



# Respiratory Research Review

Making Education Easy

Issue 26 - 2011

## In this issue:

- Osteopontin a useful biomarker in PAH?
- Thiazolidinediones: increased risk of pneumonia, LRTI
- Decreased fraction of exhaled NO in obese asthmatics
- High-flow oxygen therapy increases  $Ptco_2$
- CPAP may aid stroke recovery?
- Adenotonsillectomy benefits sleep homeostasis in OSA
- Pirfenidone promising in idiopathic pulmonary fibrosis
- Vitamin D deficiency and outcomes in CAP
- Omalizumab for severe allergic asthma
- Doppler echocardiographic estimates of pulmonary artery pressures

**Welcome** to the twenty-sixth edition of Respiratory Research Review, a unique Australian publication bringing you some of the most important research from around the world every month. Selection of papers and comments are provided by Dr Belinda Miller, Respiratory and Sleep Disorders Physician at Alfred Health, Melbourne.

This edition covers a wide range of topics. The first study that we discuss suggests that circulating levels of osteopontin, a pleiotropic cytokine that has been postulated to play a role in the pathogenesis of idiopathic pulmonary arterial hypertension, may be useful as a biomarker in this disease. In another study, the researchers found that vitamin D deficiency was associated with increased mortality in patients admitted to hospital with community acquired pneumonia during winter. The final study in this edition investigated the accuracy of Doppler echocardiography (DE)-based estimates of pulmonary artery systolic pressure (PASP). It concludes that DE estimates of PASP are inaccurate in patients with pulmonary hypertension and should not be relied on to make its diagnosis or to follow the efficacy of therapy.

I hope you find the papers selected for this issue of use to you in your practice. I welcome any feedback.

Kind Regards,

**Dr Janette Tenne**

[janette.tenne@researchreview.com.au](mailto:janette.tenne@researchreview.com.au)

## Osteopontin in patients with idiopathic pulmonary hypertension

**Authors:** Lorenzen JM et al

**Summary:** This study examined whether plasma levels of the pleiotropic cytokine osteopontin are related to disease severity and mortality in idiopathic pulmonary arterial hypertension (iPAH), using data from two cohorts of patients with iPAH: a 4-year retrospective cohort (n=70) and a prospective cohort (n=25) followed for 3 months after initiation of therapy. Forty healthy subjects served as controls. Mean circulating osteopontin levels were elevated at baseline in patients with iPAH compared with healthy controls (50.2 vs 23.7 ng/mL;  $p < 0.0001$ ). In both patient cohorts, osteopontin levels correlated with mean right atrial pressure and N-terminal pro-brain natriuretic peptide. In the retrospective cohort, osteopontin levels also correlated with age ( $r = 0.3$ ;  $p = 0.02$ ), 6-min walking distance ( $r = -0.4$ ;  $p = 0.05$ ), and New York Heart Association class ( $r = 0.4$ ;  $p = 0.001$ ). According to a multivariate analysis, baseline osteopontin levels independently predicted mortality ( $p = 0.02$ ). Proportional survival rates, based on whether osteopontin values were normal ( $< 34.5$  ng/mL) or elevated ( $> 34.5$  ng/mL) at baseline, were 100% and 80%, respectively, after 1 year; corresponding rates after 3 years were 77% and 51%.

**Comment:** Osteopontin is a cytokine whose expression is upregulated by inflammation, cancer and other conditions, is recognised as a predictor of mortality in chronic heart failure and some cancers, and has been linked to vascular smooth muscle proliferation. Thus, it has potential as a biomarker to assess and monitor treatment response in iPAH. This study found osteopontin to be of prognostic significance in iPAH, although interpretation is limited by a partially retrospective cohort, small numbers, short-term follow-up and comparison of mixed-venous and peripheral blood samples. However, it is an interesting basis for further work in this evolving area.

**Reference:** *Chest* 2011;139(5):1010-7.

<http://chestjournal.chestpubs.org/content/139/5/1010.abstract>

# RESEARCH REVIEW

## Making Education Easy



## Long-term use of thiazolidinediones and the associated risk of pneumonia or lower respiratory tract infection: systematic review and meta-analysis

**Authors:** Singh S et al

**Summary:** The risk of pneumonia or lower respiratory tract infections (LRTIs) associated with thiazolidinediones was assessed in this systematic review of data from 13 long-term (1–5.5-year duration of follow-up) randomised controlled trials of thiazolidinediones versus a placebo, metformin or sulfonylurea control for prevention or treatment of type 2 diabetes. Patient cohorts included 8163 patients receiving thiazolidinediones and 9464 patients receiving control therapy. Thiazolidinediones were associated with a statistically significantly increased risk for any pneumonia or LRTI (n=130/8163 vs 100/9464; RR 1.40; p=0.01) and serious pneumonia or LRTI (n=111/7391 vs 87/8692; RR 1.39; p=0.02).

**Comment:** Non-respiratory medications that have immunomodulatory effects in the lung are increasingly recognised; for example, statins may prove to have a significant mortality benefit in pneumonia. Thiazolidinediones act as partial glucocorticoid receptor agonists and thus have been considered as potentially favourable agents in patients with airways disease. This study is a meta-analysis of RCTs of thiazolidinediones, assessing reports of adverse events of pneumonia and LRTI. A small but statistically significant increased risk was found. Targeted prospective RCTs, with appropriate control of other risks and confounders including cardiac failure, will be needed to confirm or refute this finding.

**Reference:** *Thorax* 2011;66(5):383-8.  
<http://thorax.bmj.com/content/66/5/383.abstract>

## Decreased fraction of exhaled nitric oxide in obese subjects with asthma symptoms. Data from the population study INTERGENE/ADONIX

**Authors:** Berg CM et al

**Summary:** These researchers sought to determine if the fraction of exhaled nitric oxide (FENO) and atopy are associated with BMI and specifically whether the phenotype of asthma differs by FENO measurements between obese (BMI ≥ 30 kg/m<sup>2</sup>) and nonobese subjects. The study population consisted of 2187 men and women aged 25–74 years with asthma symptoms, who participated in the INTERGENE study cohort. Wheezing was associated with raised FENO and atopy in nonobese subjects, whereas obese subjects who reported wheezing had lower FENO than obese subjects without wheezing (16.1 vs 19.1 parts per billion; p<0.01). The prevalence of atopy was similar in both of those subgroups (25.0% vs 20.7%; p=0.4). Similarly, in 395 subjects (19%) who reported wheezing, FENO was negatively associated with BMI, waist-to-hip ratio, and percentage of body fat, whereas no significant relationships were observed in those without respiratory symptoms.

**Comment:** Previous studies have suggested an association between obesity and wheezing, with proposed mechanisms including mechanical or hormonal factors and/or common inflammatory pathways. This sizable study assessed asthma phenotypes by FENO in obese and nonobese subjects. The results suggest no association with atopy and a reduced FENO, and thus potentially reduced eosinophilic airway inflammation, with wheeziness in obesity. However, this effect was seen in men only, obese subjects were older and wheezing rather than physician-diagnosed asthma was analysed. The results are in line with previous data, and while not conclusive do suggest that wheeze in obesity is multifactorial in origin.

**Reference:** *Chest* 2011;139(5):1109-16.  
<http://chestjournal.chestpubs.org/content/139/5/1109.abstract>

### Respiratory Research Review

**Independent commentary by Dr Belinda Miller,**  
*a full-time Respiratory and Sleep Disorders  
 physician in AIRMed, Alfred Hospital, and  
 Adjunct Senior Lecturer, Monash University.*



RESEARCH REVIEW Making Education Easy

## RESEARCH REVIEW

is an independent medical publishing organisation producing electronic journals in several specialist areas. These journals provide summaries of the 'must see' studies from the most respected medical journals in the world together with a local specialist commentary indicating why they matter.

## Conference Reviews

are independent summaries of the most significant and relevant international specialist conferences. Australian specialist envoys attend and summarise the most significant conference presentations and proceedings. This creates the perfect short summary of events for those unable to attend.

## Subscribe now

or update your current subscription to Research Review, and receive many more specialist reviews FREE each month.

Click here to visit [www.researchreview.com.au](http://www.researchreview.com.au)





## Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma

**Authors:** Perrin K et al

**Summary:** Outcomes are reported for 106 patients with severe exacerbations of asthma presenting to the Emergency Department and who were randomised to therapy with high concentration oxygen (8 L/min via medium concentration mask) or titrated oxygen (to achieve oxygen saturations between 93% and 95%) for 60 min. Patients in the high concentration oxygen group were twice as likely as those in the titrated oxygen group to experience a rise in  $Ptco_2 \geq 4$  mm Hg at 60 min (44% vs 19%; RR 2.3;  $p < 0.006$ ). Notably, the high concentration group had a higher proportion of patients with a rise in  $Ptco_2 \geq 8$  mm Hg (22% vs 6%; RR 3.9;  $p = 0.016$ ). All 10 patients with a final  $Ptco_2 \geq 45$  mm Hg received high concentration oxygen therapy, and in five there was an increase in  $Ptco_2 \geq 10$  mm Hg.

**Comment:** There has been a reawakening of interest recently in the potential toxicity of high-flow oxygen therapy, both in respiratory and cardiac diseases. Hypercapnia has long been recognised to be a complication of oxygen treatment in patients with acute exacerbations of COPD, but there is much less awareness of this issue in patients with acute respiratory diseases such as asthma. Worsened ventilation-perfusion matching appears likely to be a major mechanism in both conditions. While the mean rise in  $Ptco_2$  was small, some patients had clinically concerning increases, although without an associated increase in hospitalisations. This well conducted study is a timely reminder to clinicians that titrated oxygen therapy, to achieve a targeted  $SpO_2$ , is generally preferable to high-flow therapy.

**Reference:** *Thorax* 2011 May 19. [Epub ahead of print]

<http://thorax.bmj.com/content/early/2011/05/19/thx.2010.155259.abstract>

## Early treatment of obstructive apnoea and stroke outcome: a randomised controlled trial

**Authors:** Parra O et al

**Summary:** The impact of nasal continuous positive airway pressure (nCPAP) was assessed in a cohort of stroke patients with an apnoea-hypopnoea index  $\geq 20$  events/h who were randomised to early nCPAP ( $n=71$ ; 3–6 days after stroke onset) or conventional treatment (controls;  $n=69$ ). At 1 month after stroke, a significantly higher proportion of patients in the nCPAP group compared with the conventional treatment group showed neurological improvement (Rankin scale 90.9% vs 56.3%;  $p < 0.01$ ; Canadian scale 88.2% vs 72.7%;  $p < 0.05$ ). The mean time until the appearance of cardiovascular events was longer in the nCPAP group (14.9 vs 7.9 months;  $p = 0.044$ ), although cardiovascular event-free survival after 24 months was similar in both groups. The cardiovascular mortality rate was 0% in the nCPAP group and 4.3% in the control group ( $p = 0.161$ ).

**Comment:** A relationship between stroke and sleep-disordered breathing, including evidence that sleep-disordered breathing may precede and contribute to stroke, has been established in population studies. It remains unclear however, whether CPAP is feasible and/or helpful in stroke recovery. The patients studied were not a generally representative group as severe stroke patients and those with altered conscious state were excluded. In addition, the analysis was not intention-to-treat; patients who did not tolerate CPAP were excluded. Despite these limitations, improvements in neurological function were seen in the CPAP group, and there was suggestion of a decrease in cardiovascular events. An interesting study, which should lead to larger RCTs in a wider patient group.

**Reference:** *Eur Respir J* 2011;37(5):1128-36.

<http://erj.ersjournals.com/content/37/5/1128.abstract>

## Adenotonsillectomy improves slow-wave activity in children with obstructive sleep apnoea

**Authors:** Ben-Israel N et al

**Summary:** These researchers estimated slow-wave activity (SWA) in 14 children with obstructive sleep apnoea (OSA; mean age 6.4 years; apnoea-hypopnoea index [AHI] 10.0 events/h) before and after adenotonsillectomy. Six children (age 5.4 years; AHI 9.4 events/h) with OSA that did not undergo treatment served as a comparison group. Adenotonsillectomy improved respiration without altering the duration of sleep stages. Following adenotonsillectomy,  $>50\%$  elevation of SWA during the first two sleep cycles ( $p < 0.01$ ) and a more subtle descriptor of SWA across the night ( $p < 0.0001$ ) were noted. The slow-wave slope increased by  $>30\%$  following adenotonsillectomy ( $p < 0.03$ ). No significant changes were found in SWA in the comparison group.

**Comment:** Paediatric OSA is established to be associated with adverse neurobiological effects, with improvement in many children after adenotonsillectomy. Previous studies, however, have not shown consistent changes in sleep architecture after surgery despite improvement in symptoms and AHI. This study evaluated a more subtle descriptor of sleep homeostasis, slow-wave analysis (SWA), and found an increase post-surgery, indicative of improved sleep. Small subject numbers and use of retrospective controls impair utility of these study results; however, the technique of SWA may prove a useful addition to standard sleep staging and the often difficult task of arousal scoring in (research) sleep studies.

**Reference:** *Eur Respir J* 2011;37(5):1144-50.

<http://erj.ersjournals.com/content/37/5/1144.abstract>

## Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials

**Authors:** Noble PW et al

**Summary:** Data were analysed from two randomised, concurrent trials in the CAPACITY programme involving patients (aged 40–80 years) with idiopathic pulmonary fibrosis (IPF) who were randomly assigned to oral pirfenidone or placebo for a minimum of 72 weeks. In study 004, patients were assigned to pirfenidone 2403 mg/day ( $n=174$ ), pirfenidone 1197 mg/day ( $n=87$ ), or placebo ( $n=174$ ); in study 006, patients were assigned to pirfenidone 2403 mg/day ( $n=171$ ) or placebo ( $n=173$ ). The primary endpoint was change in percentage predicted forced vital capacity (FVC) at week 72. In study 004, mean FVC change at week 72 was  $-8.0\%$  in the pirfenidone 2403 mg/day group and  $-12.4\%$  in the placebo group;  $20\%$  and  $35\%$  of patients, respectively, had a decline of  $\geq 10\%$ . A significant treatment effect was noted at all timepoints from week 24. Mean change in percentage FVC in the pirfenidone 1197 mg/day group was intermediate to that in the pirfenidone 2403 mg/day and placebo groups. In study 006, the between-group difference in predicted FVC change at week 72 was not significant; however, a consistent pirfenidone effect was apparent until week 48 and in an analysis of all study timepoints. Compared with placebo recipients, pirfenidone recipients had higher incidences of nausea, dyspepsia, vomiting, anorexia, photosensitivity, rash, and dizziness. Fewer overall deaths and fewer deaths related to IPF occurred among pirfenidone recipients than among placebo recipients.

**Comment:** IPF remains a devastating disease, with lung transplantation often the only hope for longer term palliation. This large-scale randomised study of pirfenidone in patients with non-end-stage IPF showed a small but clinically relevant dose-dependent effect on the end points of change in percentage predicted FVC, progression-free survival and 6MWT, benefits not previously observed with any other drugs. The effects were not large, and the study was not powered to assess survival or able to assess longer term responses. Whilst pirfenidone alone is far from a sufficient treatment for IPF, and a combination of therapies targeting multiple pathways of fibrosis is likely to be needed, this research may pave the way for further developments.

**Reference:** *Lancet* 2011;377(9779):1760-9.

<http://tinyurl.com/thelancet-com-journals>

## Vitamin D, innate immunity and outcomes in community acquired pneumonia

**Authors:** Leow L et al

**Summary:** This study investigated associations between mortality and serum levels of 25-hydroxyvitamin D, cathelicidin and beta-defensin-2 in a prospective cohort of 112 patients admitted to hospital with community acquired pneumonia during winter. Thirty-day mortality was significantly higher among the 15% of patients with severe 25-hydroxyvitamin D deficiency ( $<30$  nmol/L) compared with patients with sufficient 25-hydroxyvitamin D ( $>50$  nmol/L) (OR 12.7;  $p = 0.004$ ). These associations were not explained by differences in age, comorbidities, or the severity of the acute illness. While cathelicidin and beta-defensin-2 levels failed to predict mortality, lower cathelicidin showed a trend towards increased mortality ( $p = 0.053$ ). No correlations were found between cathelicidin and beta-defensin-2 levels with 25-hydroxyvitamin D.

**Comment:** Vitamin D is involved in the regulation of a large number of genes, including those involved in immunity; hence its potential role in respiratory infections. This study showed an association between severe vitamin D deficiency and mortality within 30 days in patients admitted with pneumonia, although from a mechanistic view, did not show an association with the two antimicrobial peptides measured. Association does not mean causation; low vitamin D levels may be a marker of general frailty or other confounders, but there is more than enough tantalising evidence from this and other studies to await randomised interventional studies in the near future.

**Reference:** *Respirology* 2011;16(4):611-6.

<http://onlinelibrary.wiley.com/doi/10.1111/j.1440-1843.2011.01924.x/abstract>

### contact RESEARCH REVIEW

To advertise your medical conference or educational meeting in this publication . . .

email [admin@researchreview.com.au](mailto:admin@researchreview.com.au)

or call 1300 132 322

## Omalizumab in severe allergic asthma inadequately controlled with standard therapy. A randomized trial

Authors: Hanania NA et al

**Summary:** The efficacy and safety of omalizumab was evaluated in 850 patients aged 12–75 years with inadequately controlled severe asthma receiving high-dose inhaled corticosteroids (ICS) and long-acting  $\beta_2$ -agonists (LABAs), with or without additional controller therapy. Omalizumab (n=427) or placebo (n=423) was added to existing medication regimens for 48 weeks. During the study, omalizumab was associated with a significantly reduced rate of protocol-defined asthma exacerbations compared with placebo (0.66 vs 0.88 per patient; p=0.006), representing a 25% relative reduction (incidence rate ratio, 0.75). In addition, omalizumab improved the mean overall score on the standardised version of the Asthma Quality of Life Questionnaire scores (0.29 points), reduced mean daily albuterol puffs (-0.27 puffs/day), and decreased mean asthma symptom score (-0.26) compared with placebo. Similar rates were observed between the omalizumab and placebo groups for adverse events (80.4% vs 79.5%) and serious adverse events (9.3% vs 10.5%), respectively.

**Comment:** This is a large multicentre prospective RCT of add-on therapy with omalizumab in patients with maximally treated but still poorly-controlled severe allergic asthma. The results show a significant relative reduction in asthma exacerbations and an improvement in asthma-related quality of life measures in the omalizumab group. However, the absolute reduction in exacerbations and improvement in other measures of control was quite small. The study was supported by industry. Despite these provisos, omalizumab is likely to be a valuable treatment addition in this difficult-to-manage patient group. Further work will still be needed to confirm these results and better establish dosages.

Reference: *Ann Intern Med* 2011;154(9):573-82.  
<http://www.annals.org/content/154/9/573.abstract>

## Inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension: implications for clinical practice

Authors: Rich JD et al

**Summary:** This investigation into the accuracy of pulmonary artery systolic pressure (PASP) measurements using Doppler echocardiography (DE) compared with right-sided heart catheterisation (RHC) in a cohort of 160 patients with pulmonary hypertension (PH) revealed moderate correlation between DE and RHC measurements ( $r = 0.68$ ;  $p < 0.001$ ). However, Bland-Altman analysis demonstrated a bias for DE estimates of PASP of 2.2 mm Hg with 95% limits of agreement ranging from -34.2 to 38.6 mm Hg. DE estimates of PASP were inaccurate in 50.6% of patients. Bland-Altman analyses were then performed to evaluate the agreement between RHC and DE measurements of PASP in an additional 23 consecutive patients undergoing simultaneous RHC and DE. These revealed moderate correlation between DE and RHC measurements of PASP ( $r = 0.71$ ;  $p < 0.01$ ). However, despite simultaneous DE and RHC measurements, the bias for DE estimates of PASP was 8.0 mm Hg with 95% limits of agreement ranging from -28.4 to 44.4 mm Hg.

**Comment:** Evaluation for pulmonary hypertension is increasingly performed these days. Oral therapies can be of great value in selected patients. It is tempting to consider the use of echocardiography alone to assess and monitor patients, rather than to perform the more complex right heart catheterisation (RHC). This well-conducted study reminds us that the two tests are not interchangeable; echocardiography may under- or over-estimate pulmonary artery pressures, as compared to RHC, >50% of the time. Echocardiography still has great value, by assessing RV function and size, and identifying other conditions that may cause secondary pulmonary hypertension, and possibly as an initial screening tool. RHC and echocardiography should be seen as complementary investigations.

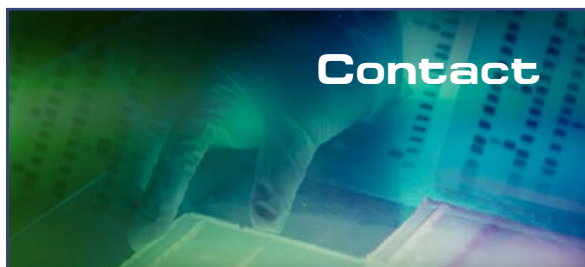
Reference: *Chest* 2011;139(5):988-93.  
<http://chestjournal.chestpubs.org/content/139/5/988.abstract>

### UPDATE YOUR CURRENT SUBSCRIPTION

to Research Review and receive many more specialist reviews FREE each month.

Click here to visit ...

[www.researchreview.com.au](http://www.researchreview.com.au)



Contact

## RESEARCH REVIEW

If you would like to contact us.

Email [admin@researchreview.com.au](mailto:admin@researchreview.com.au)

Phone 1300 132 322

## Subscribe now

or update your current subscription to Research Review, and receive many more specialist reviews FREE each month.

Click here to visit

[www.researchreview.com.au](http://www.researchreview.com.au)



**RESEARCH REVIEW** bringing you the most important studies with commentary from Australian specialists FREE each month.

**Privacy Policy:** Research Review will record your email details on a secure database and will not release it to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time.

**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.

Research Review publications are intended for Australian health professionals.