

# APSR Respiratory Research Review

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Issue 25 – 2008

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## Welcome to this edition of the APSR Research Review.

Pulmonary artery hypertension (PAH) was thought to be a rare disease in young woman with limited treatment options. Over the last decade things have changed significantly and PAH has now been recognised to be more prevalent, with an average age >50 years. Whereas in the past lung transplantation had been the only life-prolonging treatment available, we now have several medical treatments for the management of PAH. In this Research Review we highlight some of the newer evidence for indication of treatment of PAH. We will also look at some of the pathology of PAH and other causes of pulmonary hypertension.

I like to thank everybody again for the very kind feedback and ideas for inclusion for the Research Review. I hope you all enjoy reading this month's edition.

Kind regards,

**Dr Lutz Beckert**

[lutzbeckert@researchreview.co.nz](mailto:lutzbeckert@researchreview.co.nz)

## Right ventricular contractility in systemic sclerosis-associated and idiopathic PAH

**Authors:** Overbeek MJ et al

**Summary:** Differences in right ventricular (RV) pump function between systemic sclerosis-related pulmonary artery hypertension (SScPAH) and idiopathic PAH were investigated in this paper. Compared with participants with idiopathic PAH (n=17), those with SScPAH (n=13) had lower mean RV pressure (30.7 vs. 41.2mm Hg) and hypothetical isovolumic RV pressure (43.1 vs. 53.5mm Hg), but RV stroke volume index (SVI) and the hypothetical maximal SVI (SVI<sub>max</sub>) did not differ between the two groups. The investigators commented that lower contractility in SScPAH, compared with idiopathic PAH, resulted in the differences in pump function as pressures were higher for similar SVIs.

**Comment:** This group of Dutch researchers explored whether the 10% of patients with SScPAH are more prone to death because of their comorbidities, age-related factors, differences in vasculopathy or impaired RV contractility. Using data from cardiac catheters and rather ingenious modelling, they came to the conclusion that intrinsic myocardial involvement in SScPAH contributes to increased mortality. This may be due to myocardial fibrosis, abnormal collagen deposits, cardiac remodelling or changes in the coronary arteries. This study helps our understanding and may lead to more target therapies in SScPAH.

**Reference:** *Eur Respir J* 2008; 31(6): 1160-6

<http://erj.ersjournals.com/cgi/content/abstract/31/6/1160>



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## High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease

**Authors:** Goldin JG et al

**Summary:** This study compared baseline high-resolution CT (HRCT) scans with clinical features, pulmonary function tests and BAL fluid cellularity in 162 patients with scleroderma (SSc). Pulmonary fibrosis (PF), pure ground-glass opacities (GGOs) and honeycomb cysts (HCs) were evident on HRCT in 92.9%, 49.4% and 37.2% of participants, respectively. Participants with limited SSc had significantly greater incidences of HCs in upper, middle and lower lung zones compared with those with diffuse SSc. There were significant negative correlations between the extent of PF on HRCT and FVC, diffusing capacity for CO and total lung capacity, while pure GGO was positively correlated with the number of acute inflammatory cells in BAL fluid.

**Comment:** This is an important observational study based on the cohort of the Scleroderma Lung Study Research Group. Between 74–95% of patients with SSc will develop pulmonary involvement, mostly with nonspecific interstitial pneumonia. The authors presented the findings of the 12-month follow-up HRCT scans of 162 patients. Their main findings were: 1) 'ground-glass' appearances on the HRCT scan were not well correlated with 'alveolitis' on BAL and they questioned the assumption that the GGO reflects active lung inflammation; 2) baseline HRCT findings predicted the progression rate; and 3) the worse the baseline HRCT scan the faster the progression rate and the greater the response to cyclophosphamide.

**Reference:** *Chest* 2008; 134(2): 358-67

<http://www.chestjournal.org/cgi/content/abstract/134/2/358>

## Clinical outcomes of pulmonary arterial hypertension in carriers of *BMPR2* mutation

**Authors:** Sztrymf B et al

**Summary:** The effect of mutations to the bone morphogenetic protein receptor 2 (*BMPR2*) gene on clinical outcomes in PAH was investigated in this study. *BMPR2* mutations were identified in 28 and 40 participants with familial and idiopathic PAH, respectively, while 155 participants, all of whom had idiopathic PAH, did not carry the mutations. Significant differences between *BMPR2* mutation carriers vs. noncarriers included: younger age at diagnosis (36.5 vs. 46.0 years;  $p < 0.0001$ ) and death ( $p = 0.002$ ); higher mean pulmonary artery pressure (64 vs. 56 mm Hg;  $p < 0.0001$ ); greater pulmonary vascular resistance (17.4 vs. 12.7 mm Hg/L/min/m<sup>2</sup>,  $p < 0.0001$ ); lower mixed venous oxygen saturation (59 vs. 63%;  $p = 0.02$ ); lower cardiac index (2.13 vs. 2.50 L/min/m<sup>2</sup>;  $p = 0.0005$ ); and shorter time to lung transplantation or death ( $p = 0.044$ ). Overall survival did not differ significantly between the two groups.

**Comment:** This study from the French database of 223 patients with PAH investigated the clinical course of patients with *BMPR2* gene abnormalities compared with noncarriers. They found that *BMPR2* mutation carriers developed disease earlier in life, had more severe illness and died at a younger age. In the accompanying editorial, Lewis Rubin reflected on the progress made in the understanding and management of PAH, and reminded us that we still have along way to go because the median survival between diagnosis and death or transplantation is only 10 years.

**Reference:** *Am J Res Crit Care Med* 2008; 177(12): 1377-83

<http://ajrccm.atsjournals.org/cgi/content/abstract/177/12/1377>

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## Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension

**Authors:** Suntharalingam J et al

**Summary:** This pilot study explored the potential for medically managing chronic thromboembolic pulmonary hypertension (CTEPH) with sildenafil. Nineteen participants were randomly assigned to 12 weeks' treatment with sildenafil or placebo. Although exercise capacity (primary endpoint) did not differ significantly between the two groups after treatment, WHO class and pulmonary vascular resistance (secondary endpoints) were significantly improved in the sildenafil group compared with the placebo group. Significant improvements in 6-minute walk distance, cardiac index, pulmonary vascular resistance, N-terminal pro brain natriuretic peptide levels and activity and symptom components of QOL were seen among 17 subjects reassessed at 12 months.

**Comment:** CTEPH has been considered a curable form of PAH by surgical endarterectomy. As the editorial pointed out, it seemed frivolous to even consider medical management for this mechanical problem. With this background knowledge in mind, this UK-based study reported on the long term-use of sildenafil in patients with inoperable CTEPH, and helps to shift a paradigm. Although the study failed to show a difference in the 6-minute walk test, it did show improvements in both cardiac markers and QOL. We can now add sildenafil to bosentan (with caution) into our armamentarium to treat inoperable CTEPH.

**Reference:** *Chest* 2008; 134(2): 229-36

<http://www.chestjournal.org/cgi/content/abstract/134/2/229>

## Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study)

**Authors:** Galiè N et al

**Summary:** The efficacy of bosentan in patients with WHO functional class II PAH was investigated in this study. Participants (aged >12 years) were randomised to receive 6 months' treatment with bosentan (n=93) or placebo (92). The percentage of baseline pulmonary vascular resistance at 6 months was significantly lower in the bosentan group than the placebo group (83.2% vs. 107.5%;  $p < 0.0001$ ;  $n = 168$ ), and bosentan recipients had a greater change in baseline mean 6-minute walk distance at 6 months than placebo recipients (11.2 vs. -7.6 min;  $p = 0.0758$ ;  $n = 177$ ).

**Comment:** Bosentan has been shown to improve exercise capacity, haemodynamics and clinical symptoms in WHO III and IV functional class PAH. It has been argued that treatment for PAH may be more effective if patients are treated earlier. This European study reports on the findings of a RCT of 168 patients with WHO class II PAH after receiving bosentan or placebo for 26 weeks. Although the 6-minute walk test results did not change, there was a reduction in deterioration of symptoms and haemodynamic parameters. We are looking forward to seeing how this translates into improving mortality. The European funding authorities have extended their guidelines to include treatment with bosentan for patients with WHO class II PAH.

**Reference:** *The Lancet* 2008; 371(9630): 2093-100

<http://tinyurl.com/lancet-371-9630-2093>

## A randomised, controlled trial of bosentan in severe COPD

**Authors:** Stolz D et al

**Summary:** Bosentan for improving cardiopulmonary haemodynamics, and hence increasing exercise tolerance, was investigated in 30 patients with severe COPD randomised to receive either bosentan or placebo (2:1 ratio) for 12 weeks. Six-minute walk distance (primary endpoint) did not differ significantly between the active treatment and placebo groups (331 vs. 329 min). Among the secondary endpoints, there were no significant between-group differences for lung function, pulmonary artery pressure, maximal oxygen uptake and regional pulmonary perfusion pattern, while bosentan recipients experienced an increased alveolar-arterial gradient and deteriorations in arterial oxygen pressure and QOL.

**Comment:** Pulmonary hypertension has been reported in 20–91% of patients with severe COPD and has been linked to more severe symptoms and a worse clinical outcome. This small but important American study investigated whether treatment with bosentan improved right ventricular function, oxygen delivery and exercise tolerance. Unfortunately, treatment with bosentan failed to improve exercise tolerance, caused significant hypoxaemia and decreased quality of life. At this stage neither sildenafil nor bosentan should be used for the management of COPD, even if secondary pulmonary hypertension has been documented.

**Reference:** *Eur Respir J* 2008; 32(3): 619-28

<http://erj.ersjournals.com/cgi/content/abstract/32/3/619>

## Bosentan therapy in patients with PAH: the relationship between improvements in 6 minute walk distance and quality of life

**Authors:** Strange G et al

**Summary:** This retrospective analysis investigated the effect of bosentan on QOL and 6-minute walk distance (6MWD) in 69 patients with PAH. Bosentan was associated with improvements from baseline in both QOL domains and 6MWD after 3 and 6 months of treatment. A cross-sectional analysis revealed a significant correlation between QOL and 6MWD, but the relationship between changes in these two markers in response to therapy was poor.

**Comment:** This local study from several Australian PAH units reported on the correlation between QOL and 6MWD from a cohort of 69 patients from an open-label trial with bosentan. They found a good correlation between improvement in 6MWD and QOL improvement in a cross-sectional analysis. However, this relationship disappeared when analysed in longitudinal assessment. The authors concluded that both QOL and 6MWD are valid outcome measurements that provide complimentary data, and should both be used to assess the success of therapy.

**Reference:** *Respirology* 2008; 13(5): 674-82

<http://www3.interscience.wiley.com/journal/120750299/abstract>



*Independent commentary  
by Dr Lutz Beckert,  
Respiratory Physician at  
Christchurch Hospital,  
New Zealand.*

## Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension

**Authors:** Condliffe R et al

**Summary:** This prospective study explored prognoses of 469 patients with chronic thromboembolic pulmonary hypertension (CTEPH) from five UK pulmonary hypertension centres between January 2001 and June 2006. Patients managed surgically had 1- and 3-year survival rates of 88% and 76%, respectively, compared with 82% and 70% for patients with nonsurgical disease ( $p=0.023$ ). Patients managed surgically experienced significant functional and haemodynamic improvements, and although patients with nonsurgical disease also experienced initial functional improvements, these did not persist after 2 years. Among the 35% of patients who survived to 3 months after surgery but had persistent pulmonary hypertension, 94% were still alive after 5 years.

**Comment:** This article reflects on the British experience of 469 patients with CTEPH. In 236 patients, a pulmonary endarterectomy was performed with an overall surgical mortality of 16% (as low as 5% in 2006) and 3-year survival of 94%. The 148 patients who did not receive surgical therapy were given disease-modifying treatment with a prostanoid, an endothelium receptor antagonist or sildenafil in 90% of cases. The 3-year survival for the 'not surgically treated' group was 70%. Bottom line: surgical treatment is the treatment of choice for CTEPH and survival using medical treatment is better than has been reported in historic trials.

**Reference:** *Am J Resp Crit Care Med* 2008; 177(10): 1122-7

<http://tinyurl.com/AJRCCM-177-1122>

*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.*

## Heart-type fatty acid-binding protein for risk assessment of chronic thromboembolic pulmonary hypertension

**Authors:** Lankeit M et al

**Summary:** The prognostic value of heart-type fatty acid-binding protein (H-FABP) in chronic thromboembolic pulmonary hypertension (CTEPH) was assessed in 93 consecutive patients with this condition. During a median follow-up period of 1260 days, 49% of patients underwent lung transplantation, experienced persistent pulmonary hypertension following pulmonary endarterectomy or died of CTEPH-related causes. Cox regression analysis revealed that each 1-ng/mL increase in H-FABP was associated with a hazard ratio of 1.10 (95% CI 1.04, 1.18), while a multivariate analysis revealed that continuous H-FABP elevations were an independent predictor of adverse outcomes. Pulmonary endarterectomy was found to have a favourable effect on long-term outcome, but patients with a baseline H-FABP level  $>2.7$  ng/mL had a decreased probability of event-free survival following the procedure.

**Comment:** CTEPH is a life-threatening condition and a frequent cause of PAH. Up to 60% of patients with CTEPH deny symptoms of pulmonary embolism. Between 1–3.8% of patients who survive an acute VTE develop CTEPH. This group of Austrian/German authors investigated the role of H-FABP in identifying patients with CTEPH at risk of an adverse outcome. They found that H-FABP is a useful tool for risk-stratifying patients with CTEPH and it greatly outperforms troponin T.

**Reference:** *Eur Respir J* 2008; 31(5): 1024-9

<http://erj.ersjournals.com/cgi/content/abstract/31/5/1024>

## Portopulmonary hypertension: survival and prognostic factors

**Authors:** Le Pavec J et al

**Summary:** Variables affecting survival among patients with portopulmonary hypertension (PoPH) were explored in a population of 154 patients in this retrospective study. Cirrhosis was present in 136 patients with portal hypertension, and severity assessments were 51%, 38% and 11% for Child-Pugh classes A, B and C, respectively. Overall survival was 88% at 1 year, 75% at 3 years and 68% at 5 years. A multivariate regression analysis revealed that the main independent prognostic factors were cardiac index and presence and severity of cirrhosis.

**Comment:** This is a further study based on the French database of patients with PAH. The authors used the French database to investigate a subgroup of 154 patients with PoPH to identify survival rate and prognostic factors. The authors discovered that the survival of PoPH was better than expected in iPAH and not related to the WHO functional class like in iPAH. They also found no convincing evidence that treatment with medical therapy for PAH altered the outcome. The key predictor for outcome was the severity of liver disease, which means that there should be a multidisciplinary approach to managing these patients.

**Reference:** *Am J Resp Crit Care Med* 2008; 178(6): 637-43

<http://ajrccm.atsjournals.org/cgi/content/abstract/178/6/637>

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