Clinical highlights from the 2013 ERS Congress in Barcelona

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ABSTRACT This article reviews a selection of scientific presentations in the area of clinical problems, which were presented at the 2013 European Respiratory Society Annual Congress in Barcelona, Spain. This article discusses the most relevant topics of interest in the field of clinical respiratory medicine, including breakthrough reports and studies of particular interest to the healthcare professionals. Topics are presented and discussed in the context of the most up-to-date literature, including basic science and translational research. In particular, the reviewed topics deal with the areas of complex chronic obstructive pulmonary disease and asthma (even in the primary care setting), idiopathic pulmonary fibrosis (pathogenesis and therapy), advances in functional chest imaging, interventional pulmonology, pulmonary rehabilitation and chronic care.

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Introduction

The 2013 European Respiratory Society Annual Congress was held in Barcelona, Spain. This meeting is the largest worldwide in the field of respiratory medicine, with around 20 000 attendees each year. This year, a total of 4 401 abstracts were presented (77% acceptance rate), of which 50% dealt with clinical problems. Furthermore, outstanding lectures based on the most recent clinical updates were presented by international experts [1–4]. This article summarises the most relevant topics of interest in the field of clinical respiratory medicine.

Update in COPD management and comorbidities

Lopez-Campos *et al.* [5] evaluated the adherence to the Global Initiative for Chronic Obstructive Disease document for chronic obstructive pulmonary disease (COPD) exacerbations in 16 018 patients from 13 European countries. Spirometry at admission was available in only 59.4% of cases, and noninvasive ventilation was given in only 51% of the cases with a pH <7.35 and arterial carbon dioxide tension >6 kPa. Vincken *et al.* [6] led a cross-sectional study among randomly selected general practitioners who completed a questionnaire on management of patients with recently diagnosed COPD. General practitioners reported good compliance with guidelines (83%), and an appropriate step-up treatment (89%). However, 65% had followed spirometry training, and only half of COPD diagnoses were based on spirometry. Influenza and pneumococcal vaccination were performed in 84% and 72% of patients, respectively. Saleh *et al.* [7] also used the European COPD Audit database to study the risk of pneumonia in COPD patients treated with long-term inhaled steroids. 57.3% of patients were treated with a combination of long-acting β-agonist (LABA)/inhaled corticosteroids (ICS) prior to admission. Pneumonia was diagnosed in 17.9% of LABA/ICS users *versus* 19.4% of non-users (OR 0.90, 95% CI 0.83–0.98).

Martinez LLorens *et al.* [8] studied the role of sex in phenotypes in a group of 40 COPD patients. Female patients complained of more symptoms and exhibited lower exercise capacity and quadriceps force than males. This may partially be due to the vastus lateralis muscle injury and regenerations phenomena that appeared to be more evident in female COPD patients.

Suzuki *et al.* [9] studied the association between plasma amino acid levels and 5-year lung function decline in in 220 COPD patients. A multivariate regression analysis demonstrated that a decrease in proline was significantly associated with annual decline in forced expiratory volume in 1 s, independent of body mass index (BMI) and body weight loss. So, an altered plasma amino acid profile may be important to predict natural history of COPD. However, the underlying mechanisms remain unclear.

The ACCESS (Acute Candesartan Cilexetil Therapy in Stroke Survivors) study showed that about half of the 3792 primary care COPD patients had pre-defined cardiovascular disease, such as coronary artery disease (25%), peripheral vascular disease (14%), myocardial infarction (8%) and/or stroke (5%) [10]. Moreover, the 2-year mean rate of severe exacerbations requiring hospitalisation was significantly higher in COPD patients with cardiovascular diseases *versus* those without [10]. Sprooten *et al.* [11] found that diffusing capacity of the lung for carbon monoxide (HR 0.98, 95% CI 0.968–0.994) and pre-existing cardiac comorbidities (HR 1.71, 95% CI 1.011–2.878) were independent risk factors for hospital readmissions in 245 COPD patients. Verduri *et al.* [12] investigated the coexistence of left ventricular dysfunction in 70 stable COPD patients and airway obstruction in 124 subjects with chronic heart failure. Surprisingly, ventricular dysfunction was not detected in COPD, whereas airway obstruction occurred in 34% of chronic heart faliure subjects.

Sobradillo *et al.* [13] performed an observational study including 186 COPD and 112 non-COPD patients. The indication for using β-blockers were ischaemic heart disease or heart failure (left ventricle ejection fraction <40%). The use of β-blockers was significantly higher in non-COPD (99%) *versus* COPD (61%) patients. The proportion of patients with ⩾2 exacerbations per year was higher in the COPD group without β-blockers (29% *versus* 13%, p=0.026). Thus, β-blockers may have a protective effect on the development of complications and exacerbations.

Rehabilitation and chronic care

Pulmonary rehabilitation and chronic care have received a lot of attention in the literature [14–28]. In turn, several interesting research abstracts were presented at the 2013 European Respiratory Society Congress, of which many were on the topic of comorbidities [29–33]. For example, the baseline findings of the ongoing ERICA (Evaluating the Role of Inflammation in Chronic Airways Disease) study revealed that increased arterial pulse wave velocity (>10 $m \cdot s^{-1}$) and lower limb muscle weakness (maximal voluntary contraction/BMI ratio <1.2) occurred frequently in patients with COPD, while fibrinogen levels were comparable amongst the groups [34]. Janssen *et al.* [33] showed no association between symptoms of depression and markers of systemic inflammation in 2164 patients with COPD. These findings suggest that the association between extrapulmonary features and systemic inflammatory biomarkers in patients with COPD is not as

straightforward as previously suggested [35]. RUTTEN and co-workers [36, 37] showed that performing domestic activities of daily living resulted in additional enterocyte damage in patients with COPD but not in the non-COPD controls, indicating functional alterations of the gastrointestinal tract in the COPD patients.

VAN REMOORTEL *et al.* [38] found that physical inactivity and smoking, but not airflow obstruction, appeared to be the main determinants for the presence of two or more comorbidities [39]. Thus, physical inactivity seems to be an important outcome measure and a potential treatment target in patients with COPD. Therefore, it is important to understand the determinants of moderate-to-vigorous physical activity in patients with COPD [40, 41]. Using data from the Copenhagen City Heart Study, VAES *et al.* [42] reported a longitudinal decrease in self-reported physical activity in patients with COPD, which was less obvious in a non-COPD control group. Therefore, physical activity needs to be assessed and stimulated by healthcare professionals in patients with COPD [43].

SILLEN and co-workers [44–46] showed that dyspnoeic COPD patients with lower limb muscle weakness at baseline retain the ability to improve lower limb muscle function and exercise capacity following 8 weeks of high-frequency neuromuscular electrical stimulation or strength training. AREVALO *et al.* [47] also showed an improvement in muscle strength and exercise performance using elastic tubing (*i.e.* using an elastic band for resistance training instead of usual hand-held weights). In contrast, early pulmonary rehabilitation following hospitalisation for exacerbations of chronic respiratory disease, including a home component, did not accelerate recovery in functional exercise performance compared to usual care [48]. The underlying reasons for failure remain to be determined.

Chest imaging

Morphological and functional imaging

We cannot escape the impression that there is a revival of interest into conventional chest radiography. A study of general practitioners showed that radiographic verification in the diagnosis of pneumonias is necessary to reduce false clinical negatives [49]. Chest radiography has been used for over a century to diagnose pulmonary tuberculosis. PINTO *et al.* [50] reviewed the scoring systems for the diagnosis of pulmonary tuberculosis and concluded that most such scoring systems are intended to assess the need for respiratory isolation.

SMARGIASSI *et al.* [51] reviewed the role of chest ultrasound in the management of respiratory diseases and proposed a grading system for free-flowing pleural effusions. CHERNOVA *et al.* [52] showed that parameters (shape, location, extent, wall thickness and type of narrowing) of the multi-detector computed tomography scan systems, supplemented by the variability obtained during inspiration and expiration, can play an important role in the choice of surgical treatment of tracheomalacia due to cicatricial trachea stenosis in a cohort mostly consisting of patients with an iatrogenic tracheal injury during mechanical lung ventilation. DIAZ *et al.* [53] quantified the upper airways in patients with COPD using multi-slice computed tomography (MSCT)-based airway dimensions (*e.g.* wall volume, lung volume and emphysema measurements). Airway length increased with COPD severity and hyperinflation. This was accompanied by reductions in lumen volume with negligible changes in wall volume. Thus, smoking induces mechanical deformation of the airways and there is no gain of mural tissue.

ALIVERTI *et al.* [54] quantified lung parenchyma emphysema using MSCT scans acquired at both total lung capacity and residual lung volume. A so-called specific gas volume map at three levels (aortic arch, carina and 1 cm above diaphragm) was constructed [54]. This application is useful for evaluating the different stages and types of emphysema, and in evaluating either pharmacological or surgical treatments.

Lung nodule evaluation

HOREWEG *et al.* [55] evaluated the three rounds of the NELSON (Dutch-Belgian Randomized Lung Cancer Screening Trial) lung cancer screening trial. However, the screening debate will be ongoing as many issues, such as cost-effectiveness, radiation risk, adverse events from additional diagnostic testing, ability to reproduce trial results, effects of screening on smoking cessation rates and the effects of false-positive results, need to be resolved. The volume doubling time strategy can avoid over-diagnosis in lung cancer screening [56]. We must be aware that screening can rapidly change in clinical management, even if we are dealing with a slow-growing lung cancer [57].

Other techniques

KUBALE *et al.* [58] presented shear wave transthoracic ultrasound imaging as a potential tool for analysing early fibrotic changes in the subpleural space (fig. 1). Although these elastographic measurements showed a great variation, semi-quantitative analysis in comparison with high-resolution computed tomography is useful for follow-up. ZHANG *et al.* [59] differentiated normal lung tissue from idiopathic pulmonary fibrosis

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(IPF) or acute respiratory distress syndrome using this new noninvasive method. Recently published data of YSERBYT *et al.* [60] on pulmonary confocal laser endomicroscopy of distal airways confirmed that this is a promising new technique for the *in vivo* evaluation of the respiratory tract and the three-dimensional characteristics of the pulmonary acinus. HORN *et al.* [61] used hyperpolarised ^{3}He gas ventilation magnetic resonance imaging (MRI) to map bronchodilator treatment response in COPD. This concept is able to regionally resolve changes in lung ventilation in response to therapy in COPD [62]. Oxygen enhancement at MRI is an alternative modality to map bronchodilator treatment response. Using oxygen enhancement at MRI, ZHANG *et al.* [63] found a heterogeneous pattern of decreased lung oxygenation in severe asthmatics in response to salbutamol due to the so-called ventilation/perfusion imbalance. KIRBY *et al.* [64] found similar results using hyperpolarised ^{3}He with diffusion-weighted MRI.

Interventional pulmonology

Procedures for diffuse parenchymal lung diseases

Three studies compared cryobiopsy with conventional forceps for the diagnosis of diffuse parenchymal lung diseases showed a two-fold higher diagnostic yield with similar safety profiles [65–67]. Notwithstanding, surgical lung biopsy (SLB) still remains the gold standard for the diagnosis of diffuse parenchymal lung diseases. TOMASSETTI *et al.* [68] presented the first study comparing the effectiveness of cryoprobe or SLB in the multidisciplinary diagnostic approach to IPF in 117 patients with possible or inconsistent usual interstitial pneumonia (UIP) pattern on the computed tomography scan. Patients underwent cryobiopsy (50%) or SLB (50%) for definite diagnosis. Two clinicians, two radiologists and two pathologists reviewed the single cases. 55 (93%) and 58 (98%) samples were diagnosed using cryoprobe or surgery, respectively, and UIP pattern was detected with a high confidence level in 51% and 84% of cases, respectively. The change of initial consensus at diagnosis by the multidisciplinary diagnostic team following the procedure was not statically different, and nor was the 90-day mortality (1.7% and 3.4% for cryobiopsy and SLB, respectively). Similar findings have been reported by HAGMEYER *et al.* [69]. Although inconclusive, cryobiopsy may play a relevant and promising role in the diagnostic work-up of diffuse parenchymal lung diseases, especially in severe patients at high risk for SLB.

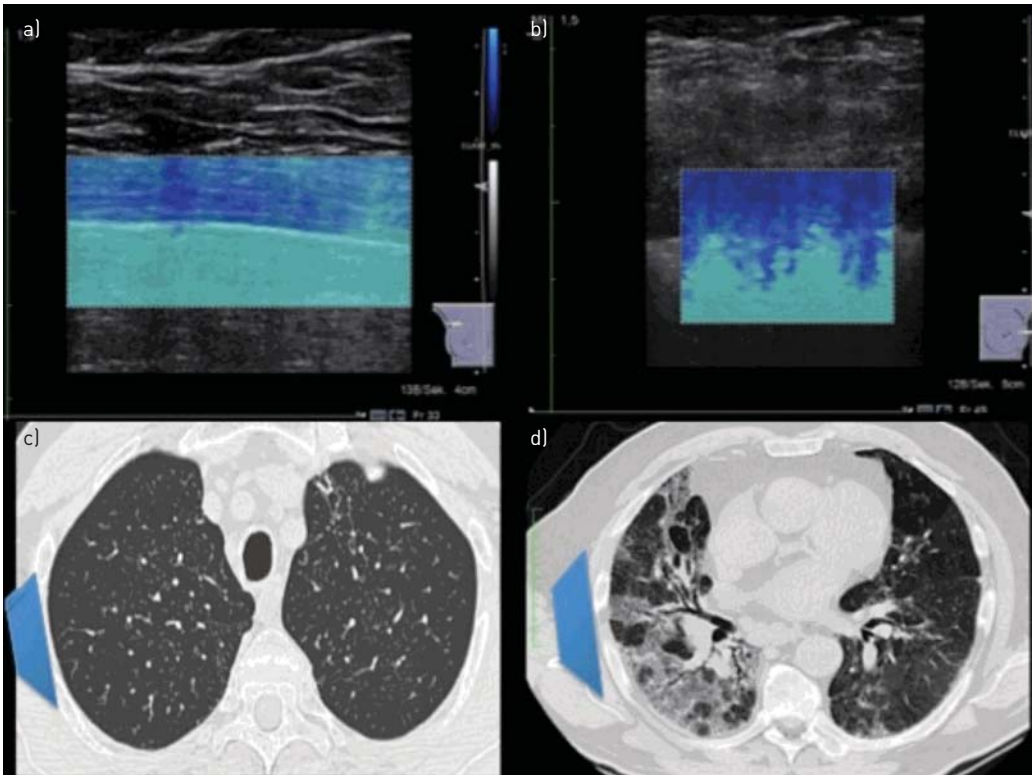

FIGURE 1 a, b) Displacement map measured by shear wave elastography showing a reduced displacement (dark blue) of subpleural structures in idiopathic pulmonary fibrosis (right) compared with normal displacement of normal lung (light blue). c, d) Two slices from the patients computed tomography scan. Reproduced from [58].

Volume reduction in obstructive lung diseases

The best evidence on efficacy and safety of lung volume reduction coil treatment comes from seven European studies involving approximately 300 patients [70–76]. Images of a single coil commonly used for this procedure and a patient's chest radiograph showing coils *in situ* are shown in figure 2. Overall, significant improvements in lung volume, exercise capacity and quality of life were observed after 3–6 months of follow-up with an acceptable safety profile in patients with homogeneous or heterogeneous emphysema, irrespective of collateral ventilation. Data on long-term efficacy were reported in two of these studies [70, 71] showing significant benefits in the first 6-month period which were sustained up to 1 year.

SCHUHMANN *et al.* [77] compared unilateral complete occlusion and bilateral partial occlusion endobronchial valve treatments using quantitative computed tomography, and concluded that complete occlusion was essential to achieve effective response. BALDI *et al.* [78] concluded that patients showing a change of inspiratory capacity >10% achieved a better effect than those without.

Diffuse parenchymal lung diseases

The incidence of IPF is not yet well known. To date, the majority of available data are from studies performed in the USA and northern Europe [79, 80]. PORRETTA *et al.* [81] estimated that annual IPF incidence in Italy ranged between 750 000 and 490 000. Incidence increased in males and people aged >75 years. In France, DUCHEMANN *et al.* [82] reported a prevalence and incidence in interstitial lung diseases (ILDs) of 48.8 and 16.1 per 100 000 per year, respectively. Sarcoidosis was the most frequent (44%; 20 per 100 000), followed by ILDs of known cause (30%; 13.3 per 100 000), and idiopathic interstitial pneumonia (15%; 6.8 per 100 000).

Idiopathic pulmonary fibrosis

Epigenetic and genetic abnormalities, senescence-related processes, altered cell-to-cell communications, uncontrolled proliferation, and abnormal activation of specific signal transduction pathways are biological hallmarks that characterise the pathogenesis of IPF and link this disorder to lung cancer [83]. Differential regulation of transforming growth factor-α, the Wnt protein signalling pathway and the cell signalling Notch pathway was recently identified by transcriptome profiling of normal appearing, microdissected alveolar septae from IPF lungs [84]. PISKULAK *et al.* [85] showed that there were no significant changes in the expression of Notch receptors and ligands on mRNA level in lung homogenates of organ donors and IPF patients. At the protein level, however, the receptor Notch1 (NICD1) and the Notch ligand Delta1 were found to be up-regulated in lungs of IPF patients and bleomycin-challenged mice. KORFEI *et al.* [86] showed a reduced expression of telomerase reverse transcriptase and the telomerase RNA component in club cells in lung tissue of IPF patients. Mucin 5B (MUC5B) promoter polymorphism was significantly associated with IPF but not systemic sclerosis or sarcoidosis [87]. The frequency of the MUC5B promoter polymorphism rs35705950-T allele was significantly higher in a German cohort of patients with IPF or nonspecific interstitial pneumonia (NSIP) than in healthy subjects [88]. However, in the Japanese cohort, the frequency of the rs35705950-T allele tended to be higher in patients with IPF than in healthy patients ($p=0.068$), but the NSIP patients and the healthy patients did not differ in this regard [88].

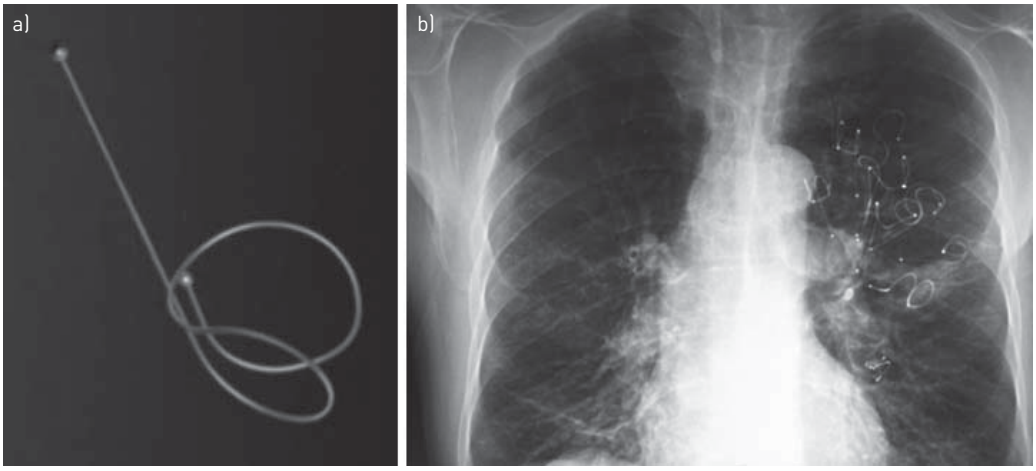

FIGURE 2 a) An example of a single coil used for the procedure. b) A chest radiograph from a patient showing the positioning of eight coils after the procedure.

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In patients with IPF, following a phase II randomised controlled trial which identified a reduction in the rate of decline in forced vital capacity and frequency of acute exacerbations in patients treated with pirfenidone, three phase III randomised controlled trials were then conducted. The results from these trials allowed pirfenidone use for the treatment of patients with mild-to-moderate IPF in a large number of countries [89]. Consistent data on the use and utility of pirfenidone in daily clinical practice were reported at the 2013 Annual European Respiratory Society Congress [90, 91].

Sarcoidosis and other diffuse parenchymal lung diseases

VORSELAARS *et al.* [92] assessed the relapse rate after discontinuation of infliximab in a cohort of 47 sarcoidosis patients. Kaplan-Meier analysis revealed a median time to relapse of 11.1 months.

VIAL-DUPUY *et al.* [93] presented an analysis of medical records of 16 patients with an acute drug-induced pneumonia admitted to an intensive care unit between 2002 and 2012. The drugs responsible were mainly amiodarone (n=5) and cytotoxic drugs (n=4). The predominant computed tomography scan pattern in all cases was ground-glass opacity, with additional honeycombing in two scan patterns and occasional reticulations and/or condensations in the others. 10 (62%) subjects required mechanical ventilation (invasive: n=8; noninvasive: n=2). The intensive care unit mortality rate was 25%, reaching 50% in intubated patients. Thus, prognosis of drug-associated acute respiratory failure is severe, particularly in subjects requiring ventilation.

General practice and primary care

Respiratory symptoms and management of COPD

CASEY *et al.* [94] randomly assigned 178 patients with COPD to an 8-week structured education programme delivered by a practice nurse and a physiotherapist, and assigned 172 patients to usual care. Patients allocated to the intervention had a significantly higher mean change in total Chronic Respiratory Questionnaire scores and the programme was feasible in primary care [95].

JONES *et al.* [96] found that the composed indices DOSE (dyspnoea score, obstruction, smoking status, exacerbations) and ADO (age, dyspnoea, obstruction) were associated with health status (by Chronic respiratory Questionnaire and St George's Respiratory Questionnaire) and predicted mortality in >5000 patients with COPD from the UNLOCK (Uncovering and Noting Long-term Outcomes in COPD to Enhance Knowledge) study.

FERNANDES *et al.* [97] evaluated the differences in risk factors, respiratory symptoms and lung function in females and males with a diagnosis of COPD in India. The prevalence of smoking (males: 100%; females: 2%) and exposure to biomass smoke (males: <1%; females: 59%) differed significantly, while lung function and daily symptoms were similar.

KRUIS *et al.* [98] showed that six large randomised controlled trials included more males, and that patients had lower lung function, more pack-years and more exacerbations per year compared to 3500 COPD patients from seven primary care databases.

Treatment and management of asthma

In a cluster randomised trial in 611 asthma patients, HONKOOP *et al.* [99] compared asthma-related quality of life and exacerbation incidence of three treatment strategies: partial control by the asthma control questionnaire (ACQ) (<1.50); strict control by the ACQ (<0.75); or strict control guided by the ACQ (<0.75) and exhaled nitric oxide (*Fe*NO; <25 ppb). Therapy was adjusted every third month based on ACQ, spirometry and *Fe*NO. After 12 months follow-up there was no difference in asthma-related quality of life or exacerbations rate. So, a treatment strategy aimed at strict asthma control, with or without *Fe*NO guidance, did not improve asthma treatment.

VAN DER MOLEN *et al.* [100] described asthma control, symptoms and exacerbations across different treatment levels in 4330 patients with asthma. Global Initiative for Asthma defined asthma control levels were low and the incidence of exacerbations was independent of treatment level. REDDEL *et al.* [101] studied factors associated with ownership of written asthma action plans in 2610 patients aged ⩾16 years with current asthma. Patients with a written asthma action plan are more likely to follow it if they were older, had higher health literacy, or felt that the action plan was practical, easy to understand or personalised towards them.

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