Welcome to issue 83 of Respiratory Research Review.

How lucky we are in NZ with our smoke-free legislation! This became apparent after we presented our local data on the effect of the Christchurch earthquake on smoking prevalence at an international conference. After the session, the chairperson reported that her town in southern Turkey had also suffered an earthquake. Winchester was quick to respond by delivering trucks with free cigarettes to ‘aid’ the suffering people. This ‘brand switching’ exercise was very successful. When our colleague enquired why the local health authorities had permitted this advertising campaign, she was punished with disciplinary measures for shedding a bad light on health authorities.

NZ has the ambitious aim to be the first country in the world to be virtually smoke free by 2025. It is likely that it will suffer international pressure, similar to that seen for the ‘nuclear-free’ campaign in the 1980s. Examples of such pressure can be read in the Lancet (Lancet 2012;380(9852):1447–8), which reads more like a script for an action movie — pressure on the headquarters of the European Respiratory Society, Klaus Rabe, puts in his editorial on drug safety in COPD (Chest 2012;142(2):271–4) — “The treatment of COPD worldwide relies on a rather limited selection of pharmacologic principles… β2-adrenoceptor agonists with largely comparable efficacy and varying durations of action … short- and long-acting anticholinergic drugs … (mainly inhaled) corticosteroids and … orally applied selective phosphodiesterase-4 inhibitors”.

We look forward to your feedback and discussion.

With season’s greetings.
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The 21st century hazards of smoking and benefits of stopping

Authors: Pirie K et al, for the Million Women Study Collaborators

Summary: This was a prospective study of 1.2 million UK women recruited between 1996 and 2001 and resurveyed 3–8 years later; mortality records showed that 6% died during follow-up. Compared with never-smokers, mortality risk was significantly increased in all baseline smokers (RR 2.26 [95% CI 2.21, 2.31]; 44% had quit when resurveyed), baseline smokers who smoked <10 cigarettes per day (1.98 [1.91, 2.04]) and those still smoking when resurveyed (2.97 [2.88, 3.07]). The risk of death from lung cancer among smokers was particularly high (RR 21.4 [95% CI 19.7, 23.2]). Individuals who quit smoking permanently at ages <10 cigarettes per day (1.98 [1.91, 2.04]) and those still smoking when resurveyed (2.97 [2.88, 3.07]). The risk of death from lung cancer among smokers was particularly high (RR 21.4 [95% CI 19.7, 23.2]). Individuals who quit smoking permanently at ages 25–34 years and 35–44 years had significantly increased risks of all-cause mortality (respective relative risks 1.05 [95% CI 1.00, 1.11] and 1.20 [1.14, 1.26]) and lung cancer mortality (1.84 [1.45, 2.34] and 3.34 [2.78, 4.03]).

Comment: Published on the 100th birthday of Sir Richard Doll, the Lancet published the Million Women Study and the accompanying editorial by Rachel Huxley and Mark Woodward (Lancet http://dx.doi.org/10.1016/S0140-6736(12)61782-5), who summarised the results: i) the mortality of smokers is triple that to never-smokers; ii) smoking throughout adulthood reduced life expectancy by about 11 years; iii) women who stop smoking before the age of 30 years avoided nearly 100% of the excess mortality, and stopping before age 40 years avoided 90% of the excess mortality. Bottom line, after Sir Richard Doll: ways must be found to limit the vast damage being done by tobacco.

Reference: Lancet 2012; Published online Oct 27, 2012
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2812%2961720-6/fulltext

Abbreviations used in this issue

CHF = congestive heart failure
COPD = chronic obstructive pulmonary disease
FEV1 = forced expiratory volume in 1 second
LV = left ventricular
NIV = noninvasive ventilation
RR = rate ratio

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Secondhand smoke exposure predicted COPD and other tobacco-related mortality in a 17-year cohort study in China

Authors: He Y et al

Summary: This study examined the association between second-hand smoke and mortality from ischaemic stroke and COPD in China. The cohort comprised 910 participants of a 17-year follow-up study. Second-hand smoke exposure was defined as exposure to another person's tobacco smoke at home or in the workplace; 249 men and women died during follow-up. People who were exposed to second-hand smoke had increased all-cause mortality (adjusted relative risk 1.72 [95% CI 1.29, 2.20]), and increased mortality due to COPD (2.30 [1.06, 5.50]), coronary heart disease (2.15 [1.00, 4.61]), ischaemic stroke (2.98 [1.10, 7.55]) and lung cancer (2.00 [0.62, 6.40]). The association between cumulative second-hand smoke exposure at home and work and the increased risk of mortality was dose-dependent.

Comment: Unfortunately China is a good place to study the effects of second-hand smoke, with 67% of the male and 4% of the female population smoking. China is also the largest producer and consumer of tobacco in the world. This is the first time that a study has prospectively shown conclusively an increase in ischaemic stroke (188%) and COPD (130%) in people who have never smoked but were exposed to second-hand smoke at their work place, home or both. Bottom line: second-hand smoke shows a dose response relationship to ischaemic stroke and COPD in never-smokers.

Reference: Chest 2012;142(4):909–18

Unrecognised ventricular dysfunction in COPD

Authors: Macchia A et al

Summary: This study evaluated the prevalence and implications of coexisting LV dysfunction in patients with COPD, and concurrent airway obstruction in patients with CHF: Patients with CHF (n=201) underwent routine spirometry, and patients with COPD (218) underwent routine echocardiographic assessment and B-type natriuretic peptide measurements before being followed for 2 years. Coexisting airway obstruction was present in 97.5% of patients with CHF, and 17% of patients with COPD had coexisting LV dysfunction. Airway obstruction in CHF patients had no impact on survival during follow-up, but the presence of ventricular dysfunction in patients with COPD slightly increased the risk of death (HR 2.34 [95% CI 0.99, 5.54]; p=0.053).

Comment: These Argentinean authors presented data from their prospective REPENSAR (‘re-think’) cohort on patients presenting with either COPD or heart failure. The authors systematically investigated participants for evidence of airflow obstruction and ventricular dysfunction. They found that 37% of patients presenting with heart failure also had COPD; 17% of patients presenting with COPD also had LV dysfunction on echocardiography. Most treating physicians were not aware of the co-existing morbidities. The presence of ventricular dysfunction increased the probability of dying 2.34-fold. Bottom line: these findings make us rethink and possibly re-investigate the safety and efficacy of pharmacological agents in ‘real-life’ populations.

http://erj.ersjournals.com/content/39/1/51.abstract

Weight gain in smokers after quitting cigarettes

Authors: Aubin H-J et al

Summary: This meta-analysis included 62 published studies of bodyweight gain among smokers who had achieved prolonged abstinence for ≤12 months and lung cancer (2.00 [0.62, 6.40]). The association between cumulative second-hand smoke exposure and mortality from ischaemic stroke and COPD was independent of increased all-cause mortality (adjusted relative risk 1.72 [95% CI 1.29, 2.20]), and increased mortality due to COPD (2.30 [1.06, 5.50]), coronary heart disease (2.15 [1.00, 4.61]), ischaemic stroke (2.98 [1.10, 7.55]) and lung cancer (2.00 [0.62, 6.40]). The association between cumulative second-hand smoke exposure at home and work and the increased risk of mortality was dose-dependent.

Comment: Unfortunately China is a good place to study the effects of second-hand smoke, with 67% of the male and 4% of the female population smoking. China is also the largest producer and consumer of tobacco in the world. This is the first time that a study has prospectively shown conclusively an increase in ischaemic stroke (188%) and COPD (130%) in people who have never smoked but were exposed to second-hand smoke at their work place, home or both. Bottom line: second-hand smoke shows a dose response relationship to ischaemic stroke and COPD in never-smokers.

Reference: BMJ 2012;345:e4439
http://www.bmj.com/content/345/bmj.e4439

Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease

Authors: Divo M et al, for the BODE Collaborative Group

Summary: These researchers systematically recorded 79 comorbidities in 1664 patients with COPD who were followed for a median of 51 months. Of these comorbidities, the prevalence of 15 differed between survivors and nonsurvivors, and of those, 12 predicted mortality and were integrated into a COPD mortality index ‘COTE’. COTE index increases were associated with an increased mortality risk from both COPD- and non-COPD-related causes (respective HRs 1.13 [95% CI 1.08, 1.18; p<0.001] and 1.18 [1.15, 1.21; p<0.001]). Furthermore, both BODE and COTE index score increases were independently associated with increased mortality risk. A COTE index score ≥4 points was associated with a significantly increased mortality risk across all BODE quartiles (HRs 2.26–2.68; p values <0.001).

Comment: The senior author is Bart Celli of the BODE index, which has made it into text books. It utilises Body mass index, airway Obstruction FEV1, Dyspnoea and Exercise capacity to determine the risk of death in COPD. Because it doesn’t take into account comorbidities, the authors used data from the ongoing BODE cohort to give us the COTE index CCCTET. They presented a ‘comorbidome’, in which the authors summarised prevalence and mortality in one diagram. Bottom line: anxiety, cancer, pulmonary fibrosis, liver cirrhosis, ulcers, diabetes, atrial flutter, CHF and coronary heart disease are associated with an increased risk of death.

http://ajrccm.atsjournals.org/content/186/2/155.abstract

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Bronchodilator use and the risk of arrhythmia in COPD: part 1: Saskatchewan Cohort Study

Authors: Wilchesky M et al

Summary: These researchers explored the relationship between bronchodilator use and cardiac arrhythmia risk in a cohort of 6018 patients with COPD aged ≥55 years, 469 of whom experienced arrhythmia (1.37 per 100 per year; 56 deaths), with each case matched to 20 controls. Arrhythmia risk was significantly associated with new use of ipratropium (RR 2.4 [95% CI 1.4, 4.0]) and long-acting β-agonists (4.5 [1.4, 14.4]), but not short-acting β-agonists (0.9 [0.5, 1.6]) or methylxanthines (1.6 [0.7, 3.7]).

Comment: This is the first of two articles investigating the risk for cardiac arrhythmias associated with use of ipratropium bromide, long-acting β-agonists, short-acting β-agonists and methylxanthines. The authors used Saskatchewan data with endpoints of an arrhythmic death or hospital admission with arrhythmia. Like all retrospective studies it has many weaknesses, not the least that no spirometry or smoking data were available, and it needs to be interpreted with caution also because of its relatively small numbers. Concerns are raised by the authors’ bottom line: short-acting anticholinergic agents and possibly long-acting β-agonists increase the risk of cardiac arrhythmias.

Reference: Chest 2012;142(2):298–304

Bronchodilator use and the risk of arrhythmia in COPD: part 2: reassessment in the Larger Quebec Cohort

Authors: Wilchesky M et al

Summary: Following from the previous study, the same researchers explored the relationship between bronchodilator use and arrhythmia risk in a large Canadian cohort of 76,661 patients with COPD. There were 5307 cases of arrhythmia (10.3 per 1000 per year; 621 deaths), each matched to 20 control patients. Cardiac arrhythmia risk was significantly greater among new users of short- and long-acting β-agonists (respective RRs 1.27 [95% CI 1.03, 1.57] and 1.47 [1.01, 2.15]), but not ipratropium bromide (1.23 [0.95, 1.57]) or methylxanthines (1.28 [0.93, 1.77]). The effects waned as duration of use increased.

Comment: The same Canadian authors used data from 76,000 patients with COPD to investigate the pro-arrhythmogenic effect of our standard therapies in COPD. This time the authors could not identify an adverse outcome after the use of anticholinergic medications; however, they raised concerns about excess cardiac arrhythmias following the new use of short- and long-acting β-agonists. Our current president of the European Respiratory Society, Klaus Rabe, has summarised the implication in a thoughtful accompanying editorial (Chest 2012;142[2]:271–4) and has given us our bottom line: “if drug safety is at our hearts, we need to invest in … and conduct the appropriate trials”.

Reference: Chest 2012;142(2):305–11
The use of non-invasive ventilation for the relief of dyspnoea in exacerbations of chronic obstructive pulmonary disease

Authors: Smith TA et al

Summary: This was a systematic review of four randomised controlled trials investigating usual medical care with versus without NIV in patients with acute COPD exacerbations. Two of the four trials reported that NIV significantly reduced dyspnoea, one reported nonsignificant relief and the fourth reported no relief. Moreover, only one trial did not contain methodological or reporting limitations.

Comment: Our colleagues in Sydney are asking an important question on our use of NIV in COPD. It is now well established that in an appropriate setting it can improve survival and reduce the need for intubation and ventilation in ICU. However, does NIV relieve dyspnoea? After reviewing the 332 studies on the use of BIPAP in COPD, they found the question on relief of breathlessness has only been addressed in four studies, providing us with weak evidence that NIV does improve dyspnoea. Bottom line: NIV in COPD improves survival and probably improves dyspnoea, but better designed studies are needed.

Reference: Respirology 2012;17(2):300–7


The DECAF score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease

Authors: Steer J et al

Summary: These researchers analysed admission data and in-hospital deaths among 920 consecutive patients hospitalised for a COPD exacerbation to identify outcome predictors; mean FEV, was 43.6% of predicted and 10.4% of patients died in hospital. They then combined the five strongest mortality predictors to form the ‘DECAF’ score. DECAF exhibited excellent discrimination for mortality (area under the receiver operator characteristic curve 0.86 [95% CI 0.82, 0.89]). Moreover, DECAF performed better than other clinical prediction tools; for example, it was a significantly stronger predictor of mortality than CURB-65 in 299 patients with coexistent pneumonia.

Comment: This study comes from Newcastle upon Tyne, where I completed my training in respiratory medicine. The authors reflected on the fact that the BODE index predicts mortality risk in stable COPD patients; however, no simple score estimates the mortality in patients admitted with an acute exacerbation of COPD. After recruiting 920 patients with an acute exacerbation of COPD in two hospitals over an 18-month period, they found that about 10% died during admission. Furthermore, they found that the five strongest predictors of mortality were Dyspnoea, Eosinopenia, Consolidation, Acidemia and atrial Fibrillation (DECAF). Bottom line: this simple clinical prediction tool can accurately stratify patients who are admitted with an acute exacerbation of COPD.


http://thorax.bmj.com/content/67/11/970

The calcium sensitizer levosimendan improves human diaphragm function

Authors: Doorduin J et al

Summary: These researchers got 30 healthy subjects to perform two identical inspiratory loading tasks after which they received the calcium sensitisier levosimendan 40 μg/kg bolus followed by 0.1/0.2 μg/kg/min continuous infusion or placebo in a crossover design. Loss of twitch contractility during postload breathing was not seen after levosimendan, compared with a 9% loss after placebo. Furthermore, levosimendan administration was associated with a significant 21% improvement in neuromechanical efficiency of the diaphragm during loading and a significant reduction in baseline frequency of diaphragm electrical activity (p<0.05 for both).

Comment: This Canadian/Dutch double-blind, placebo-controlled crossover study on 30 healthy volunteers may keep alive some hope of effective therapies in the management of COPD. Working on the premise that muscle weakness is a common phenomenon and is also associated with poorer survival in COPD, they reported on a study of the effects of a calcium sensitisier on diaphragmatic muscle strength. They demonstrated that the calcium sensitisier levosimendan improved both contractile function and neuromechanical efficiency of the human diaphragm. Bottom line: calcium sensitisers may become a new therapeutic approach in managing respiratory muscle dysfunction.


http://ajrccm.atsjournals.org/content/185/1/90.abstract

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