

APSR Respiratory Research Review

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Welcome to the latest edition of APSR Respiratory Research Review.

A warm welcome this month to our new reviewer, Dr Lutz Beckert, Respiratory Physician at Christchurch Hospital in New Zealand who takes over the reins from Professor Richard Beasley.

In this edition we feature 2 studies highlighting issues around the diagnosis and management of PE. Of particular importance is the paper by Anderson and colleagues comparing the accuracy of computed tomographic pulmonary angiography (CTPA) and ventilation-perfusion lung scanning (VQ) for the diagnosis of PE.

We hope you enjoy the latest edition and welcome your comments and feedback.

Is air travel safe for those with lung disease?

Authors: Coker RJ & Partridge MR

Summary: In this large, prospective, observational study the authors examined outcomes in 500 patients with respiratory diagnoses following airline travel. Usual pre-flight assessments including oximetry (96%), spirometry (95%), hypoxic challenge (45%) and walk test (10%) were carried out by respiratory specialists. 11% of the study population did not fly following assessment. Follow-up data were collected by questionnaire within 2 weeks of the patients return from travel. Airway and diffuse parenchymal lung disease were the most common diagnoses, occurring in 54 and 23% of subjects respectively. 12 patients died, 7 before flying and 5 within 1 month of flying. Unscheduled respiratory healthcare use was 9% in the 4 weeks prior to travel and 19% during the 4 weeks following. In comparison to the previous year the rate of medical consultations rose by 2%. In conclusion, commercial air travel appears generally safe for patients with lung disease.

Comment: With over 2 billion flights per year, it is likely that many passengers with lung disease will be undertaking air travel. This study confirms the general consensus that air travel with lung disease is relatively safe. It complements the BTS guidelines, suggesting that patients with additional risk factors and oxygen saturation above 95% can fly safely, patients with oxygen saturation below 92% should fly with supplemental oxygen and patients with oxygen saturation between 92 and 95% should have additional tests such as the hypoxic challenge test.

<http://erj.ersjournals.com/cgi/content/abstract/30/6/1057>

Reference: *Eur Respir J* 2007; 30:1057-1063



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Diagnosis of PE in hospitalised patients

Authors: Jouveshomme S et al

Summary: Data from 400 consecutively admitted hospital inpatients with suspected acute pulmonary embolism (PE) were used to retrospectively assess the diagnostic management and incidence of symptomatic venous thromboembolic events (VTE). 29% of patients had a diagnosis of PE confirmed. Using compression ultrasonography (CUS) in addition to multi-detector-row computed tomography (MDCT) for the diagnosis of PE added an incremental value of 8.6%. Lung scans excluded PE in 42% of subjects. Alternative diagnoses were obtained through a negative MDCT, or a negative MDCT plus CUS in 94 and 41 patients respectively. Inappropriate management (lack of follow-up after negative MDCT with no alternate diagnosis) occurred in 115 subjects and was associated with a 7.2% increased risk of VTE. Overall VTE occurred in 3.5% of subjects during follow-up. In conclusion MDCT plus CUS is more effective than MDCT alone for the exclusion of PE.

Comment: Over the last decade, the treatment of VTE has improved mainly through the advent of D-dimer testing, CTPA scanning, and low molecular weight heparins. This important study confirms the findings of the PIOPED II study, which concluded that a negative CTPA scan alone is not enough to exclude a PE in a high risk population.

<http://dx.doi.org/10.1183/09031936.00021507>

Reference: *Eur Respir J* 2007; 30:1117-1123

Independent commentary by Dr Lutz Beckett, Respiratory Physician at Christchurch Hospital.

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CT pulmonary angiography vs ventilation-perfusion lung scanning for suspected PE

Authors: Anderson DR et al

Summary: A randomised, single-blind non-inferiority study was used to assess whether computed tomographic pulmonary angiography (CTPA) was a safe alternative to ventilation-perfusion lung scanning (VQ) for excluding a diagnosis of PE. Subjects were 1,417 patients with acute symptoms suggesting PE - including a Wells clinical model score ≥ 4.5 or a positive D-dimer assay. Where PE was excluded by CTPA or VQ, subjects were followed-up for 3 months without anticoagulation treatment. PE was initially diagnosed in 19.2 and 14.2% of the CTPA and VQ patients respectively (difference, 5.0%; 95% CI, 1.1 to 8.9). In subjects for whom PE had been excluded, 0.4 and 1.0% of the CTPA and VQ groups respectively developed VTE during follow-up (difference, -0.6%; 95% CI, -1.6 to 0.3). One patient in the VQ group died. CTPA was not inferior to VQ for exclusion of PE, however more patients were diagnosed with PE using CTPA.

Comment: This study warrants closer inspection than is possible in this Research Review for several reasons: 1) It provides further reassurance that a CTPA is a valid method to exclude PE in patients with a positive D-dimer and modified positive Wells score. 2) It provides reassurance that VQ scanning still has a role to play as it involves much less radiation exposure and has fewer adverse effects and contraindications than CTPA. 3) It confirms the suspicion that CTPA detects significantly more PE's than VQ scanning. 4) It suggests that despite the lower rates of diagnosis and regardless of non-treatment, patients investigated with VQ scanning do not have significantly more VTE complications. 5) Importantly, neither investigation could completely exclude VTE in this study - there was a fatality in the VQ group. 6) And finally, the authors raise an important question, should every PE diagnosed via CTPA scanning warrant anticoagulation treatment?

<http://jama.ama-assn.org/cgi/content/abstract/298/23/2743>

Reference: *JAMA* 2007; 298(23):2743-2753

Fatal PE risk after discontinuing anticoagulant therapy for VTE

Authors: Douketis JD et al

Summary: This prospective cohort study examined the annual risk of fatal PE and the case-fatality rate of disease recurrence, and related these to initial presentation and aetiology in 2,052 patients with a first episode of symptomatic VTE who had discontinued anticoagulant therapy. 1,450 study subjects had DVT, 310 had PE and 292 had both. Mean duration of anticoagulant therapy was 6 months, with mean follow-up after discontinuation of 54 months. Annual risk of fatal PE was 0.49 events (95% CI, 0.36 to 0.64) per 100 person-years, and the case-fatality rate from recurrent disease was 9.0% (95% CI, 6.8% to 11.8%). For definite or probable fatal PE the annual risk was 0.19 events (95% CI, 0.12 to 0.30) per 100 person-years, and the case-fatality rate from recurrent disease was 3.8% (95% CI, 2.4% to 5.9%). These findings may provide guidance to clinicians where discontinuing anticoagulant therapy for VTE is under consideration.

Comment: This single centre study confirms previous retrospective data that pulmonary embolism is often a recurrent disease. It shows that the case fatality rate from recurrent PE is between 4 - 9%. This needs to be weighed against the risk of long term anticoagulation. At this stage international guidelines still recommend anticoagulation for 3 to 12 months following PE.

<http://www.annals.org/cgi/content/abstract/147/11/766>

Reference: *Ann Intern Med* 2007; 147(11):766-774

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Effect of ADRB2 polymorphisms on response to long-acting β 2-agonist therapy

Authors: Bleecker ER et al

Summary: This paper reports the results of two studies investigating effects of β 2-adrenergic receptor (ADRB2) polymorphisms on response to long-acting β 2-agonists in combination with inhaled corticosteroids. In study 1 (double-blind), 2,250 patients with asthma were randomised to 6-months treatment with budesonide plus formoterol maintenance and reliever therapy, fixed-dose budesonide plus formoterol, or fixed-dose fluticasone plus salmeterol. Gly16Arg genotype did not affect the rate of severe exacerbations or secondary endpoints, including FEV₁, peak expiratory flow, use of as-needed medication, and number of nights with awakenings. In study 2 (open-label), 405 asthma patients received flexible or fixed-dose budesonide plus formoterol or fixed-dose fluticasone plus salmeterol for 7 months. Between group rates of asthma exacerbations and other endpoints were similar. In conclusion, there appeared to be no pharmacogenetic effect of ADRB2 polymorphisms on therapeutic response to long-acting β 2-agonists in combination with inhaled corticosteroids in patients with asthma.

Comment: The medical community has ongoing doubts about the safety of beta agonists in the management of asthma. This study offers an appropriate explanation to the clinical observation that no particular genotypic asthma group will either benefit, or be at a disadvantage, with a regime that involves treatment with long acting beta agonists in combination with inhaled corticosteroids. This is particularly reassuring for patients with the ARG/ARG genotype, who tend to have a reduced response to short acting beta agonists.

<http://www.thelancet.com/journals/lancet/article/PIIS0140673607619060/abstract>

Reference: *Lancet* 2007; 370:2118-2125

Airway abnormalities at flexible bronchoscopy in patients with chronic cough

Authors: Decalmer S et al

Summary: In this retrospective review, the authors report on 18-months of their experience using flexible bronchoscopy as part of the diagnostic work-up of patients with chronic unexplained cough. The diagnostic algorithm used included chest radiography, pulmonary function, methacholine challenge, ear, nose and throat examination, and empirical reflux treatment. Bronchoscopy was performed where a diagnosis was still unclear. 82 bronchoscopies were conducted in patients with chronic cough (mean age 54.9 years, mean duration of cough 5 years). A diagnosis was made in 9 subjects (11%). 7 cases of tracheobronchopathia osteochondroplastica (TPO) were identified, all with early changes comprising a typical nodular appearance to the tracheal cartilage without significant airway obstruction. All would have been overlooked without bronchoscopy. Other diagnoses were one case of elongated uvula and one case of endobronchial amyloidosis. The authors conclude that "flexible bronchoscopy is indicated in persistent unexplained cough and may reveal contributing pathology."

Comment: Chronic cough is one of the most frequent presenting symptoms to a General Practitioner and especially a Respiratory Specialist. Many specialty societies have published guidelines on the management of chronic cough, however evidence is still lacking. This British study suggests that there might be a role for bronchoscopy, if investigations and treatment trials following diagnostic algorithms have been unsuccessful over a period of 18 months.

<http://archinte.ama-assn.org/cgi/content/abstract/167/22/2503>

Reference: *Arch Intern Med* 2007; 167(22):2503-2508

Second-hand smoke and health-related quality of life in never smokers

Authors: Bridevaux PO et al

Summary: The effect of second-hand smoke (SHS) on health-related quality of life (HRQOL) was examined in this cross-sectional study which used data relating to 2,500 never-smokers from the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults. HRQOL was measured using the Short Form Health Survey (SF-36). Scores for all quality of life domains were reduced by exposure to SHS. Subjects with high levels of SHS exposure at home (> 3 hours/day) had significant reductions in physical functioning, physical health, bodily pain and social functioning compared to those with no exposure. Exposure to SHS at home had a stronger negative effect on women than SHS exposure at work or in public places.

Comment: As many European countries introduce anti-smoking legislation in public places, voices doubting the value of such measures can be heard. This article from Switzerland beautifully demonstrates the adverse effects of second-hand smoke on the health-related quality of life in never smokers. Bottom line: Cigarette smoke is bad for smokers and non-smokers.

<http://archinte.ama-assn.org/cgi/content/abstract/167/22/2516>

Reference: *Arch Intern Med* 2007; 167(22):2516-2523

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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Variations in hospitalisation rates for COPD in rural and urban Victoria, Australia

Authors: Ansari Z et al

Summary: The authors used geographic variations in hospital admission rates for COPD to indicate the effectiveness of primary care services within the state of Victoria, Australia. Factors potentially impacting admission rates were assessed. Age and gender-standardised admission rates were calculated using the Victorian Admitted Episodes Dataset for 2003 to 2004. Weighted least squares regression analysis was used to identify the predictors of COPD admissions. Hospital admissions were higher in rural areas of Victoria, and were associated with socio-economic status, smoking, and remoteness of the area. These findings may provide an opportunity for "policymakers to develop targeted public health and health service interventions."

Comment: This study investigated the admission rate of patients with COPD in rural and urban areas. The authors found higher admission rates in rural areas, with socio-economic status, smoking rates and remoteness of an area being the main discriminatory factors. This study will help clinicians to identify patients at risk and inform policy makers about populations who are the most at risk.

<http://dx.doi.org/10.1111/j.1440-1843.2007.01173.x>

Reference: *Respirology* 2007; 12(6):874-880

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BODE score is a useful predictor of hospital admission in rural patients with COPD

Authors: McKellar A et al

Summary: The authors aimed to identify risk factors for hospital admission amongst COPD patients dwelling in rural New South Wales. The 32 participants were interviewed. Other data collected included demographics, consumption of health resources, COPD severity measures (BODE score) and quality of life. The mean age of the participants was 68 years, and most (65.6%) were male. Results were stratified by the number of previous hospital admissions, ≤ 2 previous admissions, or ≥ 3 admissions in the past year. Hospital admission rates were not different between groups with regard to the risk factors studied. However, patients with the higher admission rates were more likely to have a higher BODE score ($p = 0.004$), a poorer quality of life score ($p = 0.015$) and lower exercise tolerance ($p = 0.001$). In conclusion, the BODE score may have utility as a predictor of hospital admission in patients with COPD.

Comment: The BODE index was described as a risk stratifying tool in a Northern American University centre. In this study the authors were searching for risk factors (or predictors) for hospital admissions. There were no risk factors identified with the exception of the BODE score and two dimensions of the BODE score: quality of life and reduced exercise tolerance. The BODE index also appears to be a relevant tool for use in rural COPD populations.

<http://dx.doi.org/10.1111/j.1440-1843.2007.01169.x>

Reference: *Respirology (Online Early Articles)* doi:10.1111/j.1440-1843.2007.01169.x

Range and severity of symptoms amongst older adults with COPD or heart failure

Authors: Walke LM

Summary: This long-term observational cohort study assessed the range and trajectory of symptoms experienced by adults with COPD ($n = 79$) or heart failure ($n = 59$). Participants were aged 60 or older and living in the community. Symptoms were assessed as absent, mild, moderate, or severe during patient interviews conducted every 4 months for up to 2 years. 50% or more of the participants with COPD reported shortness of breath, physical discomfort, fatigue, and problems with appetite and anxiety. Amongst those with heart failure, at least 50% reported physical discomfort, fatigue, and problems with appetite. Symptoms generally increased in severity over time. Prevalence of symptoms was not different in subjects who lived or died. The authors conclude that the high burden of symptoms amongst these patient groups represents a "large unmet need for symptom assessment and treatment" and suggest that this need is also not met by current disease management guidelines.

Comment: This study reminds us that patients with COPD and heart failure have a high symptom burden and a largely unmet need to control disease specific and non-specific symptoms. Management strategies focusing on survival improvement may not necessarily meet these complaints. Or expressed differently, patients with COPD and heart failure may benefit from a similar management approach as patients with non-curable lung cancer.

<http://archinte.ama-assn.org/cgi/content/abstract/167/22/2503>

Reference: *Arch Intern Med* 2007; 167(22):2503-2508

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