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Respiratory Research Review™

Making Education Easy

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In this issue:

Welcome to the latest edition of Respiratory Research Review.

Pulmonary artery hypertension (PAH) was thought to be a rare disease in young women 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.

In addition, we review two articles about our relationship with junior doctors and medical students. One article wonders whether ethnic stereotyping contributes to underachievement of Asian medical students, and the other identifies burnout as a risk factor for suicide ideation among medical students.

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
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Ethnic stereotypes and the underachievement of UK medical students from ethnic minorities

Authors: Woolf K et al

Summary: This qualitative study explored the relationship between ethnic stereotypes and academic underachievement among medical students. Data from questionnaires administered to 27 students and 25 clinical teachers at a medical school in London, UK were analysed using the theory of stereotype threat and the constant comparative method. Although direct discrimination was not reported, both students and teachers considered that Asian students relied too much on books, were too quiet during clinical teaching sessions, communicated poorly with patients, and lacked motivation due to being impelled to study medicine by ambitious parents. In contrast, typical 'white' students were generally considered to be autonomous, confident and outgoing.

Comment: During the 1990s, ethnic stereotyping of African-American students was identified as a threat to their performance. It has been reported that members of a negatively stereotyped group feel anxious and underperform in test situations. This UK study tried to determine whether Asian medical students were negatively stereotyped. The researchers found that most subjects had a clear picture of the 'typical' Asian student in their mind with a systematic mismatch as to what makes a 'good' medical student. They argue that this negative stereotype causes distress among Asian medical students and contributes to poor test performance. The researchers give advice on how to combat these views, such as getting to know the students as individuals rather than as 'Asians'.

Reference: BMJ 2008; 337: a1220
http://www.bmj.com/cgi/content/abstract/337/aug18_1/a1220

Burnout and suicidal ideation among US medical students

Authors: Dyrbye LN et al

Summary: This study involving 4287 students from US medical schools investigated the frequency of suicidal ideation and its relationship with burnout. Burnout and suicidal ideation within the previous year were reported in 49.6% and 11.2% of participants, respectively. A multivariate analysis revealed that suicidal ideation was independently predicted by burnout and low mental quality of life. Recovery from burnout, which was reported in 26.8% of participants who met the criteria for this condition, was associated with a marked reduction in suicidal ideation.

Comment: Death by suicide is a major occupational hazard for physicians and the suicide rate is approximately 40% higher than that of the general population. There is some evidence that the road to suicide may start during medical school. This US study identified that 25% of students had suicidal ideation and confirmed the known relationship between depressive symptoms and quality of life. In addition they found a relationship between burnout and suicidal ideation. Although the incidence of burnout was high (49.6%), the good news is that 27% recovered within a year. The article also gave advice about how medical schools should consider responding to these findings. Their advice included educating students about burnout and depression, and directing them towards using the available resources that are put in place for helping students to combat depression/burnout.

Reference: Ann Intern Med 2008; 149(5): 334-41

http://tinyurl.com/aim-149-334

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 (SVImax) 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

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. 56mm Hg; p<0.0001); greater pulmonary vascular resistance (17.4 vs. 12.7mm Hg/L/min/m^2, 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^2; 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 Resp Crit Care Med 2008; 177(12): 1377-83

http://tinyurl.com/AJRCCM-177-1377

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

Research Review publications are intended for NZ Medical Professionals

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

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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://tinyurl.com/ERJ-32-619

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 endarterectomise 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

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 then 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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