despite this, the researchers only identified one cluster of infections that suggested cross infection. Paradoxically, it occurred in a centre that practices segregation. The authors reflect carefully on the limitations and causes. **Bottom line:** transmission of *P. aeruginosa* between NZ CF patients occurs infrequently.

Reference: *Eur Respir J* 2008; 32(6): 1583-90

<http://erj.ersjournals.com/cgi/content/abstract/32/6/1583>

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Secretariat, Asian Pacific Society of Respirology, Yoshikawa Bldg. No. 2,
2-9-8 Hongo, Bunkyo-ku, Tokyo, Japan 113-0033
email: kyu00671@nifty.com

Research Review acknowledges the kind support of

