Welcome to issue 101 of Respiratory Research Review, with the topic of COPD. The at-times very exciting evidence would certainly support another edition to our family of Research Review dedicated to COPD. I may just take the opportunity to congratulate my colleagues A/Prof Alister Neill and Dr Karen Falloon (Sleep Medicine), Drs Brent Caldwell and Natalie Walker (Tobacco Control) and Drs Chris Lewis and George Laking (Lung Cancer). If you haven’t done so, you should certainly look at these Research Review publications.

As a way to structure the selection of articles for this review, we are using the schema from the COPDx guidelines (www.goldcopd.org), which have just been updated almost in sync with the new GOLD guidelines (www.goldcopd.org). We chose to highlight two research articles in each arm following the COPDx paradigm.

Confirm diagnoses
COPD is still underdiagnosed (see ‘Finding the missing millions – the impact of a locally enhanced service for COPD on current and projected rates of diagnosis: a population-based prevalence study using interrupted time series analysis’ Prim Care Respir J 2013;22[1]:59–63). However, there is also a risk of over-diagnosis when treating everything seen on a CT scan (see ‘HRCT-defined emphysema is not COPD to be treated with inhalers’ Thorax 2014;69[5]:401–2).

Optimize function
Out of the plethora of articles, we chose to review the current status of bronchoscopic lung volume reduction with endobronchial valves, which is available in NZ. An article published in the BMJ gives some reassurance about the safety of benzodiazepines and opioids in the management of very severe respiratory disease.

Prevent deterioration
As a placeholder for many articles, we have chosen one article on smoking cessation suggesting some place for hope 50 years after the first Surgeon General Report on Smoking and Health; keeping us focussed on a Virtually Smoke-free Aotearoa by 2025. A group of Chinese researchers report a possible role for N-acetylcysteine to prevent exacerbation of COPD.

Develop Support
This is arguably the most important aspect in the management of COPD. We selected two articles, one comparing the impact of different content and organisation aspects of pulmonary rehabilitation programmes, while the other one is on the negative impact on exercise capacity of a hospital admission for any cause.

Manage exacerbations
This occupies us working in hospital on a daily basis. We have selected two articles of the many published; one reporting no effect of prednisone in patients requiring ventilator support, the other reporting on the beneficial effect on cardiac mortality of β-blockers in patients with COPD.

Maybe COPD isn’t all that complicated to manage after all. I greatly enjoyed the editorial by Burgel and Clini (Am J Respir Crit Care Med 2014;189[1]:7–8) titled ‘Multimorbidity in elderly patients with chronic obstructive pulmonary disease: stop smoking! go exercise?’

We hope you enjoy the selection, and are looking forward to any feedback and comments.

Kind regards
Dr Lutz Beckert
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Measurement of FEF<sub>25–75%</sub> and FEF<sub>75%</sub> does not contribute to clinical decision making

Authors: Quanjer PH et al.

Summary: The value of measuring the FEF<sub>25–75%</sub> and FEF<sub>75%</sub> over and above FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC ratio for clinical decision making was assessed using measurements from 22,767 individuals with FEV<sub>1</sub>, FVC and FEF<sub>25–75%</sub> data; 15,661 had FEF<sub>75%</sub> data. The FEF<sub>25–75%</sub> and FEF<sub>75%</sub> values were below normal values in 2.75% and 1.29% of cases, respectively, while FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC ratio were within normal limits. FEF<sub>25–75%</sub> and FEF<sub>75%</sub> failed to detect airway obstruction in 2.9% and 12.3% of cases, respectively.

Comment: In this article, leading respiratory scientists apply statistical methodology and appropriate reference values to explore the role of the so-called “midflow parameters” in detecting “small airways disease”. This article with its scientific rigour and the editorial “Question everything” (Eur Respir J 2014;43(4):947–8) explore how the misconception of ‘a parameter for detecting early respiratory disease by detecting midflow changes’ occurred. They demonstrated that the FEF<sub>25–75%</sub> measurement would have missed airflow obstruction in 12% of cases; in the 2.75% where it may have detected earlier changes, many measurements were of dubious quality, particularly in children. Bottom line: when interpreting spirometry, focus on FEV<sub>1</sub>/FVC and FEV<sub>1</sub>.


Abstract

Comparison of spirometric thresholds in diagnosing smoking-related airflow obstruction

Authors: Bhatt SP et al., for the COPDGene Investigators

Summary: Using data from the COPDGene study, the accuracy and discrimination of the GOLD (Global Initiative for Chronic Obstructive Lung Disease) recommended FEV<sub>1</sub>/FVC ratio of <0.70 was compared with lower limit of normal for diagnosing smoking-related airflow obstruction, using CT-defined emphysema and gas trapping as the gold standard. Data from 7743 participants with and without airflow obstruction, including current and former smokers, showed very good agreement between the two spirometric cutoffs (κ=0.85 [95% CI 0.83, 0.86; p<0.001]). However, participants with airflow obstruction by the fixed ratio only had significantly greater degrees of emphysema and gas trapping than: i) those positive by lower limit of normal values (4.1% vs. 1.2% [p<0.001] and 19.8% vs. 7.5% [p<0.001], respectively); and ii) smoking controls without airflow obstruction (4.1% vs. 1.9% [p<0.001] and 19.8% vs. 10.9% [p<0.001], respectively). The fixed ratio only group had more exacerbations during follow-up than smoking controls.

Comment: This study from the COPDGene project should be read with its accompanying editorial (Thorax 2014;69(5):401–2). The authors compared COPD as defined through an FEV<sub>1</sub>/FVC ratio less than the lower limit of normal and a group of people with a FEV<sub>1</sub>/FVC of <0.70. The fixed cutoff doesn’t take into account the effect of natural aging on the lung, and so found this group to be older with more pack-years of smoking (due to their age) and had CT changes of emphysema. I remain sceptical of their findings and agree with Paul Enright’s bottom line: “HRCT-defined emphysema is not COPD to be treated with inhalers”.


Abstract

Safety of benzodiazepines and opioids in very severe respiratory disease

Authors: Ekström MP et al.

Summary: These researchers prospectively evaluated the safety of benzodiazepines and opioids in 2249 Swedish COPD registry patients starting long-term oxygen therapy; the respective hospitalisation and mortality rates during follow-up were 76% and 50%. Neither benzodiazepine nor opioid use was significantly associated with increased admissions (percentage HRS 0.98 [95% CI 0.87, 1.10] and 0.98 [0.86, 1.10]), but both benzodiazepines and opioids at dosages of >30 mg/day of oral morphine equivalents were significantly associated with increased mortality (1.21 [1.05, 1.39] and 1.21 [1.02, 1.44]). Benzodiazepine and lower dose opioid use combined did not increase admissions or mortality (respective HRS 0.86 [95% CI 0.53, 1.42] and 1.25 [0.78, 1.99]).

Comment: Many COPD patients are so breathless that it affects their daily life. Clinicians have been reluctant to prescribe opioids or benzodiazepines due to concerns about respiratory depression, confusion, falls or premature death. Of the 2250 patients who started long-term oxygen in Sweden, about one-quarter were taking opioids, one-quarter benzodiazepines and 10% both. A total of 50% died within a year. Opioid use was not associated with increased death or hospital admission; benzodiazepines showed a modest increase in mortality. Randomised trials are needed to explore possible causality. Bottom line: up to 30mg of morphine daily improved breathlessness in 60% of patients with COPD.

Reference: BMJ 2014;348:g445

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Abstract

Respiratory Research Review

Independent commentary by Associate Professor Lutz Beckert.

Associate Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board with particular clinical interests in Interstitial Lung Disease, Pulmonary Artery Hypertension, Respiratory Physiology and Venous Thromboembolic Disease.

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Current status of bronchoscopic lung volume reduction with endobronchial valves

Authors: Shah PL & Herth FJF

Summary: This analysis of data from randomised controlled trials identified by searches on 'COPD', 'emphysema', 'lung volume reduction' and 'endobronchial valves' suggests that key predictors of clinical success among patients with COPD treated with endoscopic lung volume reduction to induce atelectasis of the hyperinflated lobe include complete lobar occlusion without collateral ventilation and intact lobar fissure. Greater heterogeneity in disease distribution between upper and lower lobes is also indicative. Appropriate patient selection improves the response rate from 20% (unselected) to 75%. An ‘acceptable’ safety profile was described for endobronchial valves, with the main adverse event being an excess of pneumothoraces.

Comment: Inhaler therapy has little effect on improving emphysema-predominate phenotypes of COPD. The National Emphysema Treatment Trial showed that surgical lung volume reduction surgery is beneficial for patients with upper lobe-predominant disease and low exercise tolerance; however, the cost is high and the mortality at best is 4%. These authors summarised the current thinking on the role of endobronchial valves as medical lung volume reduction surgery. Bottom line: patients with hyperinflation, FEV<45% predicted, emphysema type and intact fissures may respond to valve placement with a significant improvement in lung function and possibly increased survival.


Abstract

Smoking prevalence and cigarette consumption in 187 countries, 1980–2012

Authors: Ng M et al.

Summary: These researchers estimated daily smoking prevalence changes by age, sex and number of cigarettes per smoker per day for 187 countries over the period 1980–2012. Between 1980 and 2012, the global modelled age-standardised prevalence of daily tobacco smoking among individuals aged >15 years decreased significantly from 41.2% to 31.1% among men and from 10.6% to 6.2% among women, and the mean annualised rate of decline was significantly greater between 1996 and 2006 than over the subsequent period (10.7% vs. 0.9% [p=0.003]). Despite these declines, the number of daily smokers increased between 1980 and 2012 from 721 million to 967 million (p<0.001). Substantial variation was seen across age, sex and country for the modelled prevalence rates, with rates in some African countries being <5% for women, compared with >55% for men in Timor-Leste and Indonesia. There was also wide variability across countries for the number of cigarettes per smoker per day, with no correlation seen with modelled prevalence.

Comment: Tobacco causes 71% of all lung cancers and accounts for 22% of all cancer deaths worldwide. Smoking rates in the US have declined from 42% in 1965 to 18% in 2012 since the ‘Surgeon General’s Report’ in 1964. Tobacco control measures may have saved an estimated 8 million lives (JAMA 2014;311(2):164–71). However, some evidence suggests the decline of smoking cessation is slowing, possibly related to strained public health funding versus an 8 billion dollar tobacco advertising budget in the US alone. Actually, because of an increased population, although the rate of smokers declined, the total number of smokers increased. Bottom line: a virtual Smokefree Aotearoa by 2025 would be a huge achievement.

Reference: JAMA 2014;311(2):183–92

Abstract

Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON)

Authors: Zheng J-P et al., on behalf of the PANTHEON study group

Summary: Patients with moderate-to-severe COPD (postbronchodilator FEV/FVC ratio <0.7; FEV1 of 30–70% of predicted) were stratified according to inhaled corticosteroid use (regular or not) at baseline and randomised to receive N-acetylcysteine 600mg twice daily (n=504) or placebo (n=502) for 1 year in this trial. Acute exacerbations at 1 year were under a significantly lower rate in the N-acetylcysteine arm than in the placebo arm (1.16 vs. 1.49 per patient-year; risk ratio 0.78 [95% CI 0.67, 0.90; p=0.001]), and the respective adverse event rates were 29% and 26%, with 48 and 46 serious events in each arm, respectively, most commonly acute COPD exacerbation (6% and 7%).

Comment: The proven interventions to prevent deterioration in COPD include smoking cessation, influenza vaccination and long-term oxygen therapy if hypoxic. The role of mucolytics is still unclear, with the BRONCUS study not showing a significant effect of 600mg N-acetylcysteine on reducing exacerbations. Here a group of Chinese researchers reported that 1200mg of N-acetylcysteine reduces the exacerbation rate from 1.49 to 1.16 exacerbations per year. It had no effect on the time to the first exacerbation. I agree with the accompanying editorial’s (Lancet Respir Med 2014;2(3):166–7) bottom line: N-acetylcysteine may reduce exacerbations, but at this stage it can’t be recommended for all patients with COPD.


Abstract

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LIFE CAN’T WAIT.
Differences in content and organisational aspects of pulmonary rehabilitation programmes

Authors: Spruit MA et al., on behalf of the ERS Rehabilitation and Chronic Care, and Physiotherapists Scientific Groups, the American Association of Cardiovascular and Pulmonary Rehabilitation, the ATS Pulmonary Rehabilitation Assembly and the ERS COPD Audit team

Summary: Using a 12-question survey, this research studied the overall content and organisational aspects of pulmonary rehabilitation programmes from a global perspective. The survey, which was completed by representatives of pulmonary rehabilitation programmes from 430 centres covering 40 countries, suggested substantial differences in the settings, the case mix of individuals with a chronic respiratory disease, the composition of the pulmonary rehabilitation team, completion rates, methods of referral and types of reimbursement.

Comment: Pulmonary rehabilitation is the most effective intervention for people with COPD. It improves exercise tolerance, dyspnoea and quality of life, and reduces anxiety, depression and hospital admissions. The authors of this survey of rehabilitation courses describe differences; however, the principles are reassuringly similar given the different health systems. The greatest concern is that about 35,000 individuals participated in a course, but an estimated 65 million live with COPD. An excellent toolkit is available under: http://www.pulmonaryrehab.com.au. In keeping with the accompanying editorial (Eur Respir J 2014;43[5]:1223–6) our bottom line is: when quality control and standards are maintained, rehabilitation courses can be as different as apples and oranges – both good for your health.


Hospital admissions and exercise capacity decline in patients with COPD

Authors: Ramon MA et al., the PAC-COPD Study Group

Summary: To explore the association between hospital admissions and exercise capacity decline in patients with COPD, these researchers assessed clinical and functional variables for 342 patients with clinically stable disease (postbronchodilator FEV1 54% predicted; baseline 6MWD 433m). 6MWD decreased by 21.9m per year and 45% of patients had ≥1 hospitalisations during follow-up. Among the 50% of patients admitted only for a COPD-related cause, the proportion with a clinically significant loss in 6MWD was significantly greater than seen among those admitted for only nonrespiratory conditions (53% vs. 29% [p=0.040]). Compared with patients with no hospitalisation, those with >1 all-cause hospitalisation had a significantly greater annual decline in 6MWD after adjusting for confounders (p<0.001).

Comment: Nobody is really looking to find the opposite of a pulmonary rehabilitation programme – a way to decrease the exercise capacity of patients with COPD. These Spanish researchers may have found an effective tool to decrease 6MWD – a hospital admission. Following a well-characterised cohort of 342 participants with stable COPD, the authors noticed an impressive deterioration in 6MWD in patients admitted to hospital, independent of the cause for the hospital admission. More than one admission caused an even greater deterioration in the walk distance. Bottom line: hospital admissions for any cause lead to a decline in exercise capacity in COPD.


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Prednisone in COPD exacerbation requiring ventilatory support

Authors: Abroug F et al.

Summary: Patients with acute COPD exacerbation requiring ventilatory support underwent open-label randomisation to prednisone 1 mg/kg/day therapy for ≤10 days (n=111) or usual care (n=106). No difference was seen between the prednisone versus usual care arms for ICU mortality (primary endpoint: 15.3% vs. 14%, relative risk 1.08 [95% CI 0.6, 2.05]), noninvasive ventilation failure rate (15.7% vs. 12.7%; 1.25 [0.56, 2.8; p=0.59]), median mechanical ventilation duration (6 vs. 6 days) or median length of ICU stay (9 vs. 8 days); similar ICU mortality rates were seen in an analysis according to ventilation modality. Compared with usual care, prednisone recipients did have a higher rate of hyperglycaemic episodes requiring initiation of insulin or alteration of current doses (49.5% vs. 33%; relative risk 1.5 [95% CI 1.08, 2.08; p=0.015]).

Comment: The use of systemic steroids during an acute exacerbation of COPD is recommended by international guidelines, despite uncertainty about the optimal dose, route of administration or duration of treatment. This group of Tunisian researchers investigated the effect of prednisone on patients with a severe exacerbation of COPD requiring ventilatory support. Being a single-centre study, it is a little underpowered, despite admitting >500 patients for ventilator support, mostly noninvasive. The authors reported that more patients on prednisone were hyperglycaemic; however, their bottom line is: prednisone had no effect on mortality, noninvasive ventilation failure, length of ventilation or length of ICU stay.


Effect of β blockers on mortality after myocardial infarction in adults with COPD

Authors: Quint JK et al.

Summary: This population-based cohort study of UK electronic healthcare records investigated the effects of β-blocker use and the timing of their prescription on survival in 1063 patients with COPD who had experienced a first MI, and identified factors related to their use. β-blockers started during hospitalisation significantly increased the likelihood of survival over median follow-up of 2.9 years (fully adjusted HR 0.50 [95% CI 0.36, 0.69; p<0.001]), even in patients who were receiving a β-blocker prior to their MI (0.59 [0.44, 0.79; p<0.001]; the effect size was slightly attenuated when follow-up was started from the date of hospital discharge (0.64 [0.44, 0.94; p=0.02]).

The results were similar when propensity scores were used to adjust for differences between those prescribed and not prescribed β-blockers.

Comment: Up to one-third of deaths in patients with COPD are attributable to cardiovascular disease; the worse the FEV₁, the higher the risk. β-blocking agents have been shown to reduce mortality after MI in the general population. These British authors linked data from a national registry on MI and general practice to identify patients with COPD who were either taking β-blockers at the time of their first MI or were started on β-blockers at the time. Bottom line: β-blockers were not widely prescribed; however, when used, almost halved the risk of death following an MI.

Reference: BMJ 2013;347:f6650

Measurement of oxygen concentration delivered via nasal cannulae by tracheal sampling

Authors: O’Reilly Nugent A et al.

Summary: These researchers developed and reported on a novel method of tracheal FiO₂ measurement using a catheter placed via bronchoscopy. In 20 subjects, tracheal gas concentration analyses during six 5-minute treatments, controlling for oxygen delivery rate, respiratory rate and mouth position, showed that FiO₂ increased by 0.038 per L/min of oxygen. A respiratory rate of 15 breaths/min and oxygen supplementation via nasal cannula at 2 L/min resulted in an FiO₂ of 0.296 per L/min, but decreased by 0.012 and 0.004 per L/min at 20 and 10 breaths/min, respectively. A mean decrease in FiO₂ of 0.024 per L/min was seen when the subjects’ mouths were open. Decreases in both FiO₂ and Pₐ₎O₂ (alveolar partial pressure of oxygen) were seen with increasing minute ventilation.

Comment: In this local study, we explored the effect of oxygen delivery rate, respiratory rate and oral versus nasal breathing on the inspired oxygen concentration by sampling through a tube placed via bronchoscopy 1 cm above the carina. Two litres of oxygen via nasal cannula produced mean inspired oxygen concentrations between 27% and 29%. However, with a reduced respiratory rate, the inspired oxygen concentration was as high as 35%, while with hyperventilation and mouth breathing the concentration dropped to 24%. Christine McDonald in her accompanying editorial (Respirology 2014;19(4):469–70) gives us the bottom line: be judicious in your choice of flow rates and monitor the effectiveness closely, watching for hypoxaemia or hypercapnia.


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