

YEAR IN REVIEW

Year in review 2013: Acute lung injury, interstitial lung diseases, sleep and physiology

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Key words: acute respiratory distress syndrome, idiopathic pulmonary fibrosis, obesity, obstructive sleep apnoea, sarcoidosis.

Abbreviations: ACE, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; DL_{CO}, diffusion capacity for carbon monoxide; HIT, hypoxic inhalation test; IgG4-RD, immunoglobulin G4-related disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MAS, mandibular advancement splint; S_PO₂, oxyhaemoglobin saturation using pulse oximetry measurements.

INTRODUCTION

This Year in Review paper, the first in a series of three review papers, highlights the most relevant articles published in 2013 in *Respirology* and other respiratory medicine journals on acute lung injury, interstitial lung disease (ILD), sleep and pulmonary physiology.

ACUTE LUNG INJURY

Yuanlin Song

The outbreak of H7N9 avian influenza pneumonia in east China highlighted the significance of virus assortment in birds and the role played by transmission from birds to humans. Meanwhile, Middle East respiratory syndrome coronavirus has been an inhabitant in bats for many years and transmitted to humans with person-to-person transmission.^{1,2} Analysis of 111 patients who had confirmed H7N9 infection showed high mortality with the majority of deaths due to severe pneumonia and acute respiratory distress syndrome (ARDS).¹ Novel coronavirus infection showed respiratory distress and multiple

organ damage with mortality around 65% in affected patients.² Influenza virus infection is still a severe challenge to public health warranting continuous efforts on vaccine development.

Sepsis is also a major cause of ARDS, and it is associated with high mortality in intensive care unit patients. A recent study showed prolonged hospitalization but no increased mortality in a group of ARDS patients who had positive blood stream culture.³ However, this finding needs further investigation in a large group of ARDS patients at multiple sites.

Pathogenesis and pathophysiology

Unlike traditional ARDS, influenza-induced ARDS features both epithelial and endothelial injury with the injured epithelium and endothelium being orchestrated to provoke massive inflammation in the lungs. This leads to capillary leakage and eventual inhomogeneous alveolar flooding.^{4,5} Alveolar flooding is a process of fluid leakage with active/passive transport driven by ion movement or hydrostatic pressure. Cystic fibrosis transmembrane regulation conductance has shown participation in alveolar fluid transport to the capillary compartment. Inhibition of chloride transport worsens lung injury induced by lipopolysaccharide in a rodent model, suggesting inhibition of active fluid transport may delay lung injury recovery.⁶ Among various risk factors, bile acid aspiration induces lung injury through p38 and c-Jun N-terminal kinase phosphorylation, as well as cytosolic phospholipase A2 and cyclooxygenase-2 production, which results in attenuation of junctional proteins such as occludin, zonula occludens-1 and E-cadherin.⁷ Similarly in a *Pseudomonas aeruginosa*-induced lung injury model, claudins -3, -4 and -18 are significantly upregulated with the degree of bronchoalveolar lavage claudin level being associated with lung injury score.⁸ These results strongly suggested protection against lung injury occurs through junctional protein expression in alveolar epithelium.

Angiotensin-converting enzyme (ACE) plays a role in the pathogenesis of ARDS. bronchoalveolar lavage

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samples from ARDS patients showed increased ACE-1 but decreased ACE-2 levels.⁹ ACE-2 cleaves Angiotensin II to form Angiotensin, while ACE-1 cleaves Angiotensin I to form Angiotensin II. An angiotensin inhibitor reduced lung injury in a lipopolysaccharide-induced mouse model,¹⁰ suggesting imbalance of ACE expression in ARDS and potential therapy through downregulation of ACE-1.

Different manoeuvres have been developed to quantify lung oedema and extravascular lung water to guide management of ARDS.¹¹ A recent study using computed tomography imaging showed inhomogeneous distribution of lung injury in ARDS patients, and the level of inhomogeneity was associated with mortality.¹² Chest ultrasound has been applied in ARDS to quantify lung oedema through B-line and subpleural consolidation measurement.¹³ These imaging techniques provide additional information on lung water that may help clinical evaluation and management of fluid administration and mechanical ventilation setting.

Treatment

Low tidal volume (6 mL/kg) ventilation strategy has been shown to reduce mortality in ARDS. Does an even lower tidal volume provide additional benefit? A recent study showed ventilation with 3 mL/kg combined with extracorporeal CO₂ removal significantly increased ventilation free days in severe hypoxic patients.¹⁴ Prone position ventilation has shown improved survival in severe ARDS, although the protocol might not be applicable in most medical centres.¹⁵ Regarding ventilation mode, adaptive support ventilation is equivalent to volume control ventilation on mortality in patients with ARDS,¹⁶ which is consistent with previous reports.

The lung is eventually healed through organ-derived stem cell mobilization/repopulation and tissue regeneration. Exogenous stem cell has been extensively studied in different lung injury animal model to test the efficacy, administration route and underlying mechanism. So far, it is known that exogenous stem cells heal lung injury through engraftment, paracrine secretion, immune modulation, growth factor production and antibiotic peptide synthesis pathway.¹⁷ So far, there are more than 300 on-going clinical trials assessing stem cell therapies.^{18,19} A number of respiratory conditions are being considered as targets for stem cell treatment including ARDS and chronic progressive diseases such as idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD).^{17,20–22} The outcomes of these trials should be known in next few years.

Airway inflammation

Bronchiectasis is characterized as vicious cycle of chronic purulent airway inflammation with bronchodilation. Neutrophils play an important role in airway inflammation, and so the activity of neutrophils has been studied in idiopathic bronchiectasis and control patients.²³ The result showed similar response of neutrophils to granulocyte macrophage-colony

stimulating factor in these two groups, suggesting neutrophil phagocytosis and generation of oxidative species have been preserved in bronchiectasis patients,²³ although the exhaled condensation may not detect the difference.^{24,25} Macrolide antibiotics including azithromycin has been shown to be beneficial in reducing symptoms and exacerbations,²⁶ with an underlying mechanism thought to be biofilm disruption (which helps antibiotics penetration) and suppressive activity on airway inflammation.

INTERSTITIAL LUNG DISEASES

Toby M. Maher

Chronic fibrotic ILD, encompassing a range of conditions including IPF and connective tissue disease-associated ILD, has gained increasing prominence over the last 2 or 3 years following the emergence of effective therapies such as pirfenidone and rituximab.^{27–29} Despite a rise in clinical trial activity, the pathobiology of fibrotic lung disease remains poorly understood.³⁰ The development of IPF has previously been linked to abnormalities in lymphatic drainage and lymphangiogenesis.³¹ Data presented in *Respirology*, by Egashira *et al.* on the differential distribution of lymphatic drainage between upper and lower regions of the lung, are of particular interest for researchers trying to understand the development of fibrotic lung disease.³² Egashira and colleagues observed that lymphatic drainage in the upper lobes follows a bronchovascular distribution, while in the lower lobes, the lymphatics tend to be found in the subpleural regions. These differences may go some way to explain the typical pattern of distribution of fibrosis in individuals with IPF and merits further investigation in the context of fibrotic ILD.

Cigarette smoking is a recognized risk factor for the development of a range of ILD including IPF, respiratory bronchiolitis-ILD and desquamative interstitial pneumonitis. Active smoking has also been associated with an increased risk of developing ILD in individuals with rheumatoid arthritis.^{33,34} Furthermore, it is increasingly being recognized that ILD develops in a significant subset of individuals with emphysema.³⁵ To explore the link between cigarette smoking, ILD and emphysema, Antoniou *et al.* compared the high-resolution computed tomography scans of individuals with IPF, RA-ILD and COPD.³⁶ The authors found emphysema in a significant proportion of the patients with IPF and RA-ILD (35% and 48%, respectively). Interestingly, when compared with individuals with COPD, those with ILD and emphysema had significantly lower pack-year smoking histories. Although requiring prospective validation, this observation suggests that emphysema and pulmonary fibrosis share pathogenetic mechanisms.³⁷

Individuals with fibrotic ILD, especially those with IPF, demonstrate highly variable rates of disease progression.³⁸ This can make it challenging for clinicians to accurately convey information regarding prognosis at the point patients are diagnosed with the condition. In patients with early disease and preserved lung

function determining prognosis can be especially challenging. Kondoh *et al.* have demonstrated that as is the case for individuals with more advanced disease, a typical computed tomography appearance of usual interstitial pneumonia and the extent of honeycombing identify individuals at a high risk of early progression.³⁹ In IPF, it has previously been shown that the profusion of fibroblastic foci seen on surgical lung biopsy predicts subsequent disease progression.⁴⁰ In a study of 50 subjects, Harada *et al.* extended this observation, demonstrating that the extent of fibroblastic foci in surgical lung biopsies correlates with disease severity and subsequent progression in both IPF and fibrotic NSIP.⁴¹ While of interest, this finding lacks clinical utility because of the requirement for biopsy material.

Serum markers make an attractive target for biomarker development in ILD because of the ease of repeated sampling. Inokoshi *et al.* explored the potential of the extracellular matrix component, hyaluronan, as a diagnostic and prognostic biomarker in chronic fibrotic ILD.⁴² In their study of 49 subjects, hyaluronan was elevated compared with healthy controls and rose further in individuals undergoing acute exacerbations. Procalcitonin, a small circulating amino acid precursor of calcitonin, has been investigated as a marker of bacterial pneumonia.⁴³ Nagata *et al.* have shown that procalcitonin levels may be a useful discriminator between acute exacerbations of IPF (in which levels remain low) and bacterial-driven episodes of ARDS and pneumonia (in which, procalcitonin levels are markedly elevated).⁴⁴ These observations, however, require validation in large prospective cohorts of patients.⁴⁵

Sarcoidosis

Sarcoidosis remains an enigmatic and multifaceted condition of unknown aetiology. A number of groups have previously reported a negative correlation between active cigarette smoking and the development of sarcoid.^{46–49} Hattori *et al.* sought to assess the relationship between sarcoidosis and cigarette smoking in Japan.⁵⁰ In contrast with other studies undertaken, they found a strikingly high rate of smoking in their sarcoid patients (59.6% in men and 27.9% of women). Smoking was commoner in sarcoid patients than in age-matched controls in almost all deciles of age apart from men in their 30s. Interestingly, Hattori and colleagues noted a trend towards increased parenchymal involvement in sarcoid patients who smoked compared with those who had never smoked.⁵⁰ While these data are thought provoking, they need to be caveated with the fact that the study was retrospective and relied on smoking prevalence data for the general Japanese population that was drawn from separately conducted research.

Suchankova *et al.* undertook a study of myeloid cells isolated from the bronchoalveolar lavage of patients with sarcoid.⁵¹ They explored the expression pattern of triggering receptor expressed on myeloid cells-1 and -2. These two receptors belong to the immunoglobulin superfamily, play a role in the innate immune response to infection, and act to drive cell

fusion and granuloma formation. Both triggering receptor expressed on myeloid cells-1 and -2 expressions were increased on the cell surface of bronchoalveolar lavage cells in sarcoid when compared with bronchoalveolar lavage cells isolated from individuals with other forms of ILD. These observations support a role for infection as a trigger for the development of sarcoid. They also suggest that triggering receptor expressed on myeloid cells-1 and -2 expression levels might be effective biomarkers for discriminating between individuals with sarcoid-related ILD and ILDs of other causes.

Rare lung diseases

Rare (or orphan) lung diseases are often overlooked in the medical literature, and yet some of the most striking treatment advances in the last decade have come in ultra-rare diseases. As such, insights derived from rare diseases have often revealed disease mechanisms that contribute to the understanding of more common disorders. During 2013, *Respirology* published a state-of-the-art review of treatment options in pulmonary alveolar proteinosis.⁵² The paper by Leth *et al.* explores in detail current understanding regarding the role of granulocyte macrophage-colony stimulating factor autoantibodies as the key pathogenetic mechanism in the majority of individuals with pulmonary alveolar proteinosis and the complementary role played by novel therapeutics and whole lung lavage.

A disorder that has been increasingly recognized in the last few years is immunoglobulin G4-related disease (IgG4-RD).⁵³ The condition is characterized by raised serum IgG4, multiorgan deposits of IgG4-positive plasma cells with associated fibrosis and a good therapeutic response to corticosteroids. It has become increasingly clear that IgG4-RD results in a number of specific pulmonary abnormalities. Matsui *et al.* provide an excellent overview of the constellation of lung manifestations of IgG4-RD in their large case series of 48 individuals with IgG4-RD and lung involvement.⁵⁴ The most frequently observed findings were mediastinal adenopathy, thickening of the perilymphatic interstitium (intraalveolar septae), and, in a proportion of cases, subpleural or peribronchovascular consolidation. The apparent lymphatic spread of the disease resembles the appearances of pulmonary lymphoproliferative disease, and so the authors emphasize the importance of obtaining histological confirmation in suspected cases of IgG4-related lung disease.

Obliterative bronchiolitis is an extremely debilitating condition that is associated with a wide range of underlying factors including transplant rejection, autoimmune disease, viral infection and occupational exposures.^{55–57} The mechanism by which these diverse conditions lead to the development of obliterative bronchiolitis remains unknown. Hashimoto *et al.* sought to understand how environmental exposure to *Sauropus androgynous*, a vegetable commonly eaten in Thailand, results in some individuals developing obliterative bronchiolitis.⁵⁸ The aqueous fraction of *Sauropus androgynous* extract triggers cytokine release from monocytes. The release of the

pro-inflammatory cytokine tumour necrosis factor- α was increased by *Sauropus androgynous* extract in monocytes from healthy controls but was increased even further in monocytes derived from individuals with *S. androgynous*-induced obliterative bronchiolitis. This observation suggests that both host and environmental factors are important in the development of obliterative bronchiolitis.

SLEEP

Amanda Piper

Recent years have seen an increasing number of publications highlighting the association between sleep-disordered breathing and cardiovascular disorders such as hypertension, heart failure and stroke. If left untreated, severe obstructive sleep apnoea (OSA) is associated with an increased risk of premature cardiovascular death.^{59,60} A number of pathophysiological mechanisms linking OSA to cardiovascular morbidity have been proposed. Recurrent episodes of intermittent hypoxia arising from upper airway closure could activate inflammatory pathways impairing vascular endothelial function. Lui *et al.* provided an excellent review of the various pathways connecting endothelial dysfunction to OSA and the development of vascular abnormalities.⁶¹ In their review, evidence regarding the potential of early and effective intervention to prevent or possibly even reverse altered endothelial function associated with sleep-disordered breathing was discussed. In addition to the oxidative stress produced by apnoeic episodes, large negative pressures generated by inspiratory efforts against a closed airway create mechanical stresses on the tissues of the thorax. Kawano *et al.* tested the hypothesis that OSA could lead to pulmonary artery dilatation. In their study of 173 patients with suspected OSA, an independent association between severe OSA and an increase in the right descending pulmonary artery diameter was found.⁶²

In addition to cardiovascular consequences, a number of studies have demonstrated an association between OSA and metabolic dysfunction.^{63,64} However, whether OSA is an independent risk factor for the development of type II diabetes remains unclear. In their meta-analysis of six prospective cohort studies, Wang and colleagues found a statistically significant association between moderate-to-severe OSA and diabetes, with the risk increasing with greater OSA severity.⁶⁵ To date, the degree to which treatment of OSA reduces this risk has yet to be firmly established, although the results from the Effect of PAP Treatment on Glycemic Control in Patients With Type 2 Diabetes Study trial (NCT00509223) will help address this question.^{66,67}

A wide range of neurocognitive impairments have also been associated with OSA, most likely arising from the effects of sleep fragmentation and intermittent hypoxia. However, which domains of cognition are affected by OSA and the extent to which improvements can be achieved with continuous positive airway pressure (CPAP) are not easily discernible due

to the wide range of neuropsychological tests that have been employed. Bucks and colleagues sought to address this issue by undertaking a meta-review.⁶⁸ From the five eligible meta-analyses reviewed, OSA was found to be associated with deficits in attention/vigilance, delayed verbal and visual long-term memory, visuospatial abilities, and executive function. Treatment with CPAP was most likely to improve attention/vigilance and global cognitive function. Data from a recently published randomized, sham-controlled trial of CPAP in nearly 1100 participants with OSA over a 6-month period found that active CPAP had a significant effect on objective and subjective sleepiness.⁶⁹ However, only one of three neurocognitive domains tested showed between-group differences, and even then, this difference was transient. Executive function was better in the CPAP arm at 2 months, with the difference being greatest for those with more severe OSA. A major issue with the Kushida study was the high intellectual ability and lack of baseline cognitive impairment of the participants studied.⁶⁹ As highlighted by Bucks *et al.* cognitive reserve and selection of controls pose significant obstacles in interpreting data in this area.⁶⁸

Increasing obesity is contributing to higher prevalence rates of OSA, and accumulating evidence of the health consequences of untreated disease has given rise to greater interest in developing and testing simplified models of care to screen, assess and treat OSA.⁷⁰ The comprehensive review by Chai-Coetzer *et al.* provides an excellent synthesis of the data concerning ambulatory models of care for OSA, their cost-effectiveness and potential limitations.⁷¹ The paper also raises some interesting issues around the role of non-sleep physicians in the management of OSA. Ioachimescu and Teodorescu provide a thought-provoking review of the current literature concerning the relationship between obstructive lung diseases, such as COPD and asthma, and OSA.⁷² While the term 'overlap' is generally applied to the coexistence of OSA and COPD, similar relationships exist between asthma and OSA. Given the difficulty, at times, in clearly distinguishing between COPD and asthma based on clinical and functional criteria, these authors put forward strong arguments for incorporating obstructive lung diseases and OSA into a more general classification of obstructive lung diseases and OSA. With increasing obesity rates worldwide along with interrelated relationships between these disorders, the authors emphasize the importance of identifying OSA in patients with lung disease and *vice versa* in order to better understand response to therapy and to improve disease control.

Therapy for sleep-disordered breathing

Autotitrating CPAP devices have been available for determining an effective therapeutic pressure for fixed CPAP or for ongoing long-term home management of patients with OSA for more than 15 years. However, there was some concern from earlier work that the differing algorithms used by various manufacturers may affect the efficacy of some devices in controlling apnoea and snoring.^{73,74} Damiani and colleagues evaluated the effectiveness of two autotitrating CPAP

devices driven by different flow-based algorithms in determining a therapeutic pressure for fixed CPAP.⁷⁵ Both devices tested by the authors gave similar pressure recommendations as well as providing significant and similar improvements in sleep and breathing. One of the purported advantages of autotitrating CPAP is that a lower mean overnight pressure may be delivered to the patient. This can be beneficial in terms of pressure tolerance and side-effects. However, Luo and colleagues found in their Chinese population that pressures derived from the auto-titration were consistently greater than those determined by manual titration.⁷⁶ As identified by the authors, this may reflect the greater sensitivity of the flow sensor within the autotitrating CPAP device detecting and responding to flow limitation compared with the thermistor used during the manual titration. This study and that of Damiani *et al.* highlight the need for long-term studies to evaluate whether clinically important outcome differences exist between different devices and approaches to titration.⁷⁵

Although highly efficacious, CPAP therapy is not tolerated or accepted as long-term treatment by a significant number of patients with OSA. With this in mind, Anandam *et al.* undertook a large observational study of 570 patients with severe OSA (apnoea-hypopnoea index $\geq 30/h$) followed up for a median period of over 5 years.⁷⁷ All patients initially received CPAP, although only 177 continued on this therapy over the study period. Another 72 patients were switched to a mandibular advancement splint (MAS), and 212 declined intervention. A control group of 208 individuals with an apnoea-hypopnoea index $< 5/h$ were followed over the same time period. Cumulative cardiovascular mortality of the CPAP- and MAS-treated groups were similar to that of the control group, and mortality in all three groups was significantly lower than the untreated severe OSA group. However, no difference in mortality between patients treated with CPAP or MAS was seen even though patients treated with MAS had a higher residual apnoea-hypopnoea index compared with CPAP-treated individuals (16.3 + 5.1/h vs 4.5 + 2.3/h; $P < 0.001$). While observational, the results from this study are consistent with the findings from a recent 3-month randomized trial comparing MAS to CPAP therapy in patients with the full spectrum of OSA severity.⁷⁸ As with the Anandam study,⁷⁷ short-term health outcomes were similar despite residual events being higher in the MAS-treated group. As discussed in the editorial by Vanderveken,⁷⁹ the similarity in outcomes between the two therapies likely arise from higher compliance with MAS offsetting its lower efficacy. To date, a major limitation with MAS has been the inability to objectively monitor compliance. However, this will change with the recent development of microsensor technology permitting chips to be embedded within these devices, enabling more accurate usage monitoring.⁸⁰

Although OSA is a common finding in the majority of patients with obesity hypoventilation syndrome, CPAP is not universally successful in improving sleep-disordered breathing in this population. Salord *et al.* provide useful clinical insights into the resolution of

sleep-disordered breathing in patients with mild-to-moderate OHS and factors that could be used to predict those likely to fail CPAP therapy.⁸¹ Lower overnight oxygen saturation during optimal CPAP on the first treatment and higher partial arterial carbon dioxide concentration at 1 month were useful measures in detecting poor responders following 3 months of therapy. An interesting finding of this study was the progressive improvement in these parameters over the study period, confirming results from an earlier randomized study showing that initial 'incomplete' responders to CPAP may improve over time.⁸²

Other sleep disorders

During 2013, *Respirology* published two other excellent reviews in the area of sleep and breathing. In the first of these, Roux discussed the relationship between restless legs syndrome and sleep-disordered breathing, and provided a comprehensive overview of the effect of treating restless legs on OSA and vice versa.⁸³ The paper by Yamanaka and Sadikot outlined the impact of opioid use, highlighting the more widespread effects of these drugs on the respiratory system, not only on sleep-disordered breathing, but including immune cell function, airway reactivity and pulmonary vasculature.⁸⁴ With the increasing use of opioids in the community, this review is a timely reminder of the side-effects, these drugs beyond just causing respiratory system depression. Finally, Wang and colleagues, using a mouse model, demonstrated differential effects of hypercapnia on the synthesis of neuropeptides involved in the regulation of sleep and breathing.⁸⁵ For the most part, investigations into OSA have focused on hypoxia. Future studies examining the role of these peptides and their response to hypercapnia in humans may shed further light on the pathogenesis of OSA.

PULMONARY PHYSIOLOGY

Neil D. Eves

Lung function testing has always been central to the diagnosis and treatment of respiratory disease and, similar to 2012,⁸⁶ continued to be a considerable research focus in 2013. While there is an ongoing drive to improve reference values for spirometry, this is not necessarily the case for other less common lung function measures. Koch *et al.*⁸⁷ highlighted that many of the predicted values for static lung volumes were determined approximately 20 years ago and changes in technical equipment (i.e. lung volumes measured by gas volume vs body plethysmograph), birth cohort effects and the lack of reference data in the elderly present a number of limitations in the existing equations. As such, Koch and associates⁸⁷ collected plethysmography data for static lung volumes and airway resistance in 686 healthy, non-obese individuals aged 25–85 and provided prediction equations for these measures. The findings demonstrate that currently existing equations generally underestimate lung volumes supporting the need for contemporary reference data.

The American Thoracic Society and European Respiratory Society Guidelines for pulmonary function testing have differing recommendations regarding how bronchodilators affect single breath diffusion capacity for carbon monoxide (DL_{CO}).^{88,89} Yang *et al.*⁹⁰ report that salbutamol has no effect on DL_{CO} in normal individuals or those with fixed airway obstruction. However, in those with reversible airway disease, salbutamol increased alveolar ventilation and decreased the transfer coefficient for carbon monoxide, while the mean change in DL_{CO} was not different. Furthermore, a small group of individuals who had significant reversibility in FEV_1 demonstrated a considerable reduction in DL_{CO} after salbutamol.⁹⁰

To better understand changes in lung function in more complex diseases or in individuals unable to perform traditional pulmonary function tests (i.e. infants), alternative forms of pulmonary function testing can have considerable utility. Raoufy *et al.*⁹¹ developed two non-linear models, namely an artificial neural network and an adaptive neuro-fuzzy inference model for estimating respiratory volume based on thoracoabdominal breathing movements. These non-linear models were reported to fit spirometry volume curves significantly better than linear models, particularly during asynchronous breathing and may be useful in conditions such as asthma or to accurately quantify the variability in ventilation during prolonged respiratory monitoring. Another study⁹² utilized computerized assessment of tracheal forced expiratory noise time to expose hidden bronchial obstruction in individuals with a high probability of bronchial asthma. Acoustic forced expiratory noise time and its ratio to height, body mass and chest circumference were able to reveal acoustic features of bronchial obstruction in ~50% of patients who were spirometry negative for asthma. These findings support forced expired noise time as a promising technique for diagnosing hidden obstruction not revealed by spirometry.⁹²

Laryngeal dysfunction is an area of pulmonary disease that is currently underresearched and consists of a spectrum of conditions including chronic refractory cough, globus pharyngeus, paradoxical vocal cord movement and muscle tension dysphonia.⁹³ Laryngeal dysfunction is strongly associated with conditions such as atopic asthma and nasal disease, and can masquerade as difficult to treat asthma.⁹⁴ An important study by Vertigan *et al.*⁹⁵ provides novel information regarding how each of the conditions associated with laryngeal dysfunction are associated with abnormal laryngeal sensation and have considerable overlap in sensory dysfunction. The authors believe that these findings potentially indicate similar mechanistic pathways and may implicate sensory neural dysfunction in patients with these conditions.⁹⁵

There is growing recognition of the association between reduced lung function and adverse cardiovascular events.⁹⁶ Pearce *et al.*⁹⁷ investigated the association between fibrinogen (a cofactor for platelet aggregation and a major determinant of atherogenesis⁹⁸) and lung function in 380 individuals from the

Newcastle Thousand Families birth cohort (mean age 49–51 years). The authors report significant inverse associations between lung function and plasma fibrinogen concentration even after controlling for birthweight (controlled for gestational age and sex), breast-feeding duration, total pack years smoking and body mass index. However, this association was lost when controlling for per cent body fat instead of body mass index. While these findings are interesting, considerably more prospective research is needed to try and tease out the complex interaction between lung function and systemic inflammation and the confounding role of adiposity.

Respiratory muscle function

M-mode ultrasonography is starting to be used more extensively for the non-invasive assessment of respiratory muscle function, especially in the critical care setting.⁹⁹ Soilemezi *et al.*¹⁰⁰ utilized M-mode ultrasonography to assess diaphragm kinetics in healthy volunteers with and without the addition of an acute inspiratory resistive loading. The addition of an inspiratory resistance decreased respiratory rate and increased tidal volume and was associated with a reduction in the velocity of diaphragmatic contraction, while diaphragmatic excursion did not change from that observed with just a mouthpiece and nose clip. The authors suggest that these distinguishable changes in diaphragm motion with inspiratory loading may make diaphragm ultrasonography useful in conditions such as upper airway obstruction.¹⁰⁰

There is a considerable body of literature that looks at specific training of the respiratory muscles to try and improve functional status or athletic performance in a variety of populations.^{101,102} A recent meta-analysis by Illi *et al.* concludes that respiratory muscle training improves endurance exercise performance in healthy individuals with greater improvements in less fit subjects and in sports of longer duration.¹⁰² Edwards¹⁰³ compared the effects of 4 weeks of respiratory muscle training versus placebo (breathing at 55% vs 10% of maximal inspiratory effort respectively) and reported no changes in lung function or peak oxygen consumption in either group. However, time to volitional exhaustion during an incremental treadmill test and the velocity at peak oxygen consumption were increased with respiratory muscle training. It was postulated by the author that these performance improvements may be due to reduce effort perception following respiratory muscle training allowing subjects to tolerate higher intensity exercise for longer.¹⁰³

Pulmonary artery hypertension

The causes of pulmonary artery hypertension are poorly understood. The condition is associated with vascular remodelling due to excessive cell proliferation and reduced rates of apoptosis.¹⁰⁴ Improved understanding of the pathology of PAH may improve early diagnosis and lead to better treatments for this devastating disease. Two studies in *Respirology* in 2013 made significant contributions to understanding of the pathophysiology of this complex condition.

Kabata *et al.*¹⁰⁵ report that the prevalence of mutations in the gene for bone morphogenetic protein receptor type 2 (a receptor associated with the abnormal proliferation of pulmonary vascular smooth muscle cells and endothelial cell dysfunction) was similar in Japanese patients with PAH when compared with that reported in other populations. Furthermore, long-term survival in PAH was unaffected by mutation status.¹⁰⁵ In contrast, Edwards *et al.*¹⁰⁶ investigated changes in peripheral lymphocytes in patients with idiopathic PAH and connective tissue disease associated PH compared with healthy controls and correlated these changes with transplant free survival. The study demonstrates that deficient levels of cytotoxic CD8+ T-lymphocytes and natural killer cells in patients with PAH are associated with increased risk of death. The authors suggest that larger studies are needed to investigate the phenotypes of these cells in different disease severities and to explore the potential for therapy.¹⁰⁶

Health status and mortality prediction

A number of validated instruments are available to assess health status and to predict mortality and guide health care in patients with respiratory disease.¹⁰⁷ Two recent additions to this group of measurement tools are the COPD assessment test²³ that measures health status and the Simplified Acute Physiology Score 3, which was developed to predict mortality in critically ill patients.^{108,109} In two original studies in *Respirology* this year, Kon and colleagues¹¹⁰ reported that the COPD assessment test is responsive to pulmonary rehabilitation in respiratory disease patients without COPD and correlates with the different domains of the validated chronic respiratory disease questionnaire,¹¹¹ supporting that it is a practical alternative to more traditional measures. In contrast, Lim *et al.*¹¹² demonstrated that the general and Australasia Simplified Acute Physiology Score 3 shows poor calibration (defined as agreement between individual probabilities and actual prognosis outcomes) in Korean intensive care unit patients. However, by utilizing data from the initial development cohort, customization of the questionnaire showed good discrimination and calibration clearly demonstrating that prediction models need to be customized for use within different regions of the world.¹¹²

Hypoxaemia

Patients with respiratory disease are at risk of hypoxaemia especially during periods of increased metabolic demand such as exercise, and there is considerable need for accurate measurements of arterial oxyhaemoglobin saturation. Wilson and colleagues¹¹³ compared simultaneous oxyhaemoglobin saturation using pulse oximetry measurements (S_pO_2) at the forehead and finger in patients with COPD who desaturate during exercise. S_pO_2 values were compared with arterialized capillary samples measured before and during treadmill walking. The authors demonstrate that compared with arterialized samples, S_pO_2 was 2% lower and 2% higher with finger and fore-

head oximetry, respectively. The authors correctly state that arterialized capillary blood commonly has slightly lower oxygenation than arterial values¹¹³ suggesting that the forehead measurements are likely more accurate. However, as an arterial sample was not measured, a definitive answer cannot be ascertained. Nevertheless, these data are important as they suggest that there is a considerable need to standardize sensor types if comparisons between centres and patients are to be accurately made.¹¹³

While there are a number of potential ways to predict the extent of hypoxaemia, a patient may experience during air flight,^{114–116} the gold standard is currently the hypoxic inhalation test (HIT) that exposes patients to a similar inspired fraction of oxygen to that experienced in a regular aircraft cabin. However, HIT is only available in specialized pulmonary function testing laboratories and is not readily available to many patients with respiratory disease who would like to travel. As such, Ling *et al.*¹¹⁷ assessed whether oxyhaemoglobin saturation during HIT was associated with S_pO_2 measured at rest or following 2 min of stepping exercise, vital capacity and/or DL_{CO} in patients with respiratory disease. S_pO_2 after exercise correlated with S_pO_2 during HIT and was reported to be a better predictor of HIT S_pO_2 than resting S_pO_2 , spirometric lung function variables or DL_{CO} . Utilizing multiple linear regression, Ling *et al.*¹¹⁷ present an equation incorporating forced vital capacity as well as resting and post-exercise S_pO_2 that could be useful for predicting HIT S_pO_2 when this specialized test is not available.

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