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Abbreviations used in this issue

COPD = chronic obstructive pulmonary disease
CV = cardiovascular
FEV₁ = forced expiratory volume in 1 sec
ICS = inhaled corticosteroid
LABA = long-acting β -agonist
OR = odds ratio
QOL = quality of life
RCT = randomised controlled trial

Welcome to this winter edition of Respiratory Research Review, with the topic of COPD.

Chronic obstructive lung disease affects about 10% of the population, and is the fourth leading cause of death. Our treatment options are limited, and at times the risk-benefit ratio isn't clear. About half of the articles in this review report on important negative studies. A Dutch group report that a comprehensive self-management plan does not show any benefits in improving QOL in COPD patients. Our Wellington colleagues report no effect of adjuvant nebulised magnesium in COPD. The debate continues about the possible adverse effects on CV outcomes, particularly cardiac arrhythmias, with both long-acting anticholinergic agents and LABAs.

On the positive side, a 5-day course of prednisone 40mg was found to be just as effective as longer courses of the agent. Endobronchial methods of treating hyperinflated lungs instead of volume reduction surgery are starting to look more promising. We end with articles describing a positive adjuvant effect of acupuncture on walking distance and QOL, and, co-authored by the president of the Thoracic Society of Australia and NZ, the description of positive effects of t'ai chi on improving balance, QOL, anxiety and exercise capacity.

COPD is essentially a preventable illness in at least 80% of our patients. We begin with an interesting article that notes for a similar or even lesser amount of cigarettes consumed, the mortality from COPD continues to increase.

We hope you enjoy this selection, and look forward to your feedback and comments.

Kind regards

Associate Professor Lutz Beckert

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50-year trends in smoking-related mortality in the United States

Authors: Thun MJ et al

Summary: Data from two historical American Cancer Society cohorts (CPS I and CPS II) and pooled data from five contemporary cohort studies were used to calculate death rates and the relative risks associated with active cigarette smoking and smoking cessation in the US from 1959–1965, 1982–1988 and 2000–2010. In women who were current versus never smokers, the relative risks of death from lung cancer were 2.73, 12.65 and 25.66 in the 1960s, 1980s and contemporary cohorts, respectively; the respective values for male current versus never smokers were 12.22, 23.81 and 24.97. In the contemporary cohorts, male and female current smokers had similar respective relative risks for death from COPD (25.61 and 22.35), ischaemic heart disease (2.50 and 2.86), any type of stroke (1.92 and 2.10) and all causes combined (2.80 and 2.76). COPD-related mortality among male smokers continued to increase in the contemporary cohorts in nearly all the age groups represented in the study and within each stratum of duration and intensity of smoking. All-cause mortality was ≥ 3 -fold higher among current smokers versus never-smokers among men aged 55–74 years and women aged 60–74 years. Quitting smoking at any age dramatically lowered mortality.

Comment: The increasing risk of death from lung cancer in women is not surprising; it provides the scientific basis for Peto and Doll's statement "women who smoke like men die like men". How do we explain the increasing death rate from COPD despite the lower daily consumption of cigarettes? It's not the prevalence of COPD, but death from the disease that has increased. The authors speculated this may be related to changes by the tobacco industry that promote deeper inhalation to absorb nicotine, like the genetic selection of tobacco with a lower pH, porous wrapping paper and perforated filters. **Bottom line: the increased death from COPD in men is currently not explained.**

Reference: *N Engl J Med* 2013;368(4):351–64

<http://www.nejm.org/doi/full/10.1056/NEJMsa1211127>

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Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice

Authors: Bischoff EWMA et al

Summary: General practice patients with spirometrically confirmed COPD (n=165) were randomised 1:1:1 to receive usual care on its own, with a comprehensive self-management programme (four tailored sessions with ongoing telephone support by a practice nurse) or with routine monitoring (2–4 structured nurse consultations per year). There were no significant between-group differences for COPD-specific QOL (mean chronic respiratory questionnaire total score; primary outcome) at 24 months. Among secondary outcomes, only exacerbation management differed among the groups, with more exacerbations in the self-management versus usual care group managed with bronchodilators (OR 2.81 [95% CI 1.16, 6.82]) and prednisolone, antibiotics or both (3.98 [1.10, 15.58]).

Comment: These Dutch authors went out to prove that individual self-management plans would improve QOL of COPD patients. They offered a comprehensive programme, including knowledge of COPD, breathing techniques, managing exacerbations, maintaining a healthy lifestyle, managing stress and anxiety and home exercises. Patients in the active group used more bronchodilators, steroids and antibiotics, and were more capable of managing their exacerbations. However, they did not report an improved QOL, did not improve self-efficacy and had no reductions in exacerbations. **Bottom line: in this study, patients did not benefit from self-management programmes compared with usual care.**

Reference: *BMJ* 2012;345:e7642

<http://www.bmj.com/content/345/bmj.e7642>

The impact of depressive symptoms on recovery and outcome of hospitalised COPD exacerbations

Authors: Papaioannou AI et al

Summary: This study evaluated the impact of depressive symptoms in 230 consecutive patients hospitalised for acute exacerbations of COPD. Patients with depressive symptoms required longer hospitalisation than those without (mean 11.6 vs. 5.6 days; $p < 0.001$). Clinical variables improved during the course of the exacerbation, but significant impacts on dyspnoea and COPD assessment test score improvements were seen for depressive symptoms at admission (respective p values < 0.001 and 0.012). Patients with depressive symptoms presented with significantly more exacerbations ($p < 0.001$) and hospitalisations for acute exacerbations ($p < 0.001$) in 1 year than those without depressive symptoms. A multivariate analysis revealed that depressive symptoms independently predicted mortality in patients with COPD (hazard ratio 3.568 [95% CI 2.319, 5.556]).

Comment: This clinical study from Greece may offer an explanation for the limited effect of our interventions. These authors used the 12-item Beck's depression inventory in 230 consecutive patients admitted with an acute exacerbation of COPD. They found depressive symptoms in 39% of patients. Patients with depressive symptoms stayed longer in hospital, were more short of breath and had a >3-fold increase in 1-year mortality. A limitation is that it may not be valid to measure depressive symptoms during an acute illness. **Bottom line: depressive symptoms have a significant impact on symptoms, length of stay, exacerbation and mortality of COPD.**

Reference: *Eur Respir J* 2013;41(4):815–23

<http://erj.ersjournals.com/content/41/4/815.abstract>

Use of nebulised magnesium sulphate as an adjuvant in the treatment of acute exacerbations of COPD in adults

Authors: Edwards L et al, on behalf of the Magnesium COPD Study Team

Summary: Patients presenting with an acute COPD exacerbation who had an FEV₁ <50% of predicted after receiving nebulised salbutamol 2.5mg and ipratropium 500µg were randomised to receive nebulised salbutamol 2.5mg with either 2.5mL of isotonic magnesium sulphate (151mg per dose; n=52) or saline (placebo; n=64) on three occasions at 30-minute intervals. There was no significant difference between the magnesium and placebo groups for mean FEV₁ at 90 minutes (primary outcome; 0.78 vs. 0.81L; $p=0.67$) or hospital admissions ($p=0.69$); no participants required noninvasive ventilation.

Comment: This study was published by our colleagues in Wellington and Lower Hutt. Inspired by their success demonstrating the enhancing bronchodilator effect of nebulised magnesium in severe asthma, they investigated the effect of nebulised magnesium sulphate in acute exacerbations of COPD in 116 patients. Although magnesium is relatively cheap, easy to administer and has few adverse effects, it didn't improve FEV₁. It is possible systemic magnesium may have a positive effect on (respiratory) muscle strength. **Bottom line: nebulised magnesium as adjuvant to salbutamol has no effect on FEV₁ in an acute exacerbation of COPD.**

Reference: *Thorax* 2013;68(4):338–43

<http://thorax.bmj.com/content/68/4/338.abstract>

Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease

Authors: Dong Y-H et al

Summary: This was a systematic review and mixed treatment comparison meta-analysis of 42 RCTs (n=52,516) investigating ≥ 6 months of inhaled tiotropium (Respimat® Soft Mist™ or Spiriva® HandiHaler®), LABAs, ICSs or LABA-ICS combination for the treatment of COPD; the research focussed on the risks of CV-related and all-cause mortality. The risk of overall death was greater with use of the tiotropium Soft Mist™ inhaler than with placebo, tiotropium HandiHaler®, LABAs and LABA-ICS combination (respective ORs 1.51 [95% CI 1.06, 2.19], 1.65 [1.13, 2.43], 1.63 [1.10, 2.44] and 1.90 [1.28, 2.86]); the risks were greater for CV death, in patients with severe COPD and with higher daily doses. The active treatment associated with the lowest risk of death was combination LABA-ICSs, but no excess risk was seen for the tiotropium HandiHaler® or LABAs on their own. Direct comparison meta-analyses returned similar results, while a random effects model reduced precision.

Comment: Patients with COPD are generally older and 80% have a history of cigarette smoking; both risk factors for ischaemic heart disease and undetected arrhythmias. Anticholinergics like tiotropium and ipratropium reduce exacerbations and improve symptoms, lung function and QOL. However, they are associated with increased tachyarrhythmias and cardiac ischaemia. Many trials, in particular the large UPLIFT study, have excluded the more vulnerable patients. This meta-analysis adds weight to several systematic reviews and Cochrane reviews. The linked accompanying editorial ([Thorax](http://thorax.bmj.com/content/68/1/114-6) 2013;68[1]:5–7) and opinion ([Thorax](http://thorax.bmj.com/content/68/1/114-6) 2013;68[1]:114–6) review available evidence and give us the **bottom line: in particular the tiotropium Respimat® Soft Mist™ inhaler increases CV and all-cause mortality.**

Reference: *Thorax* 2013;68(1):48–56

<http://thorax.bmj.com/content/68/1/48.abstract>

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Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease

Authors: Gershon A et al

Summary: This nested case-control analysis of retrospective Canadian healthcare data found that 28.0% of eligible patients aged ≥ 66 years with COPD (n=191,005) had been hospitalised or attended an emergency department for a CV event. Moreover, the risk of a CV event was increased in patients who had a newly prescribed inhaled LABA or anticholinergic compared with nonusers (respective adjusted ORs 1.31 [95% CI 1.12, 1.52; $p < 0.001$] and 1.14 [1.01, 1.28; $p = 0.03$]); no significant difference was seen between inhaled LABA and anticholinergic use (1.15 [0.95, 1.38; $p = 0.16$]).

Comment: These Canadian authors explored why both long-acting anticholinergics and LABAs increase the risk of tachyarrhythmias, myocardial ischaemia, stroke and death in meta-analyses but not in RCTs. Their observational study on 191,005 patients above the age of 66 years who were prescribed long-acting bronchodilators found that 28% had a hospitalisation or emergency department visit for cardiac events. No difference between long-acting anticholinergics and LABAs was seen. The accompanying editorial (*JAMA Intern Med*; published online May 20, 2013; [doi:10.1001/jamainternmed.2013.1201]) by Prescott Woodruff is asking our **bottom line question: 'are long-acting bronchodilators in COPD a double-edge sword?'**

Reference: *JAMA Intern Med*; published online May 20, 2013

<http://archinte.jamanetwork.com/article.aspx?articleid=1689974>

Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET)

Authors: Shah PL et al, for the RESET trial Study Group

Summary: Patients aged ≥ 35 years with severe emphysema received lung volume reduction coil treatment (n=23) or best medical care (n=24) in this RCT. Compared with best medical care, lung volume reduction coil treatment was associated with a significantly greater response at 90 days post-treatment according to St George's Respiratory Questionnaire score (primary endpoint; difference -8.36 points; $p = 0.04$). There was no significant between-group difference for serious adverse events.

Comment: Last year we reviewed literature around alternatives to lung volume reduction surgery to improve dyspnoea and exercise tolerance (*Respiratory Research Review Issue 77*). The results from bronchial valves to cause collapse of hyperinflated lung have so far been disappointing; outcomes may improve focussing on intact fissures between lobes. Creating extra-anatomical bypasses between the hyperinflated lung and trachea have not been effective. Early trials with biological polymeric substances to seal, or vapour to destroy, emphysematous lungs are promising, and trials are ongoing. This study used bronchial coils to stent collapsing airways. **Bottom line: endobronchial coils improve QOL for patients with severe emphysema.**

Reference: *Lancet Respir Med* 2013;1(3):233-40

<http://www.thelancet.com/journals/lanres/article/PIIS2213-2600%2813%2970047-X/fulltext>

Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease

Authors: Leuppi JD et al

Summary: The REDUCE noninferiority RCT assigned patients with an acute COPD exacerbation to prednisone 40mg for 5 or 14 days in a placebo-controlled manner. The times to next exacerbation during 180 days of follow-up were similar for the short-term and conventional prednisone duration arms in both the intention-to-treat (n=311; $p = 0.006$ for noninferiority) and per-protocol analyses (n=296; $p = 0.005$ for noninferiority). There were also no between-group differences for time to death, the combined endpoint of exacerbation, death or both and lung function recovery. Despite the high cumulative dose of prednisone in the conventional 14-day treatment group, treatment-related adverse events, including hyperglycaemia and hypertension, were not more frequent.

Comment: Over the last 30 years, systemic steroids have become key therapeutic agents in an exacerbation of COPD to provide symptom control, accelerate lung function recovery, reduce hospital stay and reduce relapses. However, a course of steroids is as long as the proverbial 'piece of string', and most guidelines recommend 10-14 days. These researchers randomised COPD patients to either a 5- or 14-day course of prednisone 40mg. They found no inferiority in all measured endpoints with the 5-day course. As the accompanying editorial summarised (*JAMA* 2013;309[21]:2272-3), **5 days of prednisone 40mg for the treatment of COPD exacerbation - less is clearly more.**

Reference: *JAMA* 2013;309(21):2223-31

<http://jama.jamanetwork.com/article.aspx?articleid=1688035>

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Independent commentary by Associate Professor Lutz Beckert, Respiratory Physician at Christchurch Hospital. For full bio [CLICK HERE](#)



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A randomized, placebo-controlled trial of acupuncture in patients with chronic obstructive pulmonary disease (COPD)

Authors: Suzuki M et al

Summary: The COPD-Acupuncture Trial randomised patients receiving standard therapy for COPD to traditional acupuncture (n=34) or a sham procedure (n=34) applied to the same acupoints once weekly for 12 weeks. Compared with the sham procedure, acupuncture was associated with a significantly better improvement from baseline in mean Borg scale score after a 6-minute walk test (primary endpoint; -3.6 vs. 0.4; difference -3.58 [95% CI -4.27, -2.90]) and a significant improvement in 6-minute walk distance during exercise.

Comment: These Japanese researchers reported their randomised, sham-controlled trial of offering acupuncture in addition to standard treatment to patients with COPD. Their article described carefully the acupuncture points selected according to traditional Chinese medicine theory. The sham device was a blunt needle that seemed to penetrate the skin, but actually telescoped back into a guide tube. After 12 weeks of treatment, improvements were reported in the Borg score after exercise, 6-minute walk distance (78m), St George's Respiratory Questionnaire QOL score, body mass index and lung function parameters. **Bottom line: acupuncture can improve QOL above standard therapy.**

Reference: Arch Intern Med 2012;172(11):878-86

<http://archinte.jamanetwork.com/article.aspx?articleid=1151703>

Short-form Sun-style t'ai chi as an exercise training modality in people with COPD

Authors: Leung RWM et al

Summary: Forty-two patients with COPD were randomised to short-form Sun-style t'ai chi twice weekly for 12 weeks or usual medical care in this study. Compared with controls, t'ai chi significantly increased endurance shuttle walk time (mean difference 384 sec), reduced medial-lateral body sway in semitandem stand (-12.4mm) and increased the total score on the Chronic Respiratory Disease Questionnaire (11 points). The exercise intensity of t'ai chi was 53% of oxygen consumption reserve.

Comment: Over the last 20 years, pulmonary rehabilitation has become a cornerstone of COPD management to break the vicious cycle of physical deconditioning, loss of muscle mass and increasing shortness of breath. Aerobic exercises of walking, stepping, cycling in combination with muscle strengthening are part of a standard rehabilitation course. The Sydney researchers co-authored by our president of the Thoracic Society report a randomised trial using t'ai chi to improve exercise capacity, balance, physical performance, quadriceps strength, health-related QOL, anxiety and self-efficacy. **Bottom line: t'ai chi can be considered as an alternative to traditional rehabilitation for some patients with COPD.**

Reference: Eur Respir J 2013;41(5):1051-7

<http://erj.ersjournals.com/content/41/5/1051.abstract>

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