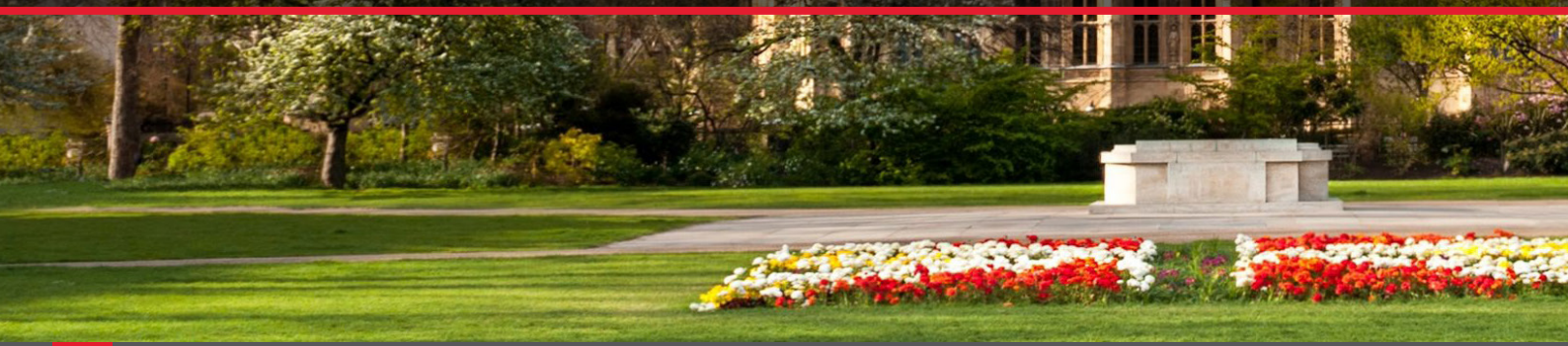
EMJ EUROPEAN MEDICAL JOURNAL

RESPIRATORY

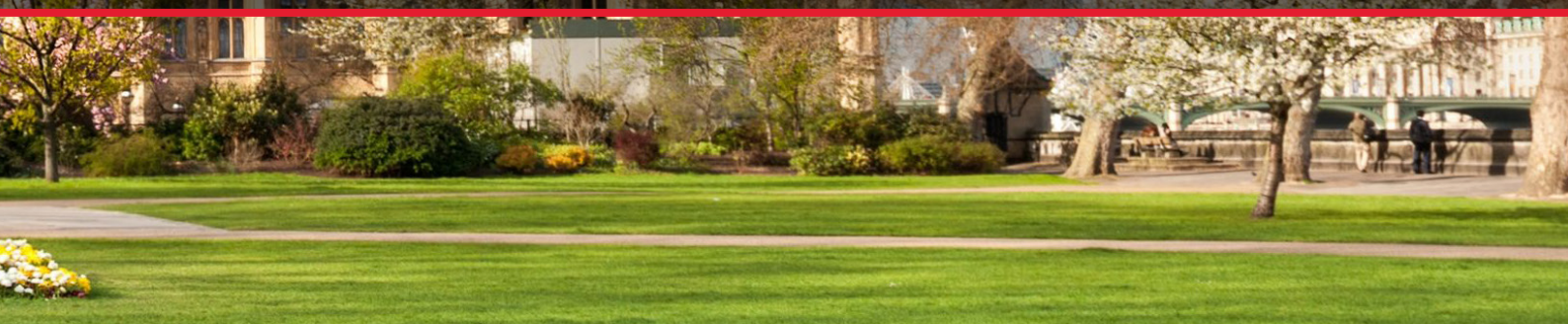
ISSN 2054-3166 — Vol 4.1 • October 2016 • emjreviews.com

INSIDE
Review of
ERS 2016
London, UK

CONTENTS



RESPIRATORY



Editorial Board

Respiratory

RESPIRATORY 4.1
OCTOBER 2016

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

Published by the European Medical Group
The MedBIC, Anglia Ruskin University, Chelmsford, CM1 1SQ

Welcome

Welcome to *EMJ Respiratory 4.1*. As ever, this journal is filled with all the latest information and updates from the field of respiratory medicine; inside we present our in-depth review of the European Respiratory Society (ERS) International Congress, as well as abstract reviews, peer-reviewed articles, and a series of fascinating interviews with some of the internationally renowned members of our Editorial Board.

Held in the city of London, UK, from 3rd–7th September, this year's ERS Congress focussed on the topic of air pollution as a major discussion point. Educational and promotional activities were provided to assist doctors in providing patients with all the information they require to maintain healthy lungs in the face of significant levels of air pollution. This year's congress was busier than ever, with 21,638 attendees and 4,100 abstracts presented. In our congress review section, you can read our pick of the most exciting research and information presented at this year's event, including a possible link between menopause and decreased lung function, how exposure to traffic pollution may affect sleeping habits, as well as many more interesting and relevant stories.

Alongside our congress review highlights, we are proud to bring you interviews from members of our esteemed Editorial Board. In these, members provide some of their thoughts, views, and career highlights, as well as their advice for medical students considering a career path in the field of respiratory medicine.

As always, we present a selection of high-quality peer-reviewed articles from across the field for your reading enjoyment. Migliore discusses the recent advancements in the area of thoracic surgery and lung transplantation, and the possible impact these may have in the future. Gemine and Lewis consider the growing body of evidence that suggests smoking cessation should be prioritised in patients who have been diagnosed with lung cancer, and in our editor's pick, Stoleski et al. evaluate the prevalence of chronic respiratory symptoms, lung function impairment, and chronic obstructive respiratory diseases in crop farmers.

We trust that you will enjoy reading this edition of *EMJ Respiratory*, and that the articles, abstracts, interviews, and congress review highlights prove of assistance to you in your own daily practice. Next year, we are looking forward to attending the 2017 ERS Congress in Milan, Italy, and bringing you further insights and developments in the field!

Spencer Gore

Director, European Medical Journal

European Medical Journal Respiratory is published annually.
For subscription details please visit www.emjreviews.com

Front cover and contents photograph: London, UK, home of ERS 2016.

Solutions to help increase clinical confidence for early detection and disease management.

LEARN

How Advanced ultrasound needle guidance techniques could help you assess patients with suspected lung cancer in performing biopsies with even greater precision than before. If you missed to pick up the testimonial: LOGIQ™ E9 with XDClear™, Contrast-Enhanced Ultrasound-Guided Biopsies at Odense University Hospital, Denmark during ERS @ the GE booth.

DOWNLOAD

Download your copy here

DISCOVER

The handheld, first of its kind 2-in-1 probe, pocket-sized visualization tool, the Vscan with Dual Probe, always connected and ready to scan. Due to its ease of use and its high diagnostic yield, hand-carried ultrasound (HCU) systems of the latest generation constitute a helpful technique for the primary assessment of pleural effusion (PE).*

DOWNLOAD

Download the Vscan™ with Dual Probe interactive Brochure

CONTACT US

If you want to learn more about our solutions and offerings in respiratory medicine.

CONTACT US

Imagination at work

*Schleder S, Dornia C, Poschenrieder F et al. Bedside diagnosis of pleural effusion with a latest generation handcarried ultrasound device in intensive care patients. Acta Radiol 2012;53:556_60.

JB43403XE

Foreword

Dr Antonio Rossi

Division of Medical Oncology, S.G. Moscati Hospital, Avellino, Italy

Dear Colleagues,

I am honoured to welcome you to this edition of *European Medical Journal Respiratory*, which will focus on the most important advances in the field of respiratory health.

Several interesting topics are discussed in the present issue by leading authorities in the field. Read about the correlation between a higher prevalence of respiratory symptoms, lung function impairment, and chronic respiratory diseases with occupational exposure among crop farmers; and digest a case of systemic lupus erythematosus complicated with pneumonia and severe respiratory failure. One updated review, looking at the growing body of evidence, further stresses that stopping smoking following lung cancer diagnosis can lead to better treatment responses, fewer treatment complications, and less recurrence of new tumours, translating into reduced mortality. A further review discusses the epidemiology, diagnosis, and therapy of increased arterial stiffness in patients with chronic obstructive pulmonary disease. Other articles report on tubeless thoracic surgery, representing an unexplored and promising field, and discuss whole-lung lavage treatment resulting in an effective method against pneumoconiosis.

The annual European Respiratory Society (ERS) International Congress, which took place in London, UK, between 3rd–7th September 2016, is strongly featured in this eJournal. The most important developments regarding respiratory diseases were presented at this international meeting, which gave the opportunity to share news among a diverse array of professionals from all over the world and involved in the clinical practice management of respiratory medicine. Basic science and clinical respiratory medicine were widely discussed throughout its impressive scientific programme.

I would like to thank the very knowledgeable Editorial Board and staff of *EMJ Respiratory*, the renowned experts in respiratory disease management, for their efforts and guidance; I look forward to their constant support of the journal in the forthcoming years.

On behalf of everyone at EMJ, I wish to thank all authors who contributed with their professionalism to the publication of this stimulating new issue of *EMJ Respiratory*.

Finally, I wish all readers a pleasant and informative read.

Yours sincerely,

Antonio Rossi

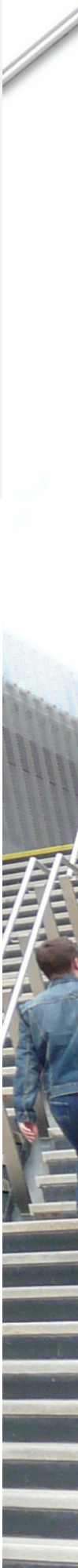
Division of Medical Oncology,
S.G. Moscati Hospital, Avellino, Italy


EXCEL
LONDON
East Entrance
ICC

ERS ANNUAL CONGRESS 2016

EXCEL CONFERENCE CENTRE,
LONDON, UK
3RD–7TH SEPTEMBER 2016

Welcome to the *European Medical Journal* review of the 26th Annual Meeting of the European Respiratory Society International Congress



The city of London, UK, was an apt choice of host city for the European Respiratory Society (ERS) congress this year as a major discussion point at the congress was air pollution. London is one of the busiest cities in the world and air pollution has been both a concern and a hotly debated topic for many years. Indeed, the Mayor of London, Sadiq Khan, recently commented on the effect air pollution in the city has had on his own personal health. On this note, the ERS 2016 congress included many educational and promotional activities to enable doctors to provide patients with all the information required regarding the maintenance of healthy lungs in spite of significant levels of air pollution. It was therefore appropriate that London, host to the most polluted street in the world (Oxford Street), became the perfect backdrop to launch the 'healthy lungs for life' campaign to develop awareness of lung disease and prevention of lung damage. Having begun in 2014, the theme of the campaign in 2016 is 'Breathe Clean Air'.

This year's event was busier than ever, indicative of the growth of the ERS; 21,638 attendees were present at the congress. On top of this, 4,100 abstracts were presented of the 5,633 that were originally submitted, including 166 late breaking abstracts. A selection of the sessions at the congress were streamed live to a number of 'hubs' across the globe and many of the sessions were also made available as a video download. Thousands of downloads were recorded on just the first day, giving a positive outlook for the future of dissemination of respiratory research regardless of whether people can attend a congress or not.

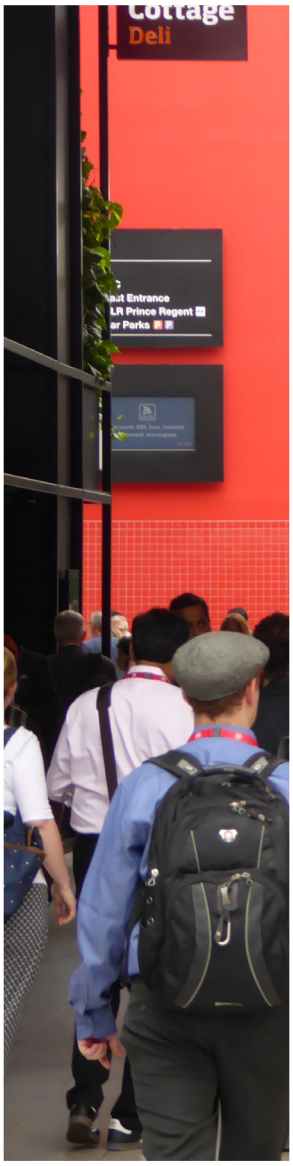
The ERS President, Prof Jørgen Vestbo, discussed the role of the society in advocating for the public at both a national and international level: "It is very important for us to mainly lobby for respiratory medicine, for lung health, in Europe and beyond. If we look back at the year that has passed I would like to highlight two things where I think we have made a difference. First of all, we have been very active together with other societies and with the Wellcome Trust to try and affect the decisions made in the European Union (EU) on the EU data directive, things that potentially could have harmed research tremendously. We have also been involved with partners in having a plain packaging event in the European

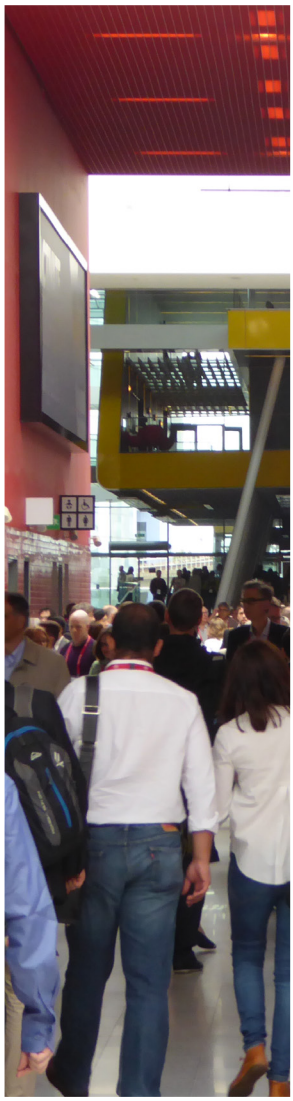
parliament; we believe that smoking cessation starts very early on and we need to prevent children from taking up smoking, and one of the ways of doing it is to advocate for plain packaging. We are very happy that several European countries have already done legislation."

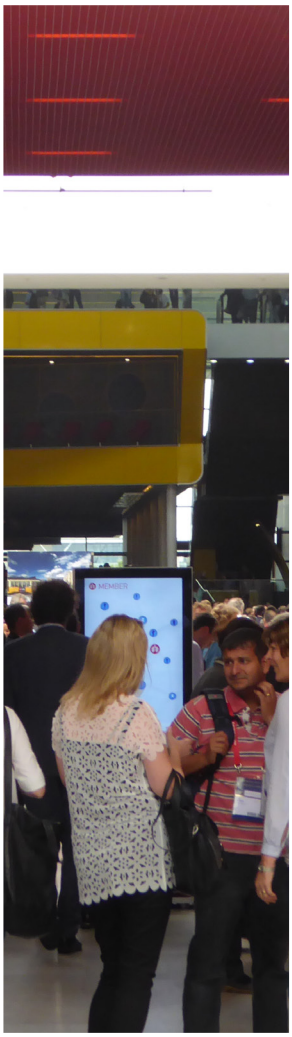
During the opening ceremony, a number of prizes were awarded for individuals' contributions to the field of respiratory health. In one notable example, Sir Malcolm Green was presented with the Congress Chair Award for his commitment to the care of patients, research, and teaching of trainees. Sir Green is well-known for his role in the founding of the British Lung Foundation. He has also been directly involved in many discoveries in both respiratory physiology and in developments in clinical practice.

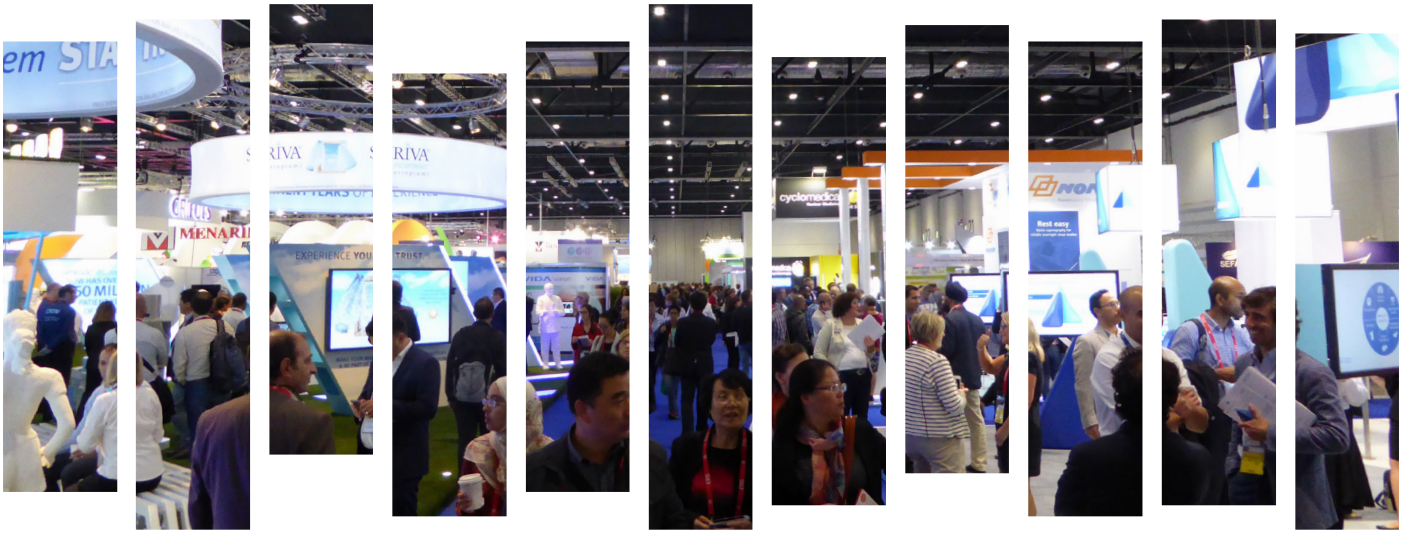
> "It is very important for us to mainly lobby for respiratory medicine, for lung health, in Europe and beyond."

In this issue of *EMJ Respiratory*, we provide a review of the most impactful research from the congress as well as summaries of presentations made this year direct from the speakers. We hope this gives you an insight into the latest in respiratory medicine and will be useful in your practice going forward.









Diagnosis of Long-Term Lung Diseases Now Aided by Artificial Intelligence

POTENTIAL has been found for using artificial intelligence to heighten the accuracy of lung disease diagnoses, according to a ERS press release dated 4th September 2016. This is a significant step forward from the methods currently used which include spirometry tests, body plethysmography tests, and diffusion tests.

> “Not only can this help non-experienced clinicians, but it also has many benefits for healthcare overall as it is time-saving in achieving a final diagnosis, as it could decrease the number of redundant additional tests clinicians are taking to confirm the diagnosis.”

A study was carried out which included 968 individuals, all of whom were undergoing their first complete lung function test. Lung function tests were performed on the patients whilst the diagnosis was agreed upon by a group of expert clinicians. The researchers then tested whether ‘machine learning’ could be used to interpret the data from these tests. An algorithm was developed by the team which considered patients’ smoking history, body mass index, and age in order to predict the most probable diagnosis.

The algorithm led to the correct diagnosis of 38% of the patients; chronic obstructive pulmonary disease was correctly identified in 74% of patients; however, all other diseases were less successfully identified. The senior author of the study, Prof Wim Janssens, Faculty of Medicine, University of Leuven, Leuven, Belgium, commented: “The beauty of our development is that the algorithm can simulate the complex reasoning that a clinician uses to give their diagnosis, but in a more standardised and objective way so it removes any bias.”

An attractive quality of artificial intelligence is its ability to interpret a whole host of patterns at one time to give a more accurate diagnosis. The first author of the study, Dr Marko Topalovic, Faculty of Medicine, University of Leuven, Leuven, Belgium, stated: "The benefit of this method is a more accurate and automated interpretation of pulmonary function tests and thus better disease detection. Not only can this help non-experienced clinicians, but it also has many benefits for healthcare overall as it is time-saving in achieving a final diagnosis, as it could decrease the number of redundant additional tests clinicians are taking to confirm the diagnosis."

Link Found Between Breastfeeding and Infant Asthma Risk

INFANTS could be protected from developing respiratory symptoms if they are breastfed, according to a ERS press release dated 4th September 2016. Chromosome 17 is the location of the 17q21 genes which are associated with an increased risk of developing asthma, and a recent study discovered that children who have variants of these genes have an amplified chance of acquiring wheeze.

The study aimed to discover whether a different variable, outside of the widely recognised environmental factors associated with the development of respiratory symptoms, such as breastfeeding, could have an effect on the specific gene associated with the progression of asthma. The study included 368 infants from the Basel-Bern Infant Lung Development birth group in Switzerland, upon whom genotyping and breastfeeding status were performed and from whom data was collected regarding occurrence and severity of respiratory symptoms.

It was found that during the weeks in which the infants were breastfed, those carrying the asthma risk genotypes had a 27% decreased risk of acquiring respiratory symptoms. Among those who were not breastfed, the carriers showed an increased risk of respiratory symptoms. Dr Olga Gorlanova, Pneumology Research Group, Children's Hospital Basel and the University of Basel, Basel, Switzerland, who discovered the association explained: "Our study is the first to show that breastfeeding can modify the effect of asthma-related genetic profiles on respiratory symptoms in the first year of life."

> "Our study is the first to show that breastfeeding can modify the effect of asthma-related genetic profiles on respiratory symptoms in the first year of life."

Consequently, during the first year of life an association between 17q21 variants and respiratory symptoms was not found. However, stratification by breastfeeding status proved that carriers of asthma risk genotypes of the strongest associated single nucleotide polymorphisms (rs7216389; AA and rs4795405; CC) did not suffer respiratory symptoms. In contrast, among those who were not breastfed, the carriers showed an increased risk of symptoms. This lead to a significant interaction effect for both single nucleotide polymorphisms (p-values for interactions 0.003 and 0.010, respectively).

4,100 abstracts submitted

Smaller Fetal Size Increases Risk of Asthma in Children Aged 5–15

ANTENATAL decisions made by pregnant women, such as avoiding smoking and alcohol, eating healthily, and exercising regularly, have been found to give rise to the life-long respiratory wellbeing of children, according to a ERS press release dated 5th September 2016.

Dr Stephen Turner, University of Aberdeen, Aberdeen, UK, and colleagues had previously determined that reduced fetal size during pregnancy increased the risk of asthma in children up to the age of 10. The newer study aimed to test the hypothesis that reduced fetal size reduces lung function and causes persistent asthma in children aged 5–15 years.

...these findings need to be replicated in other cohorts and explore whether fetuses which start small and stay small, or fetuses which become smaller from a normal size before 10 weeks, have the poorer outcomes.

The authors gathered evidence from 2,000 women that had attended the Aberdeen antenatal clinic between 1997 and 1999. Using routine ultrasound scans which recorded fetal size at trimester one (T1) and two (T2) as standard, the authors used generalised estimating equations to measure the relationship between reduced fetal size and asthma at 5, 10, and 15 years.

Z scores were broken down into four to cover the range of abnormally small to abnormally large fetuses. As each z score increased, the risk of asthma at 5, 10, and 15 years decreased (odds ratio: 0.78 [95% confidence interval (CI): 0.63–0.97], p=0.025; n=19). On average, forced expiratory volume in 1 second (FEV_1) z scores increased by 0.13 (95% CI: 0.03–0.22, p=0.007; n=833). In the stratified model, persistent asthma was associated with smaller fetal size in T1, T2, and FEV_1 compared to the previous two groups (n=587). These results were independent of confounders.

The authors concluded that higher z scores in T1 were linked to a 22% lower risk of developing asthma between these ages. Dr Turner explained that these findings need to be replicated in other cohorts and explore whether fetuses which start small and stay small, or fetuses which become smaller from a normal size before 10 weeks, have the poorer outcomes.

Antibiotics Exposure in Early Life Linked to Allergies

OBSERVATIONAL studies have been analysed in recent research to clarify the association between taking antibiotics in early life and developing allergies later in life, as reported in a ERS press release dated 6th September 2016.

Both PubMed and Web of Science databases were used to search for studies linking antibiotic consumption during the first 2 years of life with the subsequent risk of developing eczema or hayfever. In total, 22 studies which comprised 394,517 patients were selected for the examination for eczema and a further 22 studies comprising 256,609 patients were selected for the examination of hayfever. A meta-analysis was performed, calculating ORs for eczema across cohort studies, cross sectional studies, and case control studies, which were: 1.24 (95% confidence interval [CI]: 1.09–1.41; inconsistency [I2]: 60.0%); 1.41 (95% CI: 1.33–1.49; I2: 0.0%); and 1.15 (95% CI: 1.01–1.42; I2: 79.5%), respectively. For hayfever the ORs for the cohort studies, the cross sectional studies, and case control studies were 1.18 (95% CI: 1.01–1.37; I2: 74.3%); 1.56 (95% CI: 1.29–1.90; I2 63.6%); and 1.14 (95% CI: 1.04–1.26; I2: 64.8%), respectively.

The outcomes were wide-ranging with a 15–41% risk of developing eczema and a 14–56% risk of developing hayfever in later life. Moreover, the correlation between taking antibiotics and developing allergies was stronger for those treated with two, rather than one courses of antibiotics for both allergies.

> “Early life exposure to antibiotics is related to an increased risk of both eczema and hayfever later in life.”

The investigators of the study regard the variable results between both allergies to be linked to the immunomodulatory effect of antibiotics and the disturbance of micro-organisms in the gut caused by antibiotics that can lead to a reduced immune response.

Nevertheless, investigators of the study determined that there is indeed a link despite the wide variation in results. Dr Fariba Ahmadizar, Utrecht University, Utrecht, Netherlands, concluded: “Early life exposure to antibiotics is related to an increased risk of both eczema and hayfever later in life.”

Pneumonia in Adults More Likely During School Holidays

PNEUMOCOCCAL community-acquired pneumonia (CAP) was found to be significantly more likely in adults admitted to hospital during school holidays than in those admitted during term-time, according to a ERS press release dated 6th September 2016.

21,638 attendees

As child contact is a risk factor for adult pneumococcal disease, the authors hypothesised that school holidays would be associated with increased rates of adult non-invasive pneumococcal CAP as a result of changes in child contact patterns, and thus the transmission of the bacteria *Streptococcus pneumoniae*.

To put this hypothesis to the test 2,221 adults admitted with CAP were studied prospectively between September 2008 and 2013 in two hospitals that covered the catchment area of Greater Nottingham. In order to determine pneumococcal infection, the organism was identified from sterile sites, and pneumococcal antigen or pneumococcal serotype was detected in urine samples. Overall, 643 (29%) were diagnosed with pneumococcal CAP, with 203 (31.5%) of those diagnosed being admitted during the school holidays.

Using multivariable and Poisson regression models to calculate the odds of pneumococcal CAP and its relative incidence during the school holidays and term-time, an age-adjusted incidence rate ratio of adult pneumococcal CAP was determined as 1.35 (95% confidence interval: 1.14–1.59, p<001), translating as a 35% increase during school holidays.

The author of the study, Dr Priya Daniel, Clinical Research Fellow and Specialist Registrar in Respiratory Medicine, Nottingham University Hospitals Trust, Nottingham, UK, commented: "Our results demonstrate a higher incidence of pneumococcal CAP in adults hospitalised during school holiday periods compared to term-time. Duration and intensity of child contact may play an important role in pneumococcal disease transmission to adults. However, as this is an observational analysis, causality cannot be assumed."

Dr Daniel suggested that adults at higher risk could benefit from a vaccination in accordance with current national guidelines. However, better understanding of the risk factors for adults in developing severe pneumococcal CAP will help in the future targeting of vaccinations to prevent infection.

Lung Disease Risk Increases with Prolonged Cleaning Product Exposure

CLEANING chemicals used by both professionals and regular house cleaners may increase the risk of developing both obstructive and/or restrictive lung disease. Female domestic assistants and other cleaners continuously exposed to harsh products, particularly ammonia-based, are more likely to develop respiratory complications as a result of declined lung function, states research presented at this year's annual ERS International Congress held in London.

> "Cleaning products can put people's heath at risk so people should be aware of the risks and take steps to mitigate against them..."

As part of a European Community Respiratory Health Survey (ECRHS), the respiratory function (forced vital capacity and forced expiratory volume in 1 second) of >5,000 women were analysed across three time points: 1992–1994, 1998–2002, and 2010–2012. Over the course of this survey, individuals were characterised into groups, based on occupational cleaning and whether they would consider themselves the primary cleaner within their home, before spirometry values were obtained and adjusted for factors such as age, height, social class, and number of years between follow-up. Incidences of respiratory irritation and allergic airway disease were also noted.

By the third follow-up, results reflected a significant decline in lung function within those groups of home or work cleaners compared with the included control (non-cleaner) group. Individuals partaking in cleaning professions showed a 17% greater risk of damage, whereas those undertaking regular cleaning within their own homes experienced a 14% greater lung function deterioration across the 20 years assessed.

Previously published studies have already linked occupational cleaning with COPD, asthma, and various other respiratory symptoms; this study exposes a risk of obstructive and/or restrictive lung disease to anyone exposed to irritant cleaning sprays. Prof Jørgen Vestbo, President of ERS and Professor of Respiratory Medicine, University of Manchester, Manchester, UK, warned: "Cleaning products can put people's heath at risk so people should be aware of the risks and take steps to mitigate against them; if people have genuine concerns they should ensure that they discuss any symptoms and the possible link with their workplace with their doctor."

Possible Link Between Menopause and Decreased Lung Function

DECREASED lung function in women could be linked to menopause, according to research funded by the British Lung Foundation and presented at the 2016 ERS International Congress in London.

For this study, data were used from 141,076 women aged 40–70 years who had provided spirometry measurements and information on their menopausal status to the UK Biobank. The association of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), spirometric restriction (FVC<lower limit of normal [LLN]), and airflow obstruction (FEV_1/FVC<LLN) with menopausal status and age of menopause was examined using regression models that were adjusted for age, height, centre, socioeconomic status, and reproductive and lifestyle factors.

> “This research is important. General practitioners and other health professionals must be aware of the risks to lung health for women going through the menopause and work with them to prevent it being a trigger for other conditions.”

It was found that women who had been through natural menopause were 27% more likely to have lower lung function then women who were still menstruating. Furthermore, the earlier menopause occurs, the lower the lung function typically was afterwards. Amongst post-menopausal women aged 60 years or older, those women who experienced menopause before they turned 45 years old were around 20% more likely to have lower lung function than those who did not experience menopause until they were 48–53 years old. This trend was still true after smokers had been excluded from the analysis.

Speaking about the study, President of the European Respiratory Society Professor Jørgen Vestbo, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK, commented: “This research is important. General practitioners and other health professionals must be aware of the risks to lung health for women going through the menopause and work with them to prevent it being a trigger for other conditions.” The British Lung Foundation is currently conducting a year-long campaign called ‘Listen to your lungs’ to encourage women to take an online breath test to see if they need to see a doctor in order to prevent long-term lung damage.

Vitamin D Can Significantly Reduce Asthma Attacks

RECENT research presented at this year's ERS congress has found strong evidence that taking a vitamin D oral supplement as well as conventional asthma medication could help significantly lessen the severity of asthma attacks, according to a ERS press release dated 6th September 2016. According to investigators, increased vitamin D levels could help to reduce upper respiratory infections that can lead to exacerbations of asthma.

> "...taking a vitamin D supplement in addition to standard asthma treatment significantly reduced the risk of severe asthma attacks, without causing side effects."

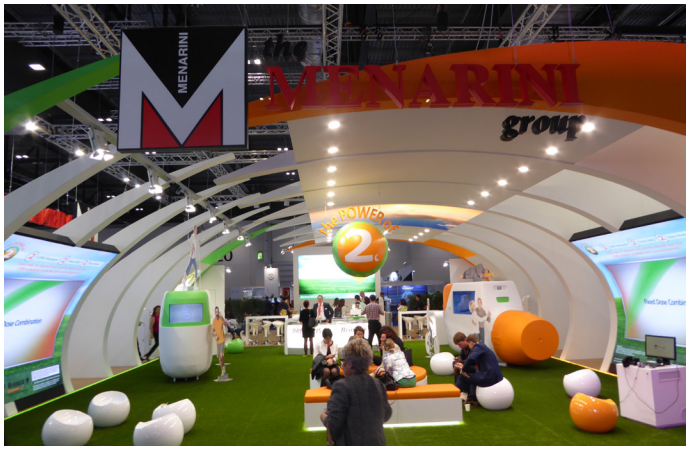
The Cochrane review analysed seven trials involving a total of 435 children and a further two studies which involved 658 adults. The administration of vitamin D was shown to reduce the rate of exacerbations requiring systemic corticosteroids (rate ratio: 0.63, 95% confidence interval [CI]: 0.45–0.88; 680 participants; 3 studies), and lowered the risk of having ≥1 exacerbation requiring an emergency department visit and/or hospitalisation (odds ratio: 0.39, 95% CI: 0.19–0.78; 963 participants; 7 studies).

Investigators found that the risk of severe asthma attacks requiring a visit to the emergency department or admission into hospital was reduced from 6% to roughly 3%. The rate of asthma attacks requiring steroid treatment was also reduced. Prof Adrian Martineau, Asthma UK Centre for Applied Research, Queen Mary University of London, London, UK, stated: "We found that taking a vitamin D supplement in addition to standard asthma treatment significantly reduced the risk of severe asthma attacks, without causing side effects."

However, the study found that vitamin D did not improve lung function or reduce day-to-day asthma symptoms. Prof Martineau added that caution must be taken with these results, pointing out that the majority of participants in the study were adults. He added that "it is not yet clear whether vitamin D supplements can reduce the risk of severe asthma attacks in all patients, or whether this effect is just seen in those who have low vitamin D levels to start with." Further analyses are currently taking place to investigate some of the unanswered questions from this review, and the results will hopefully be available within the next few months.

Long and Short-Term Air Pollution Respiratory Damage Confirmed

A PLETHORA of research has demonstrated the devastating effects of air pollution on long and short-term respiratory health, renewing calls for governments across the globe to act on the findings. The studies, presented in a ERS press release dated 2nd September 2016, have confirmed respiratory damage in patients both immediately following exposure to the pollutants, and ≥60 years afterwards.



The first of the studies looked at childhood exposure to the coal-based pollutants black smoke and sulphur dioxide and assessed how this affected the patients in later life. After factoring in socioeconomic differences, researchers concluded that urban areas with the highest coal usage (≥0.7 tonnes per acre) such as Manchester, Middlesbrough, and Nottingham, had a mortality rate from respiratory diseases that was twice as high as that in more rural areas including Bath, Canterbury, and Exeter where usage was much lower (<0.2 tonnes per acre).

> “Not only do these findings have important implications for countries like China and India that still depend on coal, but they should be a wake-up call to our own government to take air pollution from all sources more seriously.”

A second study found similar results after analysing data for 368,000 patients from across England and Wales over a 38-year period. It showed that exposure to black smoke in 1971 was associated with a 5% increased risk of respiratory mortality per 10 µg/m^3 in 2002–2009; however, this increases to 8% for patients of chronic obstructive pulmonary disease, now the fifth leading cause of death in the UK.

Alongside these results, a third study has shown that exposure to higher levels of nitrogen oxide and particle matter had an immediate negative effect on lung function after studying 2,449 healthy adults over a 4-year period. They claimed there was an average decrease within days of exposure of 0.5% lung function with every 10 µg/m^3 increase in particle matter, and a 0.2% decrease with every 1 µg/m^3 increase in nitrogen dioxide.

Prof Stephen Holgate, Department of Medicine, University of Southampton, Southampton, UK, commented on the gravity of the results: “Not only do these findings have important implications for countries like China and India that still depend on coal, but they should be a wake-up call to our own government to take air pollution from all sources more seriously.”

Reducing Anxiety and Depression in Patients with Chronic Obstructive Pulmonary Disease

INCREASED physical activity (PA) among patients with chronic obstructive pulmonary disease (COPD) could reduce their risk of anxiety and depression, results from a study presented at ERS 2016 have revealed. The study was carried out by Prof Milo Puhan and Dr Anja Frei, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland; Prof Tsung Yu, Department of Public Health, University of China, Taichung, Taiwan; and Dr Gerben ter Riet, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands.

Low PA tends to be associated with patients with COPD. This lack of PA is thought to be a major risk factor for developing comorbidities, which are prevalent in this patient population. The association between PA and seven comorbidities in COPD was thus investigated in this study. The research, reported in a ERS press release dated 5th September 2016, focussed on 409 patients from primary care practices based in the Netherlands and Switzerland. PA was initially assessed using the Longitudinal Ageing Study Amsterdam Physical Activity Questionnaire and patients were then followed for up to 5 years. In the follow-up process, patients detailed their comorbidities (cardiovascular, neurological, endocrine, musculoskeletal, malignant, and infectious diseases) and also had their mental health assessed by completing the Hospital Anxiety and Depression Scale questionnaire. Analysis was carried out through the implementation of logistic regression and survival analysis models.

> “PA promotion programmes may be considered to lower the burden of mental disorders in COPD patients.”

Based on the results, higher initial levels of PA appeared to be associated with an 11% reduction in the risk of developing anxiety over the next 5 years, as well as a 15% reduced risk of developing depression. However, no statistically significant associations of PA with the other categories of comorbidities were observed. The authors concluded: “In COPD patients, those with high PA are less likely to develop depression or anxiety over time. PA promotion programmes may be considered to lower the burden of mental disorders in COPD patients.” This highlights a possible direction for further research in the future.

Childhood BMI Linked to Adult Asthma Severity

HOSPITAL admissions for adult-onset asthma in individuals <45 years have been associated with childhood BMI, according to a ERS press release dated 5th September 2016. The research indicated that women who were overweight and men who were underweight during childhood had an increased risk of asthma in adulthood.

The researchers analysed data from 321,830 children who had annual BMI measurements recorded aged 7–13 years, which was taken from the Copenhagen School Health Records Registry. They then linked this information to asthma admissions data from the Danish National Patient Registry. To examine the association between asthma admissions and BMI z-score, Cox regression was used. Analysis was conducted using restricted cubic splines with four knots, revealing a U-shaped association for males and females.

> We hope that our findings can aid clinicians identifying asthma risks in different individuals. By understanding which individuals are at risk of developing more severe asthma, we can encourage lifestyle changes that can help reduce this risk.

Overall 5,101,123 person-years of follow-up data were analysed, revealing a higher incidence rate for females in the 1,962 incident admissions noted. The results showed a significantly higher risk of hospital admission for overweight females (39%) compared with normal and underweight females. Conversely, males who were underweight in childhood saw an increased risk of asthma admissions in early adulthood (24%). The highest hazard ratio was found in females aged 13 years at 1.39 (95% confidence interval [CI]: 1.2–1.6). For males the highest hazard ratio was at aged 12 years and stood at 1.24, (95% CI: 1.03–1.49). These differences between males and females could be due to a range of environmental factors, physical activity levels, and lung mechanics.

Lead author Prof Charlotte Suppli Ulrik, Department of Respiratory Medicine, Amager-Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark, envisioned the team's research as having a positive impact: "We hope that our findings can aid clinicians identifying asthma risks in different individuals. By understanding which individuals are at risk of developing more severe asthma, we can encourage lifestyle changes that can help reduce this risk."

Study Indicates Relationship Between Smoking and Calorie Intake

SMOKING significantly reduces calorie intake, further confirming its association with an individual's weight, according to a ERS press release dated 5th September 2016. Smoking to maintain a constant body weight has been a claim of many for decades. Although the achievement of smoking cessation is something to be praised, obesity is observed in a greater proportion of non-smokers, a statistic likely to deter people, especially females, from stopping smoking. As post-cessation weight gain (a mean weight gain around 10 kg over 5 years) is an important factor contributing to relapse, further evidence regarding the mechanisms behind this phenomenon could prove vital to improving quitting rates.

To examine the effect of smoking and abstinence on dietary intake, mood, and appetite-associated hormones, Dr Konstantina Zachari and colleagues, Harokopio University of Athens, Athens, Greece, conducted a randomised crossover study involving 14 healthy males. Individuals were required to partake in two trials following overnight abstinence from both smoking and food ingestion. During the C-cig trial, participants were asked to smoke two cigarettes of their own brand within 15 minutes, before being allowed to consume snacks *ad libitum* over 45 minutes. Calorie intake, moods related to appetite (hunger, satiety), and smoking cravings were then recorded at 60 minutes. In contrast, during the S-sham control, each individual was requested to hold a cigarette for the same period of time without lighting it. Blood samples were also recorded at various time points to establish hormone levels, including insulin and ghrelin.

> In our small study, we found that smoking had an acute effect on energy intake that could be mediated by alterations in ghrelin levels.

Results showed an acute dip in dietary intake (152 calories) after smoking, compared with the control data. Smoking did not seem to alter the participant taste preference, however an alteration in plasma ghrelin concentration was observed; a lower amount of ghrelin was detected 60 minutes after the S-sham trial. Dr Zachari explained: "In our small study, we found that smoking had an acute effect on energy intake that could be mediated by alterations in ghrelin levels. Further research is needed to investigate whether these results could be duplicated in a broader study population."

Snoring and Sleepiness: Does Pollution Play a Role?

SNORING and daytime sleepiness can have a serious impact on mental and physical wellbeing. The RHINE III study recently tested how exposure to traffic pollution may affect sleeping habits, with findings suggesting that patients exposed to high levels of pollution were 65% more likely to suffer from daytime sleepiness.

166 late breaking abstracts

The study, reported in a ERS 2016 press release, questioned 12,184 adults on their daily habits, particularly focussing on sleep disturbances and traffic exposures. Specific factors the study considered were bedrooms situated near to traffic/traffic noise and travelling for >60 minutes per day on a busy road. The participants were then asked about a number of other factors related to general health and sleep.

In the cohort, 10% lived on or near a busy road, 6% slept in a room with traffic noise, and 11% spent >60 minutes travelling along busy roads each day. Exposure to pollution was graded as low, medium, or high, with either no exposure, bedroom or outdoor exposure, or both, respectively. As exposure increased, daytime sleepiness also increased (adjusted odds ratio [AOR]: 1.65, 95% confidence interval [CI]: 1.11–2.45). This was also true for traffic noise (AOR: 1.46, 95% CI: 1.11–1.92). Habitual snoring was not associated with pollution exposure but it was associated with traffic noise (AOR: 1.29, 95% CI: 1.12–1.48).

> “Exposure to traffic should be taken into account when planning treatment for patients with sleep disturbances, because reducing noise and pollution exposure in the bedroom may have a beneficial effect.”

Ane Johannessen, Department of Global Health and Community Medicine, University of Bergen, Bergen, Norway, who was a co-author of the study said: “Exposure to traffic should be taken into account when planning treatment for patients with sleep disturbances, because reducing noise and pollution exposure in the bedroom may have a beneficial effect. Reducing exposure through relocating the bedroom away from pollution sources or making the bedroom more soundproof to protect against traffic noise, as well as mapping alternative and less polluted outdoor everyday routes, may help patients with their sleep disorders.”

Obstructive Sleep Apnoea Poses Potential Driving Risk

PATIENTS with obstructive sleep apnoea syndrome (OSAS) potentially pose a higher driving risk, according to a ERS press release dated 7th September 2016. It is widely known that some OSAS patients are more likely to be involved in traffic incidents, however doctors provide notably varying advice on this issue. This study focussed on standard deviation of lane position in a driving simulator, in order to attempt to identify potential risk and develop an objective model for distinguishing at-risk patients in the future.

As 2–4% of the general population have OSAS, the authors state that it is crucial that objective tests are in place for evaluating OSAS patients in order to ensure the safety of all those driving on the roads. An author of the study, Dr Mark Elliott, St James’ University Hospital, Leeds, UK, commented: “The current criteria are arbitrary, loosely based on evidence, and have the potential to prevent a lot of people from driving who are in fact safe to drive.”

Various data were collected from patients, including their Epworth Sleepiness Score (ESS) and oxygen desaturation index (ODI), as well as a driving questionnaire completed before using the simulator. Alongside 129 untreated OSAS patients, 79 controls took part in the study. The outcome from the use of the simulator was based on pre-set criteria with three potential results: pass, intermediate, and fail. It was found that OSAS patients were less likely to pass (31% versus 53%) and more likely to fail (20% versus 0%) than the controls. Furthermore, OSAS patients reported more incidents of tiredness at the wheel and had a higher chance of sleepiness whilst driving. Lane deviation was found to be significantly worse in those who failed the test.

Such findings represent a step towards developing an objective test to ensure greater safety on the roads in the future. For instance, the lane position deviation of OSAS patients could be compared with controls to advise whether they are at increased risk of an accident when driving.

Key Findings from 3-Year Epidemiology Study for Respiratory Health

RESULTS from a study by the British Lung Foundation (BLF) revealed that mortality rates in respiratory diseases have remained unchanged for 5 years in the UK, according to a ERS press release dated 7th September 2016.

Researchers used data collated from 2004–2013 from The Health Improvement Network database. There were 12.6 million patient records from 591 GP surgeries, equalling approximately 5% of the population. The study revealed that 585,000 diagnoses of respiratory diseases are made every year in the UK, half of which are asthma or chronic obstructive pulmonary disease (COPD). Approximately one in five people in the UK suffer from lung disease, and 11% of deaths among these are in children aged <15 years. This places a strain on healthcare services, as lung disease is responsible for >700,000 hospital admissions and >6.1 million hospital bed-days per year.

Mr Ian Jarrold, Head of Research, British Lung Foundation, London, UK, commented: "It is clear that this represents a burden on the National Health Service. The lack of movement in outcomes is something the BLF is keen to address through independent taskforces for lung health in England and Scotland."

Lung disease is influential in broadening inequalities in health in the UK. There is a link between social deprivation and the most common lung diseases, including asthma, COPD, and lung cancer. Whilst the exact causes of the association are unclear, it may be explained by higher rates of smoking and higher exposure to air pollution.

The BLF urged that lung disease receives as much attention and investment as non-respiratory cancer and cardiovascular diseases, which have a similar impact upon healthcare services. Establishing lung health taskforces and a national intelligence network for respiratory data were amongst various other recommendations made to improve treatment and chances of prevention.

"It is clear that this represents a burden on the National Health Service. The lack of movement in outcomes is something the BLF is keen to address through independent taskforces for lung health in England and Scotland."

In asthma and COPD

We need inhalers that are easy to use with fewer serious handling errors

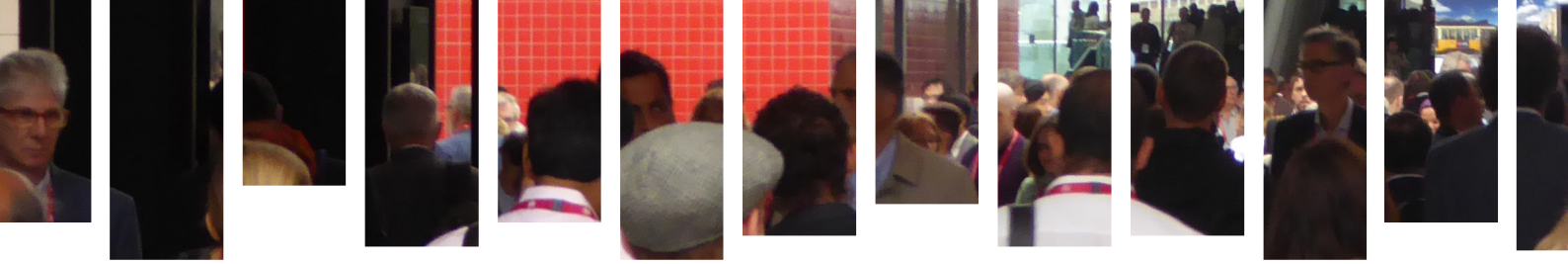
Did you notice the error in the headline?

No? Just like this error, serious handling errors made when using an inhaler can go unnoticed, and may prevent people with asthma and COPD from effectively receiving their medication. This, in turn, may result in poor symptom and disease control, as well as increased costs.[1–4] At Sanofi Generics, we believe that patients deserve an intuitive, easy-to-use alternative that complements the quality of the molecules it delivers, providing confidence with minimal handling errors.

1. Al-Jahdali, et al. Allergy Asthma Clin Immunol. 2013; 9(1): 8. **2.** Melani, et al. Respir Med. 2011; 105(6): 930–8. **3.** Yildiz, et al. Respir Care. 2014; 59: 223–30. **4.** Global Initiative for Chronic Obstructive Lung Disease (GOLD) – Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2016. Available at: http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/. Date accessed: July 2016.

SANOFI

SANGGX.RESP.15.06.0009(1) Date of preparation: July 2016



Enrico Clini

Associate Professor of Respiratory Medicine, Department of Medical and Surgical Sciences, University of Modena, Modena, Italy.

Q: What was your motivation for first entering the field of respiratory medicine?

A: Basically, I was attracted to the field since I was a young student because my father was also a specialist in the field. During my growing education at university, respiratory physiology and pathophysiology were the most attractive in terms of understanding the mechanisms underlying respiratory diseases in general, especially those leading to respiratory failure.

Q: What areas of respiratory medicine and disease are you currently focussing your research towards and what do you hope to achieve from doing so?

A: My experience grew in the last decade studying chronic obstructive pulmonary disease (COPD) as the main smoking-related disease affecting the lungs and respiratory system. In particular, I focussed my research in the area of methods for accomplishing advanced care in these individuals, especially non-pharmacological therapies, such as long-term mechanical ventilation and rehabilitation.

Q: In previous research you have discussed the significant benefits of pulmonary rehabilitation for patients with chronic respiratory diseases. In your opinion, would you say that pulmonary rehabilitation is adequately utilised for the management and maintenance of the health of these patients?

A: Experience all over the world clearly indicates that rehabilitation is underused, and few COPD patients are referred to these programmes (either as out or in-patients). Roughly but realistically, we could say that much less than 10% of symptomatic patients with indication are referred properly. Specialists themselves often misuse rehabilitation courses and mix up the likely significance of rehabilitation with palliation. Patients are therefore referred too late to this particular form of care.

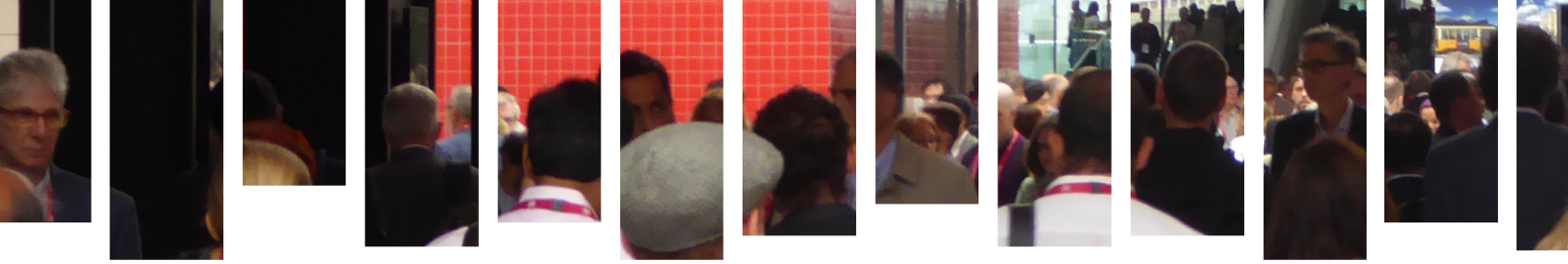
Q: Are there any obstacles that you believe can be overcome in order to improve the delivery and quality of pulmonary rehabilitation for patients with chronic respiratory disease?

A: There are no clear and definitive 'guides' on how to set up a unique model of pulmonary rehabilitation. Very different models in the community and/or in hospitals are reported, according to the different health policies in each country. In particular, Europe and North America differ significantly in terms of setting, reimbursement, and (partly) patients to care for. COPD patients, however, still remain the most epidemiologically relevant population of reference for rehabilitation. This is mainly due to the specific pathophysiology of these patients who represented models in clinical research over the last 20–30 years.

Q: What innovations and developments do you anticipate in the near future that will improve the efficacy of pulmonary rehabilitation for patients?

A: New techniques in some fields (i.e. working aids such as assisted ventilation, inhaled gas mixture, etc.) or exercise strategies (i.e. interval training) promise better results and outcomes, to reduce patients' disabilities and increase participation. Tele-health strategies may help for long-distance assessment, monitoring, and providing care in specific patients, not necessarily only those with COPD.

> "My best achievement was teaching as a professor at a university-level school of medicine, helping young doctors to expand their knowledge..."



Q: Do you expect an increased adoption of consumer biomedical devices by patients outside of the clinic? For example, the use of electrical muscle stimulation to improve health, or wearable technologies for diagnostic and health monitoring purposes?

A: This is very likely to occur, especially for the purpose of long-term maintenance of benefits/gains following hospital-based attended care.

Q: Do you think the use of consumer devices is being effectively integrated alongside the care and treatment offered by physicians and clinicians to their patients?

A: This is what mainly occurs with specific devices for chest physiotherapy (i.e. electrical muscle stimulation or wearable technologies) not yet available for other consumers to use in the long-term.

Q: From your own experience working in Europe, how can clinical diagnostic approaches be better improved?

A: Referring to COPD, a screening policy for 'at-risk' populations should be implemented at the community level. The problems still remain to be the burden of cost and (once diagnosis is performed and/or the overall management strategy is established) decisions on the priority of intervention for advanced care, due to the limited resources allocated. Indeed, we are still at the point that rehabilitation cannot be a care plan for all those who present as potentially being at risk of COPD.

Q: What has been your proudest achievement so far in your career? What future goals have you set for yourself in your work?

A: My best achievement was teaching as a professor at a university-level school of medicine, helping young doctors to expand their knowledge and interest in the specialty. Together with the clinical responsibility in the field of respiratory medicine at the hospital level, this appears to me as a major goal as well as a new starting point.

Q: What advice could you give to someone considering a career in the field of respiratory medicine?

A: I would encourage them to exchange experience, ideally to put his or her own mind to merging together clinical experience with attitude in research. Never give up learning, which is a true general advice to apply for pulmonologists too.

Anthony D'Urzo

Associate Professor, Department of Family and Community Medicine, Faculty of Medicine, University of Toronto; Chair, Primary Care Respiratory Alliance of Canada, Toronto, Ontario, Canada.

Q: What inspired you to begin a career in respiratory medicine and to focus your efforts on the promotion of primary care in lung health?

A: My interest in lung mechanics evolved into a curiosity about how to manage conditions like asthma and chronic obstructive pulmonary disease (COPD) because airflow limitation is a major driver of morbidity and mortality in these conditions. Patients with lung disease most often present to primary care physicians who are in the best position to promote prevention, early diagnosis, and management of these common chronic conditions.

Q: Do you feel that the quality of life of patients with asthma and COPD has improved since you began working in this area?

A: Respiratory literature is littered with evidence which describes that the quality of life of patients with asthma and COPD has been enhanced quite significantly. These improvements are related to achieving important milestones in the judicious use

of inhaled corticosteroids (ICS) and long-acting bronchodilators, with a view to improve current control and to reduce the risk of exacerbations. To date, there is little prospective data which clearly describes a reduction in mortality.

Q: What therapeutic approaches do you anticipate emerging in the near future that could improve the quality of life for patients who suffer from respiratory conditions?

A: Future management strategies for patients with respiratory disease should focus on disease-modifying therapies that significantly improve quality of life and are cost-effective. Quality of life outcomes should be primary variables in major trials. While asthma management will continue to focus on first-line anti-inflammatories, COPD therapy will include an evolving focus on withdrawal of ICS and promoting maximum bronchodilation. Phenotyping and endotyping appear to be emerging as important variables for individualising therapy among specific patient populations. Biologic therapies will provide new options for managing patients with conditions that are difficult to control.

Q: Do you think that within the next 5 years or so treatment will be available to improve lung function in patients with COPD?

A: The next 5 years will continue to usher in new therapies that target symptom control, quality of life, and specific disease pathways that promote improvements in lung function and outcomes like exacerbations, hospitalisation, and mortality. A primary challenge in COPD relates to a paucity of therapeutic compounds that have shown efficacy in improving the irreversible features of this condition, including loss of elastic recoil, destruction of alveolar attachments, and abnormalities in the basement membrane. There is growing recognition that there are limits to improving lung function when the disease process is advanced.

Q: What are some of the significant challenges currently facing the promotion of lung health at the primary care level, and what solutions can be devised to overcome them?

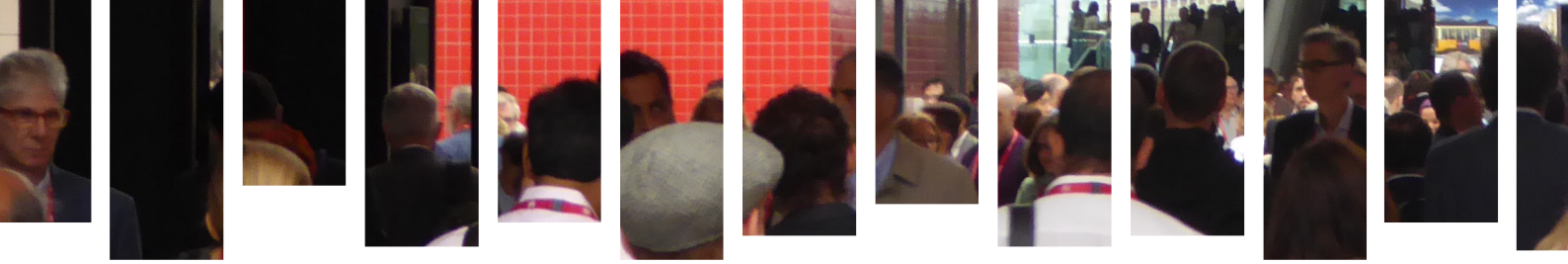
A: Perhaps the greatest challenges in promoting lung health in primary care relate to the under-utilisation of spirometry for diagnosis of asthma and COPD, findings that appear to be driven by lack of familiarity with spirometry testing and interpretation of results. This has led to reports describing both an over-diagnosis of asthma and under-diagnosis of COPD in parts of the world. Other challenges include disease control that falls short of guideline recommendations. Education focussed on objective testing for diagnostic confirmation is essential and must be delivered in a manner that is relevant to primary care. This might include access to same day spirometry and timely interpretation of spirometry results.

Q: Do you expect pharmaceutical companies to have an increasing role in the continuing research and development of new treatments for asthma, COPD, and other respiratory conditions?

A: It will be crucial for the pharmaceutical industry to continue to play a leading role in the development of new therapies across the levels of care. Since primary physicians account for upwards of 80% of prescriptions across therapeutic areas, it seems reasonable to encourage the development of very close research links between the pharmaceutical industry and primary care. Such a relationship might serve to address important care gaps in asthma and COPD management, among others, that are driven by evidence from studies that lack the appropriate balance between internal and external validity. If a new balance in evidence generation can be achieved between the pharmaceutical industry and primary care, it is hoped that both knowledge translation and individualised patient care will be enhanced in a cost-effective manner.

Q: How can physicians and those working at the primary care level ensure that research led by the pharmaceutical industry is guided towards efforts that result in the best interests of the patient?

A: The best way for primary care physicians to ensure that the pharmaceutical industry engages in research that is relevant to the needs of patients in the real world is to work to establish a



collaborative relationship, ideally in both academic and community primary care settings, that strives to carry out studies that include relevant clinical outcomes and take into consideration comorbidities that may influence pharmacotherapeutic efficacy and effectiveness.

Q: What is the current focus of your own research, and what do you hope to learn as a result of your efforts?

A: At the present time, my research interests focus on evaluating new pharmacologic approaches in the management of asthma and COPD. I am also involved in studying strategies to promote spirometry interpretation in the primary care setting including how different spirometry interpretation algorithms may influence data interpretation. This diagnostic approach is aimed at underscoring the spirometric overlap between asthma and COPD, and the risk of disease misclassification.

Q: What has been the proudest achievement of your career to date? What specific goals do you hope to achieve in future work?

A: Over many years I have enjoyed my role as the director of the Primary Care Lung Clinic in Toronto, Canada, and the opportunities to play a leading role in many important research studies focussing on state-of-the-art initiatives that highlight both diagnostic and management strategies for asthma and COPD in primary care. My hope for the future includes working with large primary care research networks with the capabilities and motivation to work closely and independently with the pharmaceutical industry. I believe that this scenario will not only create opportunities for promoting high-quality, pragmatic research at the primary care level, but it may also forge important relationships between the pharmaceutical industry, primary care physicians, and governmental regulatory agencies involved with drug approval andsafety surveillance.

Q: What advice do you have for someone considering a career in the field of respiratory medicine?

A: My advice would be to make sure you enjoy what you are doing and to be excited about how you get things done.

Andrew Bush

Professor of Paediatrics and Head of Section (Paediatrics), Imperial College London;
Professor of Paediatric Respirology, National Heart and Lung Institute, Imperial College London;
Consultant Paediatric Chest Physician, Royal Brompton & Harefield NHS Foundation Trust, London, UK.

Q: What first attracted you to the field of respiratory medicine, and then to later specialise in paediatric respirology?

A: The lungs and breathing always fascinated me, particularly because you can measure so much and test the system objectively. Respiratory physiology is, outside of my family, the love of my life. You can measure physiological behaviours as diseases change, or treatment is instituted. I started academic life by training as an adult respiratory physician and did my research with Prof David Denison in the Clinical Physiology Department of the Brompton Hospital, London, UK, perhaps one of the most brilliant minds and brilliant physiologists of his generation. It was he who confirmed my love of respiratory physiology, with a clean intellectual rigour of approach as well as a colossal sense of fun and joy in unravelling problems. I do not think I have ever been in a better environment for academic work, enjoyment, and intellectual stimulation. David was one of the few real geniuses I have met in my time. My research was in adult clinical physiology initially, but became more and more focussed on children, under Dr Elliot Shinebourne, a great paediatric cardiologist who was another really important mentor. It was

becoming a handicap not being able to handle sick children during the research procedures and relying on others and so, I went into paediatrics to learn that skill. My first job was on the University College Hospital Neonatal Unit with two of my other great heroes, Prof Osmond Reynolds and Dr Jonathan Shaw. I loved it so much that I have stayed in paediatrics ever since and became a paediatric respiratory physician thus getting the best of both worlds.

Q: What specific areas of paediatric respiratory disease are you currently exploring, and what progress do you hope to achieve from doing so?

A: My main area of interest at the moment is the measurement of airway inflammation, particularly in asthma and wheezing disorders in children. We are just about to start a big research programme funded by the Wellcome Trust to try to understand why preschool children start to wheeze and then go on to develop asthma. We will be recruiting babies soon after birth and looking at how their immune system and their epithelial cells mature and what deviates them from normal. The aim is to try to predict which babies are heading for trouble and prevent the development of early disease, which has life-long consequences. A lot of adult physicians do not realise that the roots of chronic obstructive pulmonary disease (COPD) are in early childhood, before birth, and even before conception. So if the tide of COPD is to be turned back, we must learn about early-life events.

I am also really interested in very severe asthma. We know that most children with asthma will respond to low-dose inhaled corticosteroids if properly and regularly administered, so the challenge is to find out: what is it about this child and their asthma that makes the asthma treatment resistant? We have a great multidisciplinary team and the clinical programme has enabled us to make insights in the research laboratory into why asthma is difficult. In this context, I must pay tribute to another all-time hero, Prof Clare Lloyd in Leukocyte Biology at Imperial College London, London, UK, who has been a fantastic collaborator over many years.

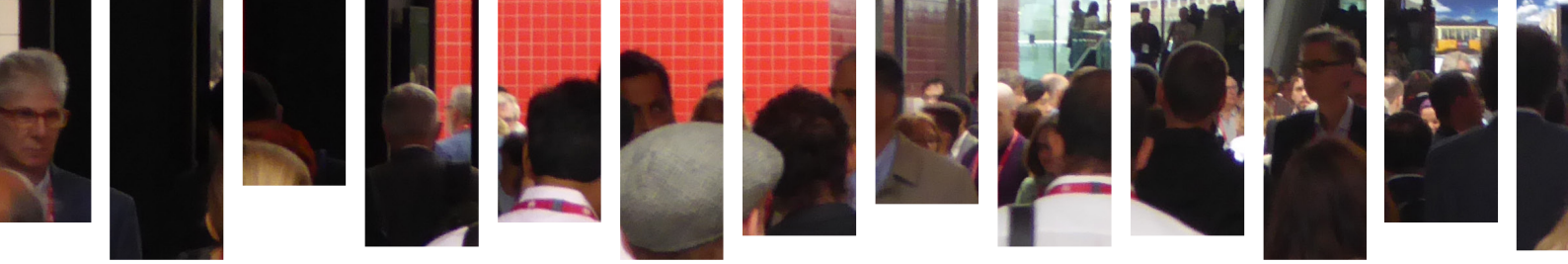
Q: One focus of your research has been on asthma in childhood and adolescence. What are some of the biggest challenges faced in the diagnosis and care of these patients?

A: Some of the biggest challenges in asthma diagnosis and care relate to the fact that we have to rely on second-hand information from parents very often. Also in younger children, we have very little in the way of objective testing. Symptom assessment is very subjective, both by families and physicians, and we need to go beyond this to objective measurements (my first love in respiratory physiology). It is disappointing that the way we assess these children, particularly young ones, has not changed significantly for many decades. We also face the challenge of being tangled in umbrella terms like 'asthma', which in reality comprises a number of illnesses. We need to start asking about what airway disease the child has and what components are treatable and how best to treat them, rather than asking, "What label can I tie to this child?" and, "What penny-in-the-slot treatment can I prescribe?"

The biggest challenge of adolescents? Adolescence! I had 20 years as the father of at least one teenage child and was just as clueless at the end of two decades as at the start. My admiration goes out to those who can get along with people during this troubling developmental period.

Q: How far has our understanding and treatment of asthma improved since you first began working in this area?

A: In terms of the understanding of asthma, the biggest advance in my time has been the realisation that much asthma is due to airway inflammation and that low-dose inhaled corticosteroids are life-changing and life-transforming. We relearn this lesson again and again when inhaled corticosteroids are made affordable in low and middle-income settings, with a staggering drop in mortality and morbidity. The converse is that we have failed to understand that if a child does not respond to low-dose inhaled corticosteroids, the likelihood is that the basics, such as adherence, need to be addressed rather



than treatment escalated. However, it is also perfectly clear that inhaled corticosteroids do not work for everybody and that some children require different approaches. We are at the dawn of an age of personalised medicine using biomarkers to guide treatment rather than the much cruder mechanisms we have used at the present time; we need to rise to this challenge.

In practical clinical terms, the role of the advanced respiratory nurse in asthma, as in many fields, has transformed the care of children. Never ask a professor anything practical, but a good nurse is worth twice their weight in platinum for getting treatment working. Our nurses have taught me so much about severe asthma, most notably, that professors sitting in clinics know exactly nothing about what really happens at home and at school.

Q: You have previously highlighted the issue of children being over-diagnosed with asthma, and the exposure of risk to negative health impacts, as the result of subsequent medical treatment. How do you think over-diagnosis has become such a prevalent issue, and do you feel that adequate steps have been made to begin tackling it?

A: I think over-diagnosis of asthma became an issue because in the past asthma was under-diagnosed and children with asthma were given antibiotics, cough medicines, and other such stuff which they really did not need. Then it became clear that a number of children with respiratory symptoms, such as a cough attributed to bronchitis, actually benefited from asthma medications. The unfortunate consequence was that things went too far, as children with any sort of respiratory symptom thought of as potentially asthmatic were given inappropriate treatment. Of course, this in part relates to the fact that asthma is a killing disease and nobody wants to miss a diagnosis or prevent a child from receiving appropriate treatment. So I think we need to move to better diagnostic tests for asthma, which is something Asthma UK has stressed. It is a real shame that we do not have modern testing for asthma. I can only contrast the crude tests we use in asthma with the sophisticated new molecular tests for tuberculosis, which have been made available even in low and middle-income settings. We need to tackle this by finding a blood or breath test for asthma and making it widely available. In the meantime, I am firmly in favour of the National Institute for Health Care and Excellence (NICE)'s approach: to insist on objective testing when this can be done.

Q: What are some of the significant challenges currently faced in the continuing research and development for effective treatments of asthma in Europe, and across the world?

A: The main challenge for new asthma treatments is first of all to make sure we maximise the best use of old treatments; KISS: Keep It Simple Stupid, and over and over again, my specialist respiratory nurses have had to teach me this lesson. So, for the vast majority of asthmatic patients, low-dose inhaled corticosteroids work very well if they are taken regularly and administered properly. Going beyond this we need to find biomarkers that will enable us to give the right treatment to the right patient. There are numerous biological agents coming to the fore for asthma but these will not work for everybody. So, for example, mepolizumab, the anti-interleukin-5 monoclonal, was initially thought not to be useful until it was targeted at particular subgroups of asthmatics. Targeting treatment, not one size fits all, is something we need to make more routine and get into our bloodstreams as asthma researchers and clinicians.

Outside of Europe the biggest challenge of all is to get the basic treatments to the poorest people. Beclomethasone, salbutamol, prednisolone, and a plastic milk bottle to make a spacer, in the hands of every family worldwide with a child with asthma would do more good than a million monoclonals. Pharma has guilt as well; instead of peddling expensive combination medications, the basics must be gotten to where they are most needed.

Q: Do you anticipate in the near-future any important innovations or developments that will have a great impact on asthma treatments, and for treating respiratory disease in general?

A: What I would like to see and believe we are on the verge of is a better understanding of the molecular and cellular pathways of asthma and targeting those pathways. Of course, the major breakthrough we need is to stop asthma developing in the first place. We know that preschool children who develop asthma and lose lung function never get it back again, and they are at risk of long-term COPD. The biggest challenge is to interrupt this cycle and I believe we can do this in the next few years.

Q: Please can you tell us about your continuing work as a National Institute for Health Research (NIHR) Senior Investigator in the UK, and the impact this has had on your own research?

A: The NIHR has opened up many new avenues for patient-focussed research and perhaps the biggest thing it has done has been to drive patient and public involvement right to the forefront of the research agenda. We can learn so much from patients but they need to be involved in planning research right from the very start, not just rubber stamping a proposal that has already been put together. Working with patients certainly has been the most important development in my career, and this has been a real NIHR drive. Other facets are keeping research standards high, and mentoring the young up-and-coming who have a NIHR Fellowship or PhD funding; in particular, allied health professionals who are a largely untapped and underused valuable resource, another really important NIHR role.

Q: What has been the proudest achievement of your career to date? What specific goals do you hope to achieve in future work?

A: Personally, persuading the finest woman in the world to marry me and stick with me. Next, my children, their partners, and my grandchildren. I suppose the professional achievement I was proudest of was the award of the Imperial College Rector's Gold Medal for Excellence in Research Supervision in 2011. Most of what I write will cease to be relevant within a few years of my retirement (if anything is at all relevant now!). However, the people that I have left behind, people who I can say that I have been part of their life story and their training, will be the sort of legacy that anybody can be proud of. To date I have supervised 36 doctoral theses to completion. These are the people (outside of my family) I am proudest of, especially the professors, the leaders of the future, who did some training with me. Their achievements have been extraordinary, despite my best efforts! In terms of future goals, I very much hope that the Wellcome Trust grant that I discussed previously will bring new insight into preschool wheeze and will enable us to interrupt the cycle of harm that is affecting so many children. When I have gone, I hope it may be said: "His sins were scarlet, but his words were read." I enjoyed my role as a paediatric Editor-in-Chief alongside Ian Pavord, my partner in crime; I loved co-authoring Airwaves, and I miss the opportunity to insult the rich, powerful, and self-important (many potential targets!).

Q: What advice do you have for medical students who are thinking of specialising in paediatric respirology?

A: Advice for medical students? Just do it. Paediatrics is the best career imaginable and paediatric respirology is the best of the best, but do be sure to get academic paediatrics into your bloodstream. Do a PhD, get on the academic track. There is a whole shedload of discoveries waiting to be made; outdo your old greying predecessors, like me. Get good mentors who will fight in your corner, do not be discouraged when you get rejections; remember that the first edition of Gray's anatomy was absolutely slated by a reviewer yet >40 editions and >160 years later it is still going strong, whereas the name of the reviewer has sunk into well-deserved obscurity! The English composer John Ireland told my father, his pupil: "Always please yourself, but do not be too easily pleased!"

I have never regretted going into paediatric respirology and I would not change what I do even if I won the national lottery. If there is a luckier guy than me on the planet, they are either seriously delusional or on an illegal high!

α1 ANTITRYPSIN DEFICIENCY (AATD) THERAPIES.

THEY ARE NOT ALL THE SAME.

Respreeza®:

- **The first and only proven disease-modifying agent in AATD** (RAPID trial)[1,2]
- **Early treatment option independent of FEV_1 percentage**[3]
- **Indicated for all AATD genotypes**[3]
- **Lowest infusion volume at 1g/20ml**[3,*]
- **Well tolerated with the highest purity**[4,5,*]

Proof changes everything

Respreeza®
alpha$_1$-proteinase inhibitor (Human)

[1] Chapman KR, Burdon JGW, Piitulainen E, et al; for the RAPID Trial Study Group. Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;386(9991):360–368.

[2] Chorostowska-Wynimko J. Disease Modification in Emphysema Related to Alpha-1 Antitrypsin Deficiency, COPD: Journal of Chronic Obstructive Pulmonary Disease. 2016; DOI: 10.1080/15412555.2016.1178224.

[3] Respreeza® SPC.

[4] Data on file.

[5] Sandhaus R, Chapman KR, Burdon J, et al. Integrated safety across six clinical trials of alpha-1 augmentation therapy. Poster presented at: European Respiratory Society; September 6–10, 2014; Munich, Germany.

*Compared to Prolastin and Alfalastin.

Respreeza® 1000 mg. 1. Composition: Respreeza is a highly purified, pasteurized, nanofiltered, lyophilized, stable human plasma alpha$_1$-proteinase inhibitor (A_1-PI) concentrate. One vial contains approximately 1,000 mg of human alpha1-proteinase inhibitor (derived from the plasma of human donors). After reconstitution with 20 ml solvent, the solution contains approximately 50 mg/ml of human alpha$_1$-proteinase inhibitor. Other ingredients: sodium chloride, sodium dihydrogen phosphate monohydrate, and mannitol. Respreeza contains 1.9 mg sodium per ml of reconstituted solution (81 mmol/l). **2. Indications:** Indicated for maintenance treatment, to slow the progression of emphysema in adults with documented severe A_1-PI deficiency (e.g., genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ). Indicated in patients with progressive lung disease (e.g. lower forced expiratory volume per second (FEV_1) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of A1-PI deficiency. **3. Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Immunoglobulin A (IgA)-deficient patients with antibodies against IgA, due to the risk of severe hypersensitivity. **4. Special warnings and special precautions for use:** Caution should be taken when administering Respreeza to individuals who have experienced anaphylaxis or severe systemic reactions to another A_1-PI product. *Hypersensitivity:* Respreeza contain traces of IgA. IgA deficient patients may develop antibodies to IgA and are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Suspected allergic or anaphylactic type reactions may require immediate discontinuation of the infusion, depending on the nature and severity of the reaction. *Home-treatment:* Limited data regarding the use of Respreeza in home-treatment is available. Potential adverse reactions must be taken into account before considering the home-treatment. It is the responsibility of the doctor to decide the eligibility of patients for home-treatment. The treating doctor should conducts the appropriate training for the eligible patients regarding the usage and administration of Respreeza. *Transmissible agents:* Multiple measures are taken to prevent the risk of infections from human plasma donors. Multiple measures are effective against enveloped viruses (e.g., human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV)), non-enveloped hepatitis A (HAV), and parvovirus B19 virus. However, the risk of transmitting infectious agents from unknown or emerging viruses and other pathogens cannot be completely excluded. *Smoking:* Smoking is an important risk factor for the development of emphysema in patients with A_1-PI deficiency. Smoking or tobacco use should be completely avoided. *Sodium content:* Respreeza contains approximately 1.9 mg sodium per ml of reconstituted solution (81 mmol/l). This should be taken into consideration for patients on a controlled sodium diet. **5. Undesirable effects:** Dizziness, headache, dyspnoea, nausea are common adverse reactions associated with the use of Respreeza. On very rare occasion anaphylactic reactions, hypoaesthesia, hyperhidrosis, pruritus, chest pain, chills, and pyrexia have been observed. Hypersensitivity or allergic reactions have been observed, and may in some cases progress to severe anaphylactic reactions. The safety and effectiveness of Respreeza in the paediatric population and elderly patients (65 years of age or older) have not been established. **6. Prescription status:** Prescription-only drug. **7. Marketing Authorization Holder:** CSL Behring GmbH, Emil-von-Behring-Str. 76, 35041 Marburg, Germany.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002739/human_med_001904.jsp&mid=WC0b01ac058001d124

MODIFYING ALPHA-1 ANTITRYPSIN DEFICIENCY-RELATED EMPHYSEMA: FROM EVIDENCE TO PRACTICE

This symposium took place on 6th September 2016 as a part of the European Respiratory Society (ERS) International Congress in London, UK

Chairpersons

Noel Gerard McElvaney,[1] Ilaria Ferrarotti[2]

Speakers

Joanna Chorostowska-Wynimko,[3] Kenneth R. Chapman,[4] A. Rembert Koczulla[5]

1. Professor of Medicine, Head of Department, Royal College of Surgeons, Dublin, Ireland
2. Centre for the Diagnosis of Hereditary Deficiency of α1-antitrypsin, Department of Internal Medicine and Therapeutics, Pneumology Section, University of Pavia, Pavia, Italy
3. Department of Genetics and Clinical Immunology, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
4. Professor of Medicine, Asthma and Airway Centre of the University Health Network, University of Toronto, Toronto, Canada
5. Department of Internal Medicine, Section of Pulmonary Diseases, University of Marburg, Marburg, Germany

Disclosure: Prof McElvaney has received funding support from CSL Behring, Grifols, Bayer, and Vertex. Dr Ferrarotti has received travel grants and honoraria from CSL Behring and Grifols. Prof Chorostowska-Wynimko has received grants, personal fees, and non-financial support from Grifols, grants from Baxalta US Inc, and grants and personal fees from CSL Behring. Prof Chapman has received consulting fees from AstraZeneca, Boehringer Ingelheim, CSL Behring, GSK, Grifols, Kamada, Merck, Novartis, Pfizer, Roche, and Takeda. Prof Chapman has also received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Grifols, GSK, Merck, Novartis, and Takeda and has received research grants/contracts from Amgen, AstraZeneca, CSL Behring, Genentech, GSK, Grifols, Kamada, Novartis, Roche, and Sanofi. Prof Koczulla has received honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, Grifols, GSK, Menarini, and Novartis.
Acknowledgements: Writing assistance was provided by Mia Cahill of ApotheCom.
Support: The symposium and the publication of this article was funded by CSL Behring. The views and opinions expressed are those of the authors and not necessarily CSL Behring or the International Congress of the European Respiratory Society.
Citation: EMJ Respir. 2016;4[1]:35-42.

MEETING SUMMARY

The symposium discussed the role of disease modification in alpha-1 antitrypsin deficiency (AATD)-related emphysema. Evidence from the recent RAPID trial and its extension trial showed that treating AATD patients with intravenous alpha-1 antitrypsin (alpha-1 proteinase inhibitor; [A_1-PI]) therapy slowed the rate of lung density decline and had a disease-modifying effect. By modifying the course of disease, survival can be extended by several years. Dr Ferrarotti opened the symposium by introducing the topic of AATD-related emphysema, highlighting the latest epidemiological data, and providing an overview of the treatment landscape. Prof Chorostowska-Wynimko then addressed how to determine the disease modification that occurs in AATD, focussing on the clinical trial design (classical parallel-group, placebo-controlled trial design versus a 'late-start' study design) and clinical outcomes (forced expiratory volume in 1 second [FEV_1] versus computed tomography [CT] lung density). Prof Chapman explained the results and the post hoc analyses of the RAPID trials; a sustained reduction in lung density decline rate that proves to have a

disease-modifying effect. Prof Koczulla closed the symposium by relating current evidence to the real-life management of patients, notably how patients should be monitored and the prospect of home-based care.

Welcome and Introduction

Professor Noel Gerard McElvaney and Doctor Ilaria Ferrarotti

AATD is a genetic disease that increases the risk of developing lung disease; in particular, emphysema. AATD-related emphysema is a rare disease, with an incidence of 1 in 4,000 to 1 in 10,000. In the past, intravenous treatment with A_1-PI could not be shown to be effective using comparatively crude spirometric outcomes. However, the RAPID trial showed the efficacy of A_1-PI treatment in slowing down emphysema progression using the more sensitive and specific outcome measure of lung density.

Determining Disease Modification in A_1-PI Antitrypsin Deficiency: Challenges and Lessons Learned

Professor Joanna Chorostowska-Wynimko

Disease modification is best defined as a sustained change in disease state, which is the result of a given therapeutic intervention and characterised by an improvement in or stabilisation of a disease. This is usually due to a reduction in the rate of disease progression that occurs following a therapeutic intervention and may persist after the intervention is discontinued.[1] Disease-modifying therapy should impact the pathological and pathophysiological mechanisms underlying the disease rather than addressing clinical symptoms of the disease alone.[2]

To differentiate disease-modifying therapy from symptomatic therapy, the therapy must alter the rate of decline to slow down disease progression. Currently, none of the approved pharmacological therapies for chronic obstructive pulmonary disease (COPD) have demonstrated an unequivocal disease-modifying effect. One important reason for this is that multiple pathological mechanisms can lead to COPD and no single therapy targets all mechanisms. The accepted mode of proving therapeutic efficacy is the parallel-group, placebo-controlled trial design, which has limitations in the assessment of chronic, slowly progressing diseases that lack sensitive biomarkers or responsive outcome measures. Recently, it was suggested that the optimal clinical trial design for chronic diseases is the 'late-start' study design; this consists of two phases. The first phase followed the standard design whereby patients are randomised into parallel active treatment or placebo groups and any effect observed in the active group may be related to the symptomatic effects of the therapy. In the second open-label phase, patients either continued on active therapy (the Early-Start group) or were shifted from the placebo to active therapy (Delayed-Start group). In the second phase, the disease-modifying effect was analysed by assessing if the difference between both arms was maintained until the end of the study, following which the therapy may be considered as truly disease-modifying.[1]

Although FEV_1 is the accepted biomarker for COPD, it is not the ideal biomarker to address disease modification for several reasons: FEV_1 does not reflect COPD and emphysema mechanisms, it is an indirect measure; it is variable day-to-day and prone to high intra-subject variability, and has a non-linear decline over time.[3] FEV_1 correlates poorly with other outcomes that are applied to clinical trials (such as dyspnoea, exercise capacity, quality of life, number of exacerbations) and is affected by comorbidities, which is a major concern in patients with COPD.[4]

The biomarker broadly accepted in the scientific literature as a reliable and sensitive biomarker of disease progression and decline in AATD-related emphysema, is CT lung densitometry. It reflects changes in lung structure allowing a reviewer-independent quantification of disease severity and distribution, has higher reproducibility and sensitivity compared with lung-function outcomes, and correlates with other outcomes (e.g. the diffusing capacity of the lungs for carbon monoxide [DL_{CO}], FEV_1, mortality, and quality of life).[5] A recent study by Green et al.[6] directly showed the significant link between lung density decline and survival of patients with AATD and emphysema. In the same study, lung-function outcomes were assessed in relation to lung density: FEV_1 was less sensitive but more specific in predicting CT lung density than using the transfer coefficient for carbon monoxide (KCO) (corrected for lung volume) and DL_{CO}.[6] Taken together these physiological measurements of lung disease have very low negative predictive values for CT density decline.

As the causative process has been identified, AATD-associated emphysema should be a good model to evaluate a possible disease-modifying effect of therapy, represented by the sustained slow down of emphysema progression following therapeutic intervention. One of the largest trials exploring the modifying effect of A_1-PI therapy on patient survival included an observational cohort of more than 1,100 patients.[7] Patients with FEV_1 <50% predicted were stratified according to therapeutic intervention into ever-treated and never-treated groups. The mortality rate was significantly higher in the never-treated group (47%) compared with the ever-treated group (18%), and it was demonstrated that FEV_1 decline was significantly slower in patients with AATD with FEV_1 35–49% predicted (p=0.03). Confounding factors of this study included the observational design, varying length of treatment, the socioeconomic background of patients (different healthcare delivery systems and socioeconomic factors), and the use of an inadequate biomarker (FEV_1).[7]

Two randomised trials, the Danish-Dutch study[8] and the EXACTLE study,[9] used lung density decline as a biomarker. Neither study reached statistical significance but the pooled analysis of the two datasets was statistically significant (p=0.006) and showed that A_1-PI therapy affects the rate of lung density decline in AATD-related emphysema.[10] Unfortunately, both studies were underpowered and it was concluded that a larger number of patients was necessary to demonstrate the modifying effect, which is challenging because AATD is a rare disease. Enrolling more patients would mean increasing the number of trial centres, imposing challenges on the standardisation of measurements, and increasing cost. To prove disease modification in AATD, more patients are required, a longer study duration is needed, and most importantly the trial design must allow for assessments that prove that the treatment effect is maintained and not just symptomatic.

Disease Modification in Alpha-1 Antitrypsin Deficiency: Changing the Course of Disease Progression with Intravenous A_1-PI Therapy

Professor Kenneth R. Chapman

The RAPID trial was designed specifically to be able to demonstrate the effect of A_1-PI therapy on CT lung density: 180 non-smoking patients with A_1-PI <11 µM and FEV_1 35–70% predicted, were randomised to receive intravenous A_1-PI therapy 60 mg/kg or placebo once weekly for 24 months. The study design of the RAPID trials is shown in Figure 1. A differential withdrawal was noted with patients in the placebo group being more likely to withdraw before the end of the study than patients in the treatment group (p=0.04). Of those enrolled, 153 patients completed the first phase of the RAPID trial; 84 in the treatment group and 69 in the placebo group. The RAPID Extension trial followed the patients for an additional 24 months.

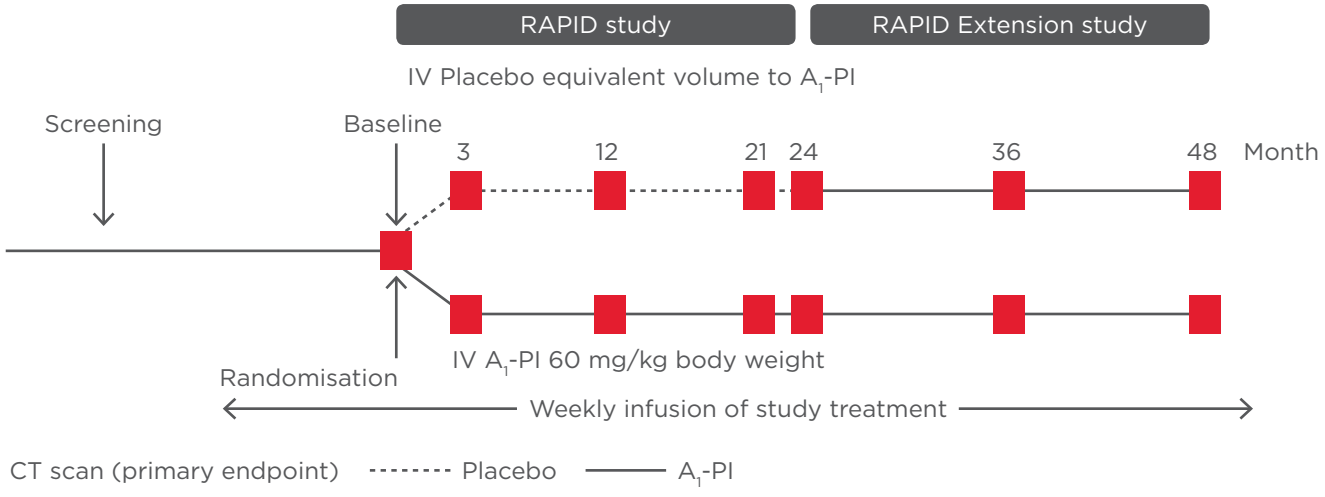


Figure 1: The RAPID and RAPID Extension Trial Study Design.[2]
Primary endpoint: Lung density measured by CT scan at 0, 3, 12, 21, 24, 36, and 48 months.
CT: computed tomography; A_1-PI: alpha-1 proteinase inhibitor; IV: intravenous.

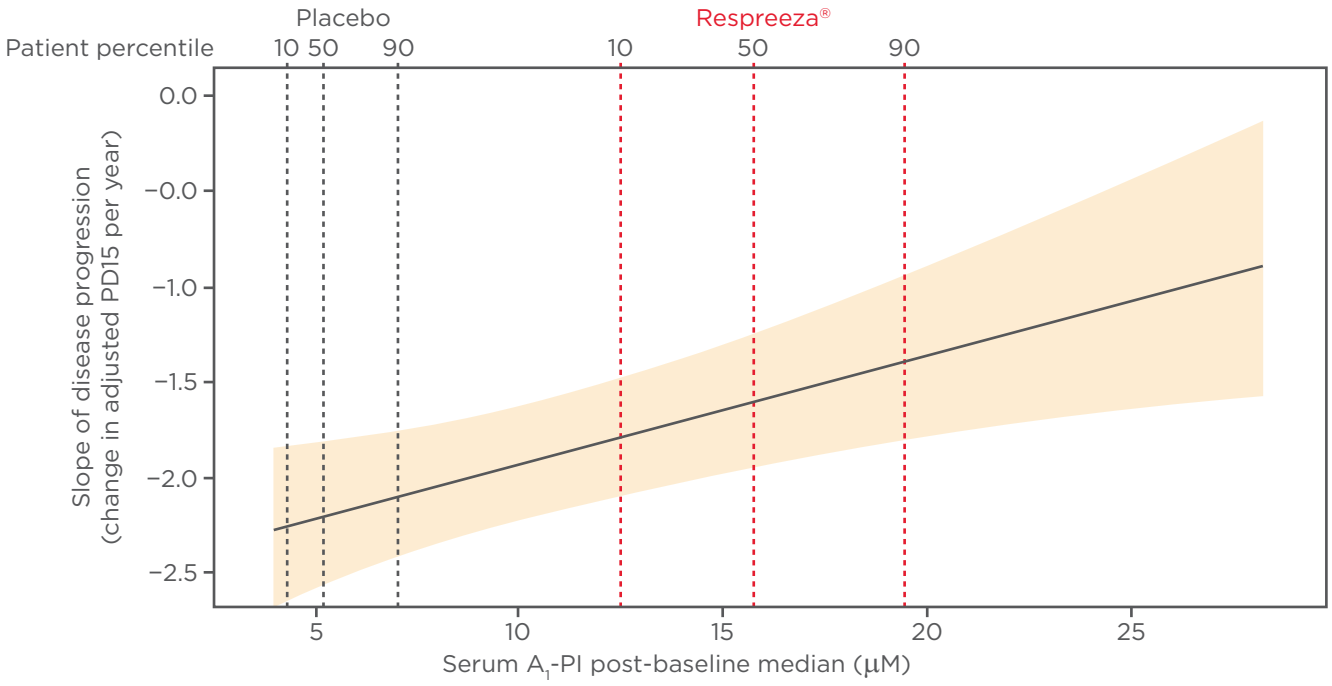


Figure 2: Achieved intravenous alpha-1 antitrypsin levels associated with the rate of change in lung density: RAPID Study.[11]

A_1-PI: alpha-1 proteinase inhibitor; PD15: 15th percentile point.

Patients in the treatment group continued on therapy (Early-Start group) and those in the placebo group were switched to active treatment (Delayed-Start group). All patients who completed the RAPID trial were eligible for the extension trial, except American patients (RAPID Extension trial n=140) (Figure 1). Patient baseline demographics were well balanced for both groups in the RAPID trial: average age was 53.8 years and 52.4 years in the treatment and placebo groups, respectively. Adjusted lung density at the 15th percentile point (PD15) CT was 45.5 g/L and 48.9 g/L for treatment and placebo groups, respectively.[11]

The primary endpoint, loss of lung density, is a surrogate for the loss of lung tissue and was used as the pathological correlate for progression of emphysema. The progression rate of emphysema is determined by a change in lung density measured by a CT scan of the whole lung. The PD15 is extracted from the frequency distribution of lung voxels and is defined by low density units (Hounsfield unit) at which 15% of the voxels in the histogram have a lower density. From prior work, it is known that a shift in PD15 is a way of quantifying loss of lung density.[10,12]

The final outcome was assessed in both groups after 24 months for the randomised placebo-controlled phase and 48 months for the open-label Extension phase of the study.[11] During the RAPID trial, patients in the placebo group had a significantly greater lung density decline compared to those in the A_1-PI treatment group. In the RAPID extension trial, the decline in lung density in the Early-Start group was similar to the first phase, whereas the loss in lung density slowed in the Delayed-Start group. However, lung density lost during placebo treatment was not regained once patients were switched to active treatment.

The results from the RAPID trials allowed the investigators to determine a threshold for a rapid or slow decline in lung density; a decline of >2 g/L per year was considered a fast decline. When the results at 24 months were expressed as a proportion of rapid and slow decliners, 73% and 26% of Early-Start patients were slow and rapid decliners, respectively. Delayed-Start patients (i.e. on placebo) had more or less equal stratification between slow and rapid decline, with 48% slow decline and 49% rapid decline. In the extension phase, the proportion of slow to rapid decliners in the Early-Start group was maintained but in the Delayed-Start group an improvement to 75% slow decliners and 25% rapid decliners was observed.[13]

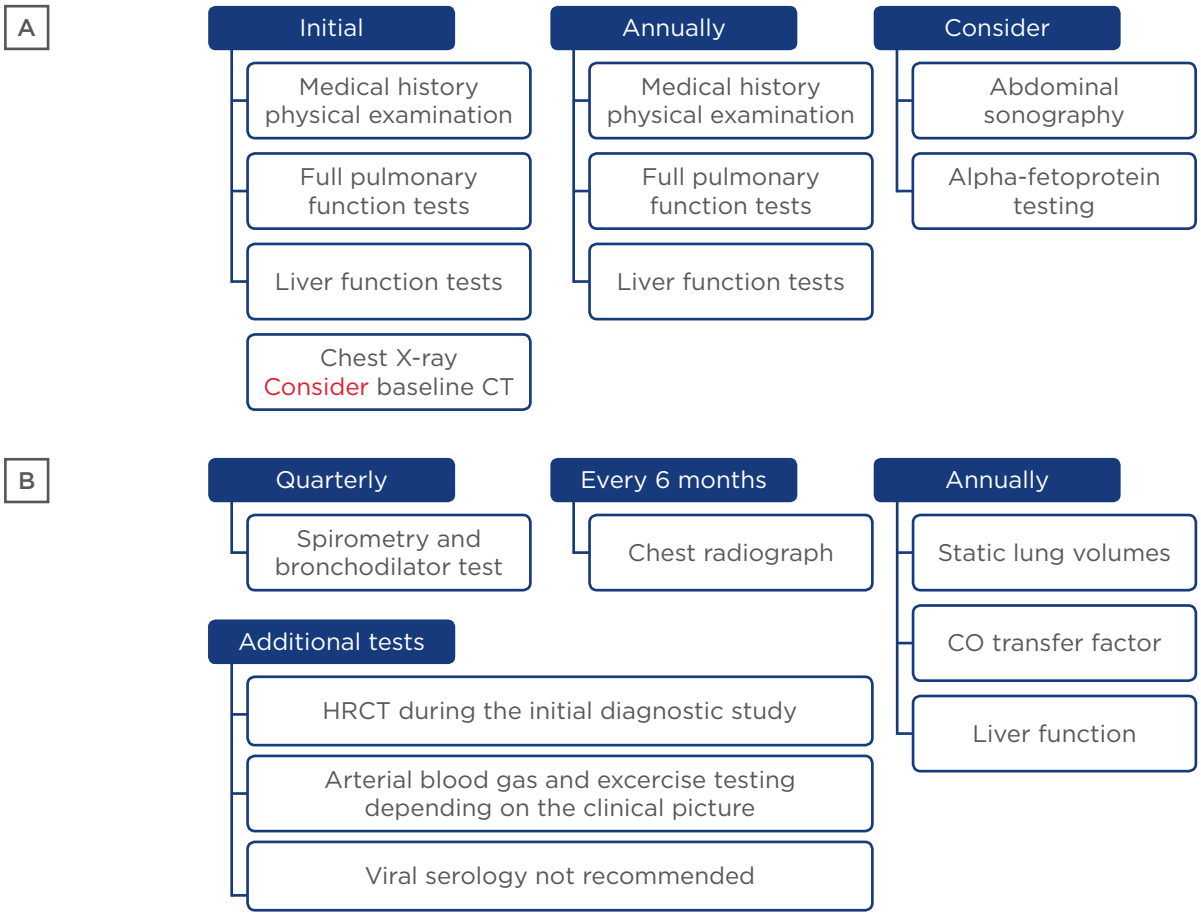


Figure 3: Clinical practice guidelines for monitoring alpha-1 antitrypsin deficiency.

A) Recommendations from the New England Journal of Medicine;[20] B) recommendations from the Spanish Guidelines.[18]

CT: computed tomography; CO: carbon monoxide; HRCT: high-resolution computed tomography.

Factors resulting in a range of serum levels achieved after the infusion of 60 mg/kg include differences in volumes of distribution between men and women, and obese and lean patients. A linear relationship between the plasma levels and the change of adjusted PD15 was observed, suggesting a dose-response to A_1-PI therapy and that higher doses may have a greater effect on slowing disease progression (Figure 2).[11]

In previous studies it was shown that desmosine and isodesmosine (biomarkers of elastin degradation) are higher in the plasma and sputum of patients with AATD compared with patients with non-AATD-related COPD.[14,15] In the RAPID trial desmosine/isodesmosine concentrations were significantly correlated with a loss of lung density, as measured by CT scan.[16] Moreover, after 4 years the traditional but insensitive pulmonary function markers of obstructive lung disease (FEV_1 and forced vital capacity) correlated with the more sensitive marker of CT lung density.[17] By the end of the RAPID trial six patients had died or undergone lung transplantation. The average lung density when these terminal events occurred was 20 g/L, while the average lung density at the start of the trial was 46 g/L. In the RAPID trial placebo-treated patients had a lung density loss of 2.2 g/L/year and active-treated patients had a loss of 1.5 g/L/year, differences that would mean a 6-year life extension in Early-Start patients.[11]

Caring for Patients with Alpha-1 Antitrypsin Deficiency: What Guidelines Do Not Tell You

Professor A. Rembert Koczulla

Monitoring Patients Receiving Intravenous A_1-PI Therapy in Real Life

Currently there is no clear consensus on how often to monitor patients with AATD. Imaging is

crucial to measure baseline severity of disease, rule out other diseases, and guide therapeutic options. However, guidelines[18,19] vary in their recommendations and therefore clinical presentation should guide diagnostics. Silverman and Sandhaus[20] recommend that during the initial assessment, patients with AATD should have a medical history taken, a full physical examination, full pulmonary function testing, liver function testing, and a chest X-ray; baseline CT should also be considered. Annual follow-up abdominal sonography and alpha-fetoprotein testing should be considered in addition to routine tests (Figure 3a).[20] The Spanish guidelines[18] differ slightly, recommending quarterly spirometry including bronchodilator testing, chest radiography every 6 months, and annual static lung volumes, carbon monoxide transfer factor, and liver function testing (Figure 3b). Liver function testing is recommended annually by Silverman and Sandhaus[20] and the Alpha-1 Foundation. Elastography based on sonography[21] and magnetic resonance elastography are non-invasive tests that are currently being explored and may help identify patients with AATD liver disease in the future. Patients with concomitant COPD should be followed up with CT scans or assessed using the modified Medical Research Council (MRC) scale 4–6 weeks after an exacerbation and discharge from hospital.[19]

The Practical Side of Intravenous A_1-PI Therapy

A_1-PI therapy is recommended by the American Thoracic Society/European Respiratory Society (ATS/ERS) for patients with severe AATD and 30–65% FEV_1 predicted, although newer guidelines recommend therapy for a broader range of disease severities.[22,23] In the European Union (EU), three approved products and differences in infusion time exist, although in Prof Koczulla's experience this is not an issue for patients. Differences in drugs have been demonstrated; Zemaira®/Respreeza® contains 1% impurities, mainly albumin, whereas Prolastin® contains 38% impurities.[24] With the differences in purity and application time between the marketed products, one product may meet specific patient needs better than the other.

Patient Issues: What Can I Offer?

Patients that are on a weekly intravenous therapy regimen often ask for guidance on how to continue treatment when they go on holiday. One option would be to infuse a double dose to cover a 2-week treatment period. In the RAPID trial, bi-weekly infusion of 120 mg/kg demonstrated a favourable safety profile with no overall increase in the incidence or severity of adverse events for 120 mg/kg and 60 mg/kg doses of A_1-PI, versus corresponding doses of placebo.[25] The Spanish guidelines recommend up to 180 mg/kg doses accommodating 3-weekly dosing.[18] It should be considered that if an increased dose is administered, a higher volume and a larger amount of sodium will also be administered which will need to be taken into account with coexisting diseases.

In Ireland and France, home-based care is established for patients with AATD. A German study[26] of seven patients and >1,000 infusions (administered by visiting nurses) over 3 years observed no hospitalisations, no allergic reactions, and no severe adverse events. During the weekly visits nurses assessed general health and measured pulse, blood pressure, and oxygen saturation. Additional assessments included a monthly exacerbation-history questionnaire and quarterly spirometry measurements with blood gas analysis. It was concluded that A_1-PI therapy at home was feasible and safe, and achieved consistently high quality-of-life scores.[26]

Non-Pharmacological Treatment

Non-pharmacological therapy is supported by The Global Initiative for Chronic Obstructive Lung Disease (GOLD), where 10–45 minutes of daily to weekly exercise is recommended for patients with chronic disease.[19] A statement by Spruit and the ATS/ERS recommends that patients with chronic disease should exercise with a combination of resistance and endurance training.[27] Resistance training should be 2–3 times per week with 60–70% of maximum load, 1–3 sets each with 8–12 repetitions, and should be increased if undertaken in two successive sessions, to 13–14 repetitions where possible. Endurance training can include walking, cycling, or rowing and should be 3–5 times per week with an intensity of 60% of maximum load for 20–60 minutes.[27]

Question and Answer Session

Q: What would you like to see included in the next ERS statement on AATD?

Prof Chorostowska-Wynimko replied that screening is a key factor and a lack of screening means that many patients are misdiagnosed or have

delays in treatment initiation, and that a clear message to physicians should be to utilise screening techniques.

Prof Chapman commented that screening has been limited because previously there was no evidence for treatment efficacy. Following the results of the RAPID trials however, it should be mandatory for pulmonologists to screen and identify suitable patients so that they can begin timely treatment with A_1-PI therapy.

Prof Koczulla added that physical activity should be included as although there is a lack of evidence in AATD patients, there is a paucity of data in the COPD population.

Q: What type of patient is suitable for self-administration of intravenous A_1-PI therapy?

Prof Koczulla replied that patients must be able to cope with the task of administering an infusion and several checks would be necessary before implementing this system. Offering the appropriate training, as in other indications where self-administration is frequent, is of great importance. It will not be attractive to all patients alike. It may be an important option for patients with a long commute to their physician, however some patients may not be willing to undergo self-administration because the weekly visits to the clinic offer them a greater sense of security and a chance to socialise.

Q: There is a difference between the FEV_1 range given in the summary of product characteristics of the licensed products and also in the different treatment guidelines. Do you treat patients with FEV_1 >65% or <30%?

Prof Chapman replied that as previously discussed, the FEV_1 only partially reflects the disease process of progressing emphysema in patients with AATD. The new guidelines published this year recommend treatment if FEV_1 is <30% of the predicted value and to consider treatment for >65% when progressive disease is evident. This would be on-label treatment according to the summary of product characteristics for Respreeza.

Q: Do you think that there is a subgroup of patients who would benefit more from A_1-PI therapy?

Prof Chorostowska-Wynimko replied that clinical observation has demonstrated that there is a subpopulation of patients other than rapid decliners that would benefit more from A_1-PI therapy. However, such patients are difficult to characterise and it is a subjective observation.

Prof McElvaney added that although there is a reasonable amount of data on CT scans and FEV_1 measurements, there is a lack of data on DL_{CO} and other measurements and a need to further explore this to better phenotype patients.

Prof Chapman added that CT scan measurements were used in the RAPID trials and posed the idea of using lung density to track an individual patient rather than examining the subjective picture of emphysema on a CT scan and FEV_1 measurements. Lung density could be used to quantify and determine whether a patient is a rapid decliner over a period of 1 or 2 years.

REFERENCES

1. Halpin DM, Tashkin DP. Defining disease modification in chronic obstructive pulmonary disease. COPD. 2009;6(3): 211-25.

2. Chorostowska-Wynimko J. Disease Modification in Emphysema Related to Alpha-1 Antitrypsin Deficiency. COPD. 2016;12:1-9. [Epub ahead of print].

3. Vestbo J et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011;365(13):1184-92.

4. Agusti A, Sin DD. Biomarkers in COPD. Clin Chest Med. 2014;35(1):131-41.

5. Parr DG et al. Validation of computed tomographic lung densitometry for monitoring emphysema in alpha1-antitrypsin deficiency. Thorax. 2006;61(6): 485-90.

6. Green CE et al. Lung density associates with survival in alpha 1 antitrypsin deficient patients. Respir Med. 2016;112:81-7.

7. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. Am J Respir Crit Care Med. 1998;158(1):49-59.

8. Dirksen A et al. A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. Am J Respir Crit Care Med. 1999;160(5 Pt 1):1468-72.

9. Dirksen A et al. Exploring the role of CT densitometry: a randomised study of augmentation therapy in alpha1-antitrypsin deficiency. Eur Respir J. 2009; 33(6):1345-53.

10. Stockley RA et al. Therapeutic efficacy of α-1 antitrypsin augmentation therapy on the loss of lung tissue: an integrated analysis of 2 randomised clinical trials using computed tomography densitometry. Respir Res. 2010;11:136.

11. Chapman KR et al. Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. Lancet. 2015; 386(9991):360-8.

12. Dirksen A et al. Progress of emphysema in severe alpha 1-antitrypsin deficiency as assessed by annual CT. Acta Radiol. 1997;38(5):826-32.

13. McElvaney NG et al. Increased proportion of slow decliners in patients with alpha-1 protease inhibitor (A1-PI) deficiency following treatment with A1-PI. Eur Respir J. 2016;48:Suppl.60, 1768.

14. Akagawa M, Suyama K. Mechanism of formation of elastin crosslinks. Connect Tissue Res. 2000;41(2):131-41.

15. Ma S et al. Measurements of desmosine and isodesmosine by mass spectrometry in COPD. Chest. 2007;131(5):1363-71.

16. Ma S et al. The effect of alpha-1 protease inhibitor (A1PI) on biomarkers of elastin degradation in alpha-1 antitrypsin deficiency (AATD): an analysis of the RAPID/RAPID Extension trials. Chronic Obstr Pulm Dis (Miami). 2016; In press.

17. Teschler H et al. Correlation between change in lung density and lung function parameters in treated alpha-1 protease inhibitor (A1-PI) deficiency. Eur Respir J. 2016;48(Suppl. 60):OA1767. [In press].

18. Vidal R et al. [Guidelines for the diagnosis and management of alpha-1 antitrypsin deficiency]. Arch Bronconeumol 2006;42(12):645-59.

19. Global Initiative for Chronic Obstructive Lung Disease. 2016. Available at: http://www.goldcopd.com. Last accessed: 15 September 2016.

20. Silverman EK, Sandhaus RA. Clinical practice. Alpha1-antitrypsin deficiency. N Engl J Med. 2009;360(26):2749-57.

21. de Lédinghen V, Vergniol J. Transient elastography (FibroScan). Gastroenterol Clin Biol. 2008;32(6 Suppl 1):58-67.

22. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168(7):818-900.

23. Sandhaus RA et al. The Diagnosis and Management of Alpha-1 Antitrypsin Deficiency in the Adult. Chronic Obstr Pulm Dis (Miami). 2016;3(3):668-82.

24. Cowden DI et al. A pilot study comparing the purity, functionality and isoform composition of alpha-1-proteinase inhibitor (human) products. Curr Med Res Opin. 2005;21(6):877-83.

25. Seersholm N et al. Safety of bi-weekly infusion of A1-PI augmentation therapy in RAPID. Eur Respir J. 2015;46:PA999.

26. Wilke A, Grohé C. [Prospective evaluation of clinical parameters of AAT patients with i. v. prolastin therapy in a homecare setting]. Pneumologie. 2013; 67(10):545-50.

27. Spruit M et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188(8): e13-64.

DEVICE MATTERS: LOOKING BEYOND THE DRUG

This satellite symposium took place on 4th September 2016 as a part of the European Respiratory Society (ERS) International Congress in London, UK

Chairperson

Helen Reddel[1]

Speakers

Kai-Michael Beeh,[2] John Haughney,[3] Sinthia Bosnic-Anticevich,[4] Henry Chrystyn[5]

1. Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia
2. Insaf Respiratory Research Institute, Wiesbaden, Germany
3. Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK
4. School of Medical Sciences, University of Sydney, Sydney, Australia
5. Inhalation Consultancy Limited, Leeds, UK; Faculty of Health and Human Sciences, University of Plymouth, Plymouth, UK; Research in Real Life (RiRL), Cambridge, UK

Disclosure: Prof Reddel has received honoraria for advisory board membership and provision of independent medical education from AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Merck Mundipharma, and Teva Pharmaceuticals, and research grants from AstraZeneca and GSK. Dr Beeh is employed by an institution that has received honoraria for consultancy and speaking services from Ablynx, Almirall, AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Chiesi, Cytos, ERT, GSK, Mundipharma, Novartis, Pohl Boskamp, Takeda, and Zentiva, and compensation for the design and performance of clinical trials from Almirall, Altana/Nycomed, AstraZeneca, Boehringer, Cytos, GSK, Infinity, Medapharma, Merck Sharp & Dohme, Mundipharma, Novartis, Parexel, Pearl Therapeutics, Pfizer, Teva Pharmaceuticals, Sterna, and Zentiva. Dr Haughney has received fees for consulting and speaking services, and significant support for his department, research, travel, and accommodation from Almirall, Boehringer Ingelheim, Chiesi, AstraZeneca, GSK, Merck Sharp & Dohme, Mundipharma, Napp Pharmaceuticals, Novartis, Orion Pharma, Pfizer, Sanofi-Aventis, Teva Pharmaceuticals, and Zentiva. Prof Bosnic-Anticevich has received honoraria for consultancy services from AstraZeneca, GSK, Mundipharma, and Teva Pharmaceuticals. Prof Chrystyn has received sponsorship to carry out studies and honoraria for consultancy and speaking services from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Innovata Biomed, Meda, Mundipharma, Napp Pharmaceuticals, Norpharma, Orion Pharma, Sanofi-Aventis, Teva Pharmaceuticals, Trudell Medical International, UCB, and Zentiva.
Acknowledgements: Writing assistance was provided by Dr Blair Hesp, CMPP, of ApotheCom.
Support: The symposium was sponsored by Teva Pharmaceuticals. Authors received honoraria for preparation and delivery of their presentations. The views and opinions expressed are those of the authors and not necessarily of Teva Pharmaceuticals.
Citation: EMJ Respir. 2016;4[1]:43-50.

MEETING SUMMARY

Prof Helen Reddel opened the symposium by discussing the need to examine the modifiable non-pharmacological factors in the treatment of asthma and chronic obstructive pulmonary disease (COPD) that can be addressed to improve clinical outcomes. Dr Kai-Michael Beeh set the scene and discussed the need to review patient behaviour and drug delivery mechanisms to improve outcomes for patients with asthma and COPD. Dr John Haughney then discussed how patient preferences for inhalers can impact real-world outcomes. Prof Sinthia Bosnic-Anticevich outlined the challenges in learning and maintaining correct inhaler technique, while Prof Henry Chrystyn highlighted how inhaler design can help minimise the impact of inhaler errors on clinical outcomes. Prof Helen Reddel closed the session by bridging the gap between guidelines and clinical care, describing ways to incorporate regular checking and training of inhaler skills into a range of settings.

The meeting objectives were to look beyond drugs to the role of devices in optimising asthma and COPD management, to understand the impact of inhaler technique on treatment efficacy, to review how patient perspectives about their inhaler can impact on clinical outcomes, and to discuss how to implement current clinical guidelines on inhaler technique in day-to-day clinical care.

Introduction

Professor Helen Reddel

Much of the discussion surrounding improving treatment outcomes for patients with asthma and COPD focusses on developing new pharmacotherapies. However, there are a number of modifiable non-pharmacological factors that can also be targeted. Patient lifestyle changes such as quitting smoking may offer significant gains, but from a therapeutic perspective there is also the opportunity to improve not just the efficacy, but the delivery of pharmacotherapy for asthma and COPD using new devices and improved inhaler technique.

Looking Beyond the Drug in Asthma and Chronic Obstructive Pulmonary Disease

Doctor Kai-Michael Beeh

Global healthcare spending has increased steadily over the past decade.[1] However, while increasing investment in healthcare initially corresponded to fewer hospitalisations for patients with asthma, increasing expenditure has not translated into further benefits in recent years.[2] Therefore, the focus for improving outcomes for patients with asthma or COPD has turned to allocating healthcare resources to strategies beyond drug therapy, such as increasing therapeutic adherence and personalising patient care.

Outcomes for patients with asthma may also be stagnating because physicians are misdiagnosing asthma severity. A 2014 National Review of Asthma Deaths report following an audit of asthma deaths in the UK found that of the 155 people who died from asthma, 58% were labelled by their physician as having mild or mild-to-moderate asthma.[3] These concerns have been validated in a Canadian study where physicians were asked to rate disease severity in patients with confirmed uncontrolled asthma.[4] Despite having confirmed uncontrolled asthma, 43% of these patients were labelled by the physician as having adequate, good, or very good asthma control, indicating that physicians are misunderstanding or underestimating the importance of the concept of asthma control.[4] However, inaccurate physician assessment of asthma control may be due to patients' inability to accurately recall their symptoms or a poor perception of some symptoms.[5]

As they are chronic conditions, therapeutic adherence is the cornerstone of both asthma and COPD management. Treatment adherence (>80% use of medication) in patients with COPD, in particular, is associated with a significantly lower risk of severe exacerbations and a reduced risk of mortality.[6] Despite this, adherence is relatively poor, with approximately 25–46% of patients remaining adherent to maintenance therapy.[7]

While it could be argued that a large proportion of these patients have mild disease and therefore do not require frequent medication, it has been demonstrated that adherence is independent of disease severity.[8] For this reason, it is now recognised that there are multiple behavioural features which underpin medication non-adherence including:[9]

- At-risk behaviours
- Patients not applying their preventive strategies, such as smoking cessation
- Use of non-observed medications
- Missed appointments
- Erratic/intermittent adherence
- Auto-adjustment of doses

Inhaler satisfaction is also strongly associated with increased therapeutic adherence, with one study demonstrating that greater patient-rated inhaler satisfaction is associated with better physician-assessed treatment compliance.[10] Despite clinical outcomes being reliant on adherence and patient satisfaction, these features are rarely taken into consideration in health technology assessments evaluating pharmaceuticals.

The emergence of phenotype-based drugs for asthma has also made the personalisation of therapy possible. For example, the anti-interleukin-5 therapy reslizumab has shown significant benefit in reducing the annual exacerbation rate for patients with elevated blood eosinophils (≥400 cells/μL).[11]

By tailoring treatment according to this phenotype, potential non-responders can be identified and avoid unnecessary exposure to a drug that is likely to be ineffective.

In conclusion, increased healthcare expenditure does not necessarily translate to better clinical outcomes for patients with COPD or asthma, highlighting the need to prioritise resource allocation to increase the value of patient care.[1,2] Existing options for resource allocation include disease assessment and monitoring and management of the disease. Additionally, the emergence of phenotype-based drugs for asthma makes treatment personalisation a reality[11] and further resources should be allocated towards tailoring treatment towards the likelihood of a clinical response.

Do Inhalers and Their Correct Use Contribute to Good Patient Management?

Doctor John Haughney

Achieving good asthma control is complex, with many contributing factors, such as diagnosis, concomitant conditions, inhaler technique, compliance, and drug therapy selection.[5] While good asthma control is an elusive goal for many patients, it may be achieved by addressing each of the following factors.[5] Key determinants of the effectiveness of inhaled treatments include:[12]

- Efficacy through pharmacological properties
- Optimal drug delivery
- The way treatments are used (e.g. correct inhaler technique and treatment adherence)

Advances over the last 20–30 years in inhaler drug delivery technology have improved inhaler efficiency.[5,13] However, the study of inhalers in randomised controlled trials (RCTs) was slowed by the publication of findings from a systematic review in 2001, in which it was demonstrated that alternative inhaler devices were no more effective than pressurised metered dose inhalers (MDI).[14] This led to pressurised MDIs becoming the recommended first-line delivery device.

However, the question arises as to whether the findings of these RCTs can be generalised to real life. Compared with the real world, selection bias in RCTs can exclude patients with poor device technique, and clinical studies are conducted with an increased focus on educating subjects on inhaler technique and promoting treatment adherence. A further systematic review of inhaler efficiency showed that when each device is used with the correct inhalation technique, each device offers equivalent efficacy.[13] However, many patients do not know how to use their device correctly and incorrect inhaler use is associated with poor asthma control.[5,15] Therefore, poor inhaler technique and adherence are key contributors to treatment failure in real life.

A real-world study examining the relationship between inhaler satisfaction, treatment adherence, and outcomes has reported that drug delivery attributes of the inhaler and higher adherence are related to better treatment outcomes.[16] While the relationship was not statistically significant, it was noted that being able to use the device properly was related to optimal medication delivery, and therefore likely to contribute to device satisfaction and improved asthma control.[16] The FINHALER study examined patient preferences across three different devices and found that whilst an intuitive device can play a role in achieving correct device technique and improved compliance, face-to-face education is essential for achieving a high prevalence of correct inhaler technique and improving patient outcomes.[17]

Individual perceptions and preferences should be considered during inhaler treatment selection, where factors such as adherence and inhalation technique are associated with patient preference.[12] A structured approach to individual patient treatment is important, as is an understanding that good control will not be achieved by a 'magic bullet' but rather by an attempt to better manage all elements, including device selection and correct inhaler technique.

Inhaler Device Mastery: Results from Handling Studies

Professor Sinthia Bosnic-Anticevich

Considering the plethora of information available to inhaler users, the fact that inhalers are still routinely used incorrectly is a multifaceted problem. Recent data show that 73% of patients consider their inhaler technique to be good or excellent, 86% of patients consider their inhaler easy to use, and as many as 96% of patients have not had their inhaler technique checked in the last

12 months.[18,19] Therefore, while there is a need to actively train inhaler users on proper technique, it has previously been shown that written package inserts alone may be ineffective.[20,21]

Furthermore, considering that a high proportion of patients inaccurately believe that their technique is adequate,[18] there appears to be a disconnect between inhaler technique theory and practice, as mastery at the time of teaching does not translate into maintenance of correct inhaler technique over time.[20,21] In particular, many common inhaler errors that can translate into poorer clinical outcomes are related to both the incorrect operation of the device itself as well as poor inhalation technique.[5,15]

In a recent proof-of-concept study, methods of instructing subjects on optimal inhaler technique have been investigated in non-asthma sufferers who were naïve to correct inhaler technique.[22] Subjects were provided with one of two dry powder inhalers (DPIs), a Turbuhaler® (AstraZeneca) or a Spiromax® (Teva Pharma), without any formal training.[23,24] If correctly using the inhaler was not immediately intuitive, participants were given written instructions to assist them. If this was not effective subjects were instructed using a video, and if they were still unable to demonstrate correct inhaler technique individual feedback was provided on the particular errors they were making.[23,24] One month after receiving training, patients were required to demonstrate their inhaler technique and it was found that there was a significant difference between the two inhalers.[23,24] A significantly greater proportion of subjects who failed to intuitively demonstrate correct inhaler technique with both inhalers, but who had received written and video instruction, maintained correct inhaler technique.[23,24] Moreover, subjects who had received written or video instruction were also more likely to maintain correct inhaler technique when using a Spiromax compared with a Turbuhaler.[23,24] Subjects also reported a preference for Spiromax.[23,24] Interestingly, a learning effect was found in that after subjects were taught the proper technique for the first inhaler, they were faster at demonstrating correct inhaler technique with the subsequent inhaler.[23,24]

Overall, correct inhaler technique is an important skill to master but it appears to be subject to skill fade. The correct technique for using some inhalers, such as the Spiromax, does however appear to be easier to maintain than others, such as the Turbuhaler, and appropriate instructional techniques need to be investigated.[21,23,24,26] Identifying patient-related factors and predictors of poor inhaler usage when patients begin to use inhalers could help to alleviate long-term problems with inhaler technique before they manifest.

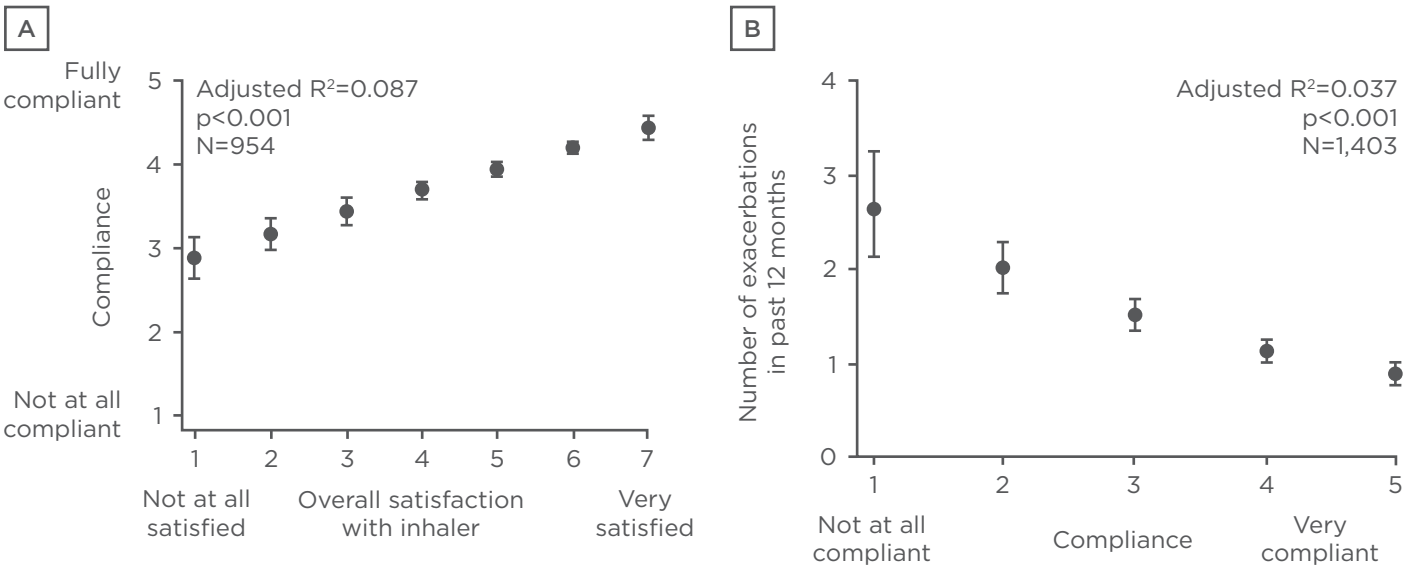


Figure 1: Relationship between A) patient compliance and overall satisfaction with inhaler, and B) patient compliance and exacerbations for patients with chronic obstructive pulmonary disease expressed as mean ±95% confidence intervals.

Coefficients of determination (R^2) are derived from a generalised additive model.

Adapted from Chrystyn 2010.[10]

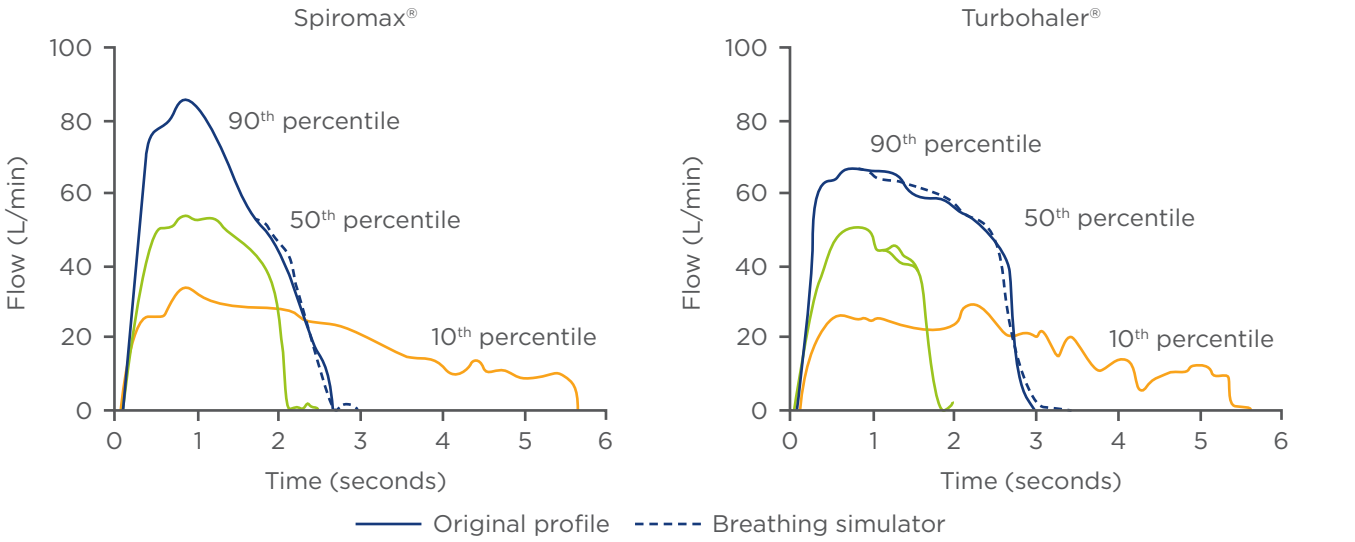


Figure 2: Selected (source) and replayed (simulated) flow profiles for patients using the Spiromax® and Turbuhaler® inhalers using weak (10th percentile), medium (50th percentile), and strong (90th percentile) inhalation profiles.
Adapted from Chrystyn 2015.[36]

The Patient's Perspective: What is Happening Outside the Clinic?

Professor Henry Chrystyn

Real-world patients rarely have perfect inhalation technique and inhaler errors contribute to the more than €400 million in annual healthcare costs in the UK alone (>€500/person with asthma or COPD annually).[26] Therefore, to achieve optimal outcomes for patients with asthma or COPD it is necessary to provide an inhaler that is simple and intuitive to use, while also being minimally affected by a patient's technique to ensure maximum efficacy.[27,28] Patients who are satisfied with the ease of use and efficacy of their inhaler are more likely to have good treatment adherence and to comply with any treatment instructions leading to a positive feedback loop as they achieve improved disease control and greater satisfaction with their inhaler (Figure 1).[10]

Inhaler errors can be classified into three categories:

- Dose emission errors
- Dose preparation errors
- Inhalation manoeuvre errors

Dose emission and preparation errors are often a function of the inhaler device itself. MDIs offer consistent dose emission, whereas the dose emission for DPIs ranges from consistent to erratic. Dose preparation errors are also device-specific, and can be a result of the operation and loading of the device, orientation when used, or whether or not the device is shaken prior to use.

Preparing the dose in the wrong orientation is one of the most common inhaler errors, but the orientation of a Spiromax inhaler does not affect dose emission.[29-31] The removal of dose orientation as an inhaler error accounts for a large proportion of the 39% lower odds of inhaler errors after 12 weeks of using a Spiromax versus a Turbuhaler inhaler (95% confidence interval: 16–56%, p=0.003), highlighting the ability of inhaler design to minimise errors.[32]

Inhalation errors are common for all inhalers and relate to the generic instruction to inhale as fast as you can and to continue for as long as possible. This instruction is necessary to ensure appropriate flow-dependent dose emission, particularly for DPIs,[33,34] but given that inhalation errors are patient as opposed to device-dependent, no significant difference in inhalation errors was observed between the Spiromax and Turbuhaler.

As peak inspiratory flow is also highly variable between patients,[35,36] device design is often the most effective method for minimising the impact of flow rate on dose emission. For example, Spiromax offers consistent fine particle dose delivery, regardless of inhalation profile (Figure 2), whereas the fine particle dose delivery with a Turbuhaler is flow-dependent.[36]

Table 1: Opportunities to demonstrate proper inhaler technique in healthcare and community settings.

Setting	Opportunity
Specialist clinics or a clinic where respiratory function laboratory testing is performed	• Patients can be asked to demonstrate their current inhaler technique when given a bronchodilator during spirometry • Patients can be educated about proper inhaler technique alongside other routine clinical education, such as self-management education
Hospital ward	• Inhaler technique can be demonstrated either while the patient is on the ward or upon hospital discharge
Emergency department	• Time may be severely limited, so proper processes need to be implemented to ensure that a consistent technique is taught to staff and subsequently passed onto patients • Inhaler technique can be demonstrated either while the patient is in the department or upon discharge
Primary care	• During scheduled review visits • After discharge from hospital • On tablets or a television, while patients are in the waiting room
Pharmacy	• When a new prescription is dispensed, because the pharmacist is the last healthcare professional to see a patient prior to using their inhaler • Patients presenting with a flare-up
In the community	• Patient organisations and clubs, or lay educators, can teach and/or correct inhaler technique

Therefore, patients with asthma or COPD should use inhalers that minimise the risk of errors through effective and intuitive inhaler design as this can improve clinical outcomes and treatment adherence, which is likely to translate to these patients and place a reduced economic burden on healthcare systems.

Inhaler Skills Training: Bridging the Gaps Between Guidelines and Clinical Care

Professor Helen Reddel

The Global Initiative for Asthma (GINA) strategy report together with multiple national guidelines emphasise the importance of correct inhaler technique and adherence for patients with asthma. While these resources recommend that inhaler skills training should be provided frequently, e.g. before initiating therapy, during self-management education, after hospital discharge, and before stepping up therapy, healthcare professionals (HCPs) have a limited timeframe within which they can check and communicate the correct technique with their patients.

Despite this, practical steps can be taken to ensure that correct inhaler technique skills are taught and maintained. At every opportunity, inhaler technique should be checked and re-checked. As a guide, HCPs should aim to follow the three 'E's:

- Equipment: HCPs should have appropriate equipment available to demonstrate correct inhaler technique. Placebo inhalers and inhaler technique checklists are suitable tools for demonstrating proper inhaler usage and instructing a patient
- Expertise: HCPs should practice the technique required for different inhalers until they are familiar; videos are available, e.g. www.nationalasthma.org.au/health-professionals/how-to-videos
- Expectation: HCPs should encourage all staff to routinely check their patients' inhaler technique, reinforce proper technique, and correct errors

An effective way to start a conversation with patients about their inhaler technique is to ask "Can you show me how you use your inhaler at present?" There are several scenarios where demonstrating proper inhaler technique can be incorporated into clinical practice (Table 1). Media platforms such as World Asthma Day are also effective in reminding both practitioners and patients to check that inhaler technique is being taught and used correctly.

Perhaps the key message is to help HCPs understand that not all inhaler devices are the same and that inhaler skills training is needed.[37,38]

Although both HCPs and patients can be taught the correct use of inhalers, errors often re-emerge over time. For HCPs, using inhaler technique checklists to check and correct their patients' inhaler technique may help to maintain their own skills.[38] For patients, the simple solution of placing a label with a checklist of steps on their inhaler with their initial inhaler technique errors was highlighted; this was recently found to improve maintenance of correct technique compared with no label when patients were assessed 3 months later (Basheti et al., unpublished data). More technological tools have been developed, including educational apps for patients, however the relative success of these interventions is still unclear.[39]

In conclusion, it is important to reinforce that teaching correct inhaler technique is the responsibility of every member of a healthcare team, and although HCP roles are demanding there is a need to be creative about how proper inhaler technique can be taught in clinical practice.

Question and Answer Session

Q: In regards to children learning inhaler technique, who do they learn it from and are they learning it correctly?

Prof Bosnic-Anticevich replied that most patients with asthma start using an inhaler as a child and it is important to look at the scenario and environment in which they are learning to use their inhalers. The aim should be for the child to be autonomous in their use of inhaler and transition to managing their medications themselves. Data show that parents have concerns about medications and may not know how to properly use the inhalers, and would like to receive more education.

Q: What can we do in current research to increase awareness of the importance of patient perspective and variability between patients?

Dr Beeh replied that the best way to persuade regulators is to generate good evidence that accounting for patient perspective and variability is linked to meaningful outcomes, and that this can be demonstrated with clinical studies on inhaler technique and adherence.

REFERENCES

1. The Henry J. Kaiser Family Foundation. Snapshots: Health Care Spending in the United States & Selected OECD Countries. 2011. Available at: http://kff.org/health-costs/issue-brief/snapshots-health-care-spending-in-the-united-states-selected-oecd-countries/. Last accessed: 14 September 2016.

2. Anderson HR et al. 50 years of asthma: UK trends from 1955 to 2004. Thorax. 2007;62(1):85-90.

3. National Review of Asthma Death. Why asthma kills. The National Review of Asthma Deaths (NRAD). 2014. Available at: https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills. Last accessed: 14 September 2016.

4. Boulet LP et al. Evaluation of asthma control by physicians and patients. Can Respir J. 2002;9(6):417-23.

5. Haughney J et al. Achieving asthma control in practice: Understanding the reasons for poor control. Respir Med. 2008;102(12):1681-93.

6. Vestbo J et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax. 2009;64(11):939-43.

7. Covvey JR et al. A comparison of medication adherence/persistence for asthma and chronic obstructive pulmonary disease in the United Kingdom. Int J Clin Pract. 2014;68(10):1200-8.

8. Gamble J et al. The prevalence of nonadherence in difficult asthma. Am J Respir Crit Care Med. 2009;180(9):817-22.

9. Bourdin A et al. Adherence in severe asthma. Clin Exp Allergy. 2012;42(11): 1566-74.

10. Chrystyn H et al. Impact of patients' satisfaction with their inhalers on treatment compliance and health status in COPD. Respir Med. 2014;108(2):358-65.

11. Castro M et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015;3(5):355-66. Erratum in: Lancet Respir Med. 2015;3(4):e15.

12. Roche N et al. Effectiveness of inhaler devices in adult asthma and COPD. EMJ Respir. 2013;1:64-71.

13. Dolovich MB et al.; American College of Chest Physicians, American College of Asthma, Allergy, and Immunology. Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/ American College of Asthma, Allergy, and Immunology. Chest. 2005;127(1):335-71.

14. Brocklebank D et al. Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering corticosteroids in asthma. BMJ. 2001;323(7318):896-900.

15. Levy ML et al. Asthma patients' inability to use a pressurised metered-dose inhaler (pMDI) correctly correlates with poor asthma control as defined by the global initiative for asthma (GINA) strategy: a retrospective analysis. Prim Care Respir J. 2013;22(4):406-11.

16. Price D et al. Establishing the relationship of inhaler satisfaction, treatment adherence, and patient outcomes: a prospective, real-world, cross-sectional survey of US adult asthma patients and physicians. World Allergy Organ J. 2015;8(1):26.

17. Sandler N et al. Evaluation of inhaler handling-errors, inhaler perception and preference with Spiromax, Easyhaler and Turbuhaler devices among healthy Finnish volunteers: a single site, single visit crossover study (Finhaler). BMJ Open Resp Res. 2016;3(1):e000119.

18. Öztürk C et al. Evaluation of inhaler technique and patient satisfaction

with fixed-combination budesonide/formoterol dry-powder inhaler in chronic obstructive pulmonary disease (COPD): data on real-life clinical practice in Turkey. Tuberk Toraks. 2012;60(4):301-13.

19. Basheti IA et al. Counseling about turbuhaler technique: needs assessment and effective strategies for community pharmacists. Respir Care. 2005;50(5):617-23.

20. Fink JB, Rubin BK. Problem with inhaler use: a call for improved clinician and patient education. Respir Care. 2005;50(10):1360-74.

21. Bosnic-Anticevich SZ et al. Metered-dose inhaler technique: the effect of two educational interventions delivered in community pharmacy over time. J Asthma. 2010;47(3):251-6.

22. Research in Real-Life. CRITIKAL study protocol. Version 5.4. 2015. Available at: http://www.encepp.eu/encepp/openAttachment/fullProtocol/10058;jsessionid=Dj1ekuuVTLkBnT-x6AxkNrTX8SYcrxSx9a6HAgglFAqnfstKBwkV!1388761727. Last accessed: 14 September 2016.

23. Bosnic-Anticevich S et al. Investigating the maintenance of inhaler device mastery of healthcare professionals. Abstract 2323. European Academy of Allergy and Clinical Immunology 2015 Annual Congress. 6-10 June, 2015. Available at: http://www.professionalabstracts.com/eaaci2015/iplanner/. Last accessed: 1 October 2016.

24. Bosnic-Anticevich S et al. Investigating inhaler device mastery in pharmacist trainees. Eur Respir J 2015;46(Suppl):PA701.

25. Lewis A et al. The economic burden of asthma and chronic obstructive pulmonary disease and the impact of poor inhalation technique with commonly prescribed dry powder inhalers in three European countries. BMC Health Serv Res. 2016;16:251.

26. Ovchinikova L et al. Inhaler technique maintenance: gaining an understanding from the patient's perspective. J Asthma. 2011;48(6):616-24.

27. Chrystyn H, Haathala T. Real-life inhalation therapy – inhaler performance and patient education matter. Eur Respir Dis. 2012;8(1):11-8.

28. Laube BL et al. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J. 2011;37(6):1308-31.

29. Molimard M et al. Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care. J Aerosol Med. 2003;16(3):249-54.

30. Melani AS et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med. 2011;105(6):930-8.

31. Canonica GW et al. Spiromax, a new dry powder inhaler: Dose consistency under simulated real-world conditions. J Aerosol Med Pulm Drug Deliv. 2015;28(5):309-19.

32. Chrystyn H et al. Evaluation of inhaler technique mastery for budesonide formoterol Spiromax® compared with Symbicort Turbohaler® in adult patients with asthma: Primary results from the Easy Low Instruction Over Time [ELIOT] Study. Thorax. 2015;70(Suppl 3):A154-5.

33. Palander A et al. In vitro comparison of three salbutamol-containing multidose dry powder inhalers. Clin Drug Investig. 2000;20(1):25-33.

34. Weuthen T et al. In vitro testing of two formoterol dry powder inhalers at different flow rates. J Aerosol Med. 2002;15(3):297-303.

35. Azouz W et al. Inhalation characteristics of asthma patients, COPD patients and healthy volunteers with the Spiromax® and Turbuhaler® devices: a randomised, cross-over study. BMC Pulm Med. 2015;15:47.

36. Chrystyn H et al. Effect of inhalation profile and throat geometry on predicted lung deposition of budesonide and formoterol (BF) in COPD: An in-vitro comparison of Spiromax with Turbuhaler. Int J Pharm. 2015;491(1-2):268-76.

37. Toumas M et al. Comparison of small-group training with self-directed internet-based training in inhaler techniques. Am J Pharm Educ. 2009;73(5):85.

38. Basheti IA. The effect of using simulation for training pharmacy students on correct device technique. Am J Pharm Educ. 2014;78(10):177.

39. Huckvale K et al. The evolution of mobile apps for asthma: an updated systematic assessment of content and tools. BMC Med. 2015;13:58.

WHY, WHEN, AND HOW? OPTIMISING THE MANAGEMENT OF PATIENTS WITH SEVERE EOSINOPHILIC ASTHMA

Summary of the symposium which took place on 5th September 2016 as a part of the European Respiratory Society (ERS) International Congress in London, UK

Chairperson

Ian Pavord[1]

Speakers

Roland Buhl,[2] Richard W. Costello,[3] Mario Castro[4]

1. Professor of Respiratory Medicine, University of Oxford, Honorary Consultant Physician, University of Oxford Hospitals NHS Trust, Oxford, UK

2. Professor of Medicine, Head of the Pulmonary Department, Mainz University Hospital, Mainz, Germany

3. Associate Professor of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland

4. Asthmas and Airway Translational Research Unit, Washington University School of Medicine, St Louis, Missouri, USA

Disclosure: Prof Pavord has received speaker's honoraria from AstraZeneca, Boehringer Ingelheim, Aerocrine, Respivert, Teva, and GSK; and advisory panel fees from Almirall, AstraZeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey, and Napp. Prof Pavord has also received sponsorship honoraria from Boehringer Ingelheim, GSK, AstraZeneca, and Napp. Prof Buhl has received speaker/consulting honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Roche, and Teva, and has received research support from Boehringer Ingelheim, GSK, Novartis, and Roche. Prof Costello is a speaker and advisory board member to Aerogen, Boehringer Ingelheim, GSK, Novartis, and Teva, and has received grant support from Aeorogen, Vitalograph, and GSK. Prof Costello has an active patent on use of acoustic analysis to assess inhaler technique of use. Prof Castro has received royalties from Elsevier, speaker fees from Boeringer Ingelheim, Boston Scientific, Genentech, and Teva and has received consulting fees from AstraZeneca, Boston Scientific, Holaira, NeoStem, Neutronic, Novartis, Roche, Sanofi Aventis, Teva, and Therabron. Prof Castro has also received funding from AsthmaNet, the American Lung Association, Severe Asthma Research Programme, Amgen, Boehringer Ingelheim, Genentech, Gilead, GSK, Invion, Johnson & Johnson, Medimmune/AstraZeneca, Novartis, Pfizer, Sanofi Aventis, Teva, and Vectura.
Acknowledgements: Writing assistance was provided by Mia Cahill of ApotheCom.
Support: The publication of this article and the symposium at the International Congress of the European Respiratory Society (ERS) were funded by Teva Pharmaceuticals B.V. The views and opinions expressed are those of the authors and not necessarily Teva Pharmaceuticals B.V. or the ERS.
Citation: EMJ Respir. 2016;4[1]:51-59.

MEETING SUMMARY

The main objectives of this symposium were to explore the challenges faced when treating patients with severe eosinophilic asthma, to evaluate the key clinical assessments that are available for early disease recognition, and to discuss the latest personalised treatment options that could shape future management strategies. Prof Ian Pavord opened the symposium by introducing uncontrolled severe asthma, focussing on the challenges and unmet needs of patients. Prof Buhl then delved into the basics of eosinophilic asthma from a molecular and physiological point of view, discussing the clinical relevance and characterisation of eosinophilic patients. Prof Costello focussed on the key clinical assessments (diagnosis, adherence, and phenotyping) and management of patients. Prof Castro summarised the latest evidence from studies of mepolizumab, benralizumab, reslizumab, anti-interleukin (IL)-4, and anti-IL-13 therapies, and how this relates to clinical practice.

A New Era for Patients with Uncontrolled Severe Asthma

Professor Ian Pavord

Patients with severe asthma are a small subgroup of patients, comprising 5–10% of the total asthma population (approximately 300 million patients worldwide). Despite taking appropriate treatments and adhering to therapies, ≤5% of patients have severe refractory asthma. Eosinophilic asthma is the cause of severe refractory asthma in 50–60% of patients, making them potential candidates for anti-IL-5 treatment.[1-3] Patients with severe asthma are a very important subgroup as they require high-intensity treatment; those receiving Global Initiative for Asthma (GINA) Step 4 (medium/high-dose inhaled corticosteroid or long-acting β-agonist) or Step 5 (add-on therapy e.g. mepolizumab) treatment to control their asthma or who remain uncontrolled despite treatment.[4] Severe asthma patients account for >80% of all direct healthcare costs in asthma and are therefore important from a health services point of view.[1-3]

The European Respiratory Society/American Thoracic Society (ERS/ATS) define severe asthma as requiring high-dose combination treatment, often with other therapies, for at least a year or that which requires systemic corticosteroids for at least half a year to prevent it from becoming uncontrolled, or which remains uncontrolled despite high-intensity treatment. Asthma can become uncontrolled because of poor symptom control (Asthma Control Questionnaire [ACQ] score >1.5 or Asthma Control Test score <20), frequent severe exacerbations (≥2 bursts of corticosteroids in previous year); the occurrence of one serious exacerbation resulting in hospitalisation; intensive care unit admission or mechanical ventilation in the previous year; persistent airflow limitation (post-bronchodilator forced expiratory volume in 1 second [FEV_1] <80% predicted); or if controlled asthma worsens on tapering of treatment.[5]

A survey conducted in patients with asthma highlighted that they are most concerned about exacerbations, episodes of asthma that do not respond to bronchodilators,[6] and the burden associated with oral corticosteroid therapy.[7,8] Severe asthma exacerbations are the most clinically important manifestations of asthma and result in death in 1,200 cases per year in the UK.

How Should We Approach the Clinical Assessment of Patients with Severe Asthma?

When assessing a patient for severe asthma it is critical to identify: i) those who have pseudo-asthma or comorbid asthma, in which another factor is responsible for the symptoms (i.e. dysfunctional breathing or upper airway problems); ii) patients who have not mastered inhaler technique, self-management, or have poor adherence; and iii) those with genuine severe disease. Assessment should centre on whether there is objective evidence of airway dysfunction and airway inflammation, and if there are other factors contributing to symptoms.

Phenotyping Disease

After carrying out basic measurements of spirometry, fractional exhaled nitric oxide (FeNO), and blood eosinophils, the phenotype of the patient can be determined. This is important as severe asthma is heterogeneous, particularly in the way eosinophilic airway inflammation relates to airway dysfunction. Two main groups of discordant patients exist, inflammation-predominant and symptom-predominant,[9] suggesting that a symptom-guided approach will not achieve optimum results in these patients. Measuring airway inflammation is the only way to assess for discordant phenotypes and there is clinical value in doing so; targeted treatment to normalise inflammation leads to improved patient outcomes.[10] This key conceptual insight provided the basis for successful pilot studies of anti-IL-5 treatment in severe eosinophilic asthma.[11,12]

Eosinophilic Inflammation Under the Lens

Professor Roland Buhl

Eosinophilic Asthma: The Basics

IL-5 mediates eosinophil maturation and mobilisation in the bone marrow as well as activation of the cells. Eosinophils are delivered to the lungs via the blood stream where they are involved in smooth muscle hypertrophy (eventually leading to airway hyper-responsiveness), matrix deposition (leading to remodelling in some patients), and goblet cell metaplasia and mucous production. Until relatively recently, it was thought that T helper 2 (Th2) cells, as part of the adaptive immune system, were the main source of IL-5 before it was discovered that innate lymphoid Type 2

cells (ILC-2) produce IL-4, IL-5, and IL-13 at higher concentrations compared to Th2 cells. The ILC-2 pathway is part of the innate immune system and as such, unlike in allergic asthma, is not triggered by allergens but rather by microbes, pollutants, and other epithelial danger signals, although both pathways eventually lead to similar inflammatory and functional changes in the asthmatic lung.[13] Asthma can therefore be categorised as Type 2 (T2) high or low asthma based on biomarkers reflecting the T2 cytokine signature, among them blood and sputum eosinophils, FeNO, and serum periostin.[14-16] T2 high asthma is characterised by high eosinophil numbers and/or high FeNO or periostin levels, indicating high concentrations of T2 cytokines IL-5 and IL-13. Approximately 40–60% of patients with severe asthma have eosinophilic asthma;[17] eosinophils, when activated, release various mediators that damage lung tissue and induce airway hyper-responsiveness and mucous hypersecretion. The number of sputum and blood eosinophils correlates with disease severity.

Clinical Relevance of Eosinophilic Disease

In a study by Malinovschi et al.,[18] an increasing number of blood eosinophils and increasing concentrations of nitric oxide (NO) in exhaled breath were correlated with a higher prevalence of asthma attacks and asthma-related emergency department visits. Similarly, a strong independent predictor of asthma mortality is blood eosinophilia; patients with blood eosinophils ≥450/µL have a 2-fold higher mortality risk.[19] The prognostic relevance of blood eosinophils was also demonstrated in a study of 130,248 patients aged 12–80 years in which blood eosinophils greater than or less than 400 µL were significantly correlated with acute respiratory events, severe exacerbations, and poor asthma control (Figure 1).[20]

How to Characterise a Patient with Severe Eosinophilic Asthma

When assessing blood cell differentials, it is important to use absolute numbers rather than percentages. This can be calculated simply by dividing leukocytes/µL of blood by 100 and multiplying by the percentage of eosinophils. Large clinical trials indicate that the probability and magnitude of a relevant clinical response to drugs inhibiting IL-5 increases with increasing eosinophil numbers, and that a threshold eosinophilia relevance may be around 300–400 eosinophils/µL. The importance of defining the severity of eosinophilia can be seen in a study by Corren et al.,[21] which explored the effects of reslizumab on lung function stratified by baseline eosinophil thresholds. The change from baseline in FEV_1 was not statistically significant in patients with <400 eosinophils/µL blood but showed meaningful improvement in those with severe eosinophilia (≥400 eosinophils/µL blood).[21]

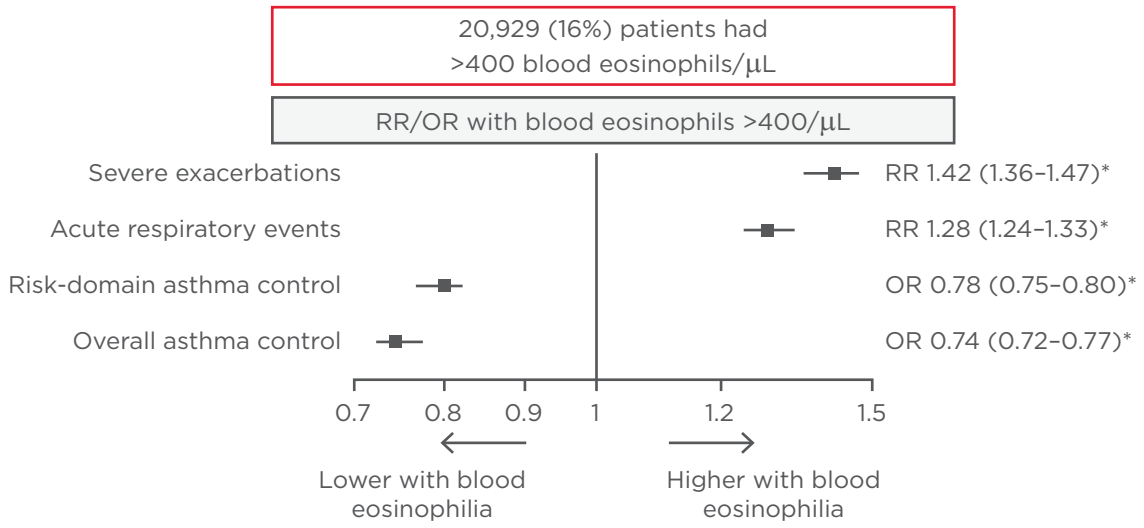


Figure 1: Relative risk of severe exacerbations, acute respiratory events, and overall asthma control in 21,000 patients with blood eosinophils levels >400/µL.[20]

*Adjusted for age, sex, BMI, smoking status, and Charlson comorbidity index score; p<0.0001 for all comparisons.

RR: relative risk; OR: odds ratio.

In Prof Buhl's opinion, typical patients with severe eosinophilic asthma have late-onset of disease, are highly symptomatic, and have frequent exacerbations and eosinophilia in their blood and sputum. Many patients have an increased NO concentration in each exhaled breath and some patients have upper airway complications, including nasal polyposis, compromised senses of smell and taste, and usually respond well to oral corticosteroids.

Exploring the Diagnostic Workup: Key Clinical Assessments

Professor Richard Costello

It is well established that eosinophils localise to the subepithelial space of the airways of patients with asthma.[22] In animal models, this is strongly associated with subepithelial thickness and it is postulated that subepithelial fibrosis leads to chronic fixed airway obstruction. Costello et al.[23] have shown interweaving nerve fibres co-localised with eosinophils, which perhaps mediates cough and sensations of chest tightness. Eosinophil infiltration correlates with the symptoms described; obstruction, reversibility during an exacerbation, and mucous production.

Mucous is very important in asthma as it plugs the airways in patients with fatal asthma,[24] and is frequently seen on imaging; multiple detector computed tomography (CT) scanning has shown that 58% of asthmatics had mucous in at least one segment.[25] Immunofluorescence microscopy reveals eosinophils in the subepithelial space and strands of mucous within mucous plugs that tether mucopolysaccharides together, making the mucous tenacious. When referring to mucous in the context of eosinophilic asthma, mucous plugging rather than a bronchitis phenotype must be thought about, from the occasional sighing-type feature sometimes described by patients to the acute ventilatory failure that occurs in an acute severe asthma attack or the regional heterogeneity that leads to an increase in alveolar–arterial gradient and dysfunctional ventilation.

Clinical Assessment and Management of Patients with Severe Eosinophilic Asthma

When assessing patients with asthma, certain features should be looked for to allow accurate identification of those who may be suitable for anti-IL-5 therapy. Firstly, the diagnosis of asthma must be confirmed; secondly, patient adherence to therapy should be reviewed; and thirdly, the patient should be ascribed to a phenotype.

Prof Costello described a case of a 55-year-old man with a 15-year history of asthma that was uncontrolled and had persistent symptoms, particularly in the last 5 years despite long-acting beta-2 agonist/inhaled corticosteroid (LABA/ICS) use. He presented with cough, wheeze, and breathlessness on moderate exertion, and had nasal congestion and loss of smell. The patient's diagnosis was confirmed with spirometry. According to the GINA recommendations, stepping up treatment should be considered if symptoms remain uncontrolled but inhaler technique and adherence must be checked first.[4] Adherence and technique can be checked by examining the patient's inhaler, asking them to demonstrate technique, checking for deposition of medication on the epiglottis, and checking pharmacy refill records.

If patients are to be funnelled through Stage IV treatment onto Stage V, adherence needs to be objectively assessed. Inhaler Compliance Assessment (INCA) technology can be utilised to record audio of inhaler use. An acoustic recording device is attached to the inhaler and each step of use is recorded. The recordings are then downloaded and signal processing analysis identifies when, how regularly, and how well the inhaler is used, which is presented as a calendar graph. The visual representation can be used for follow-up to identify if intervention helps asthma control and as feedback on inhaler technique.

The patient was placed on the INCA programme for 2 months, which confirmed good adherence and was ascribed by measuring peripheral blood count, which revealed 400 eosinophils/cm^3 with elevated immunoglobulin E (IgE). This phenotype suggested that the patient would benefit from anti-eosinophilic therapy.

Applying Evidence to Clinical Practice: Options for Patients with Uncontrolled Severe Eosinophilic Asthma

Professor Mario Castro

The ATS/ERS guidelines outline six clinical phenotypes with physiological associations and specifically-targeted therapies, even though

some associations and treatments have not been evaluated prospectively in randomised controlled trials. The eosinophilic asthma phenotype, however, has a preponderance of evidence demonstrating high serum IgE, recurrent exacerbations, high FeNO, and response to three different anti-IL-5 drugs that substantiate this unique phenotype.[5] Several determinants of an anti-IL-5 response should be considered: exposure to the drug; disease severity; level of baseline control; blood eosinophil level; prevention of further eosinophil infiltration; and other patient factors (e.g. associated comorbidities and allergy).

Mepolizumab: The DREAM Trial

The DREAM trial[26] compared the effectiveness of the anti-IL-5 drug mepolizumab at 75 mg, 250 mg, and 750 mg administered intravenously (IV) once a month over 1 year. The primary endpoint, clinically significant exacerbations, was dramatically reduced compared with placebo for all three doses (exacerbation rate: placebo=2.40/year; 75 mg=1.24/year; 250 mg=1.46/year; 750 mg= 1.15/year) (Figure 2). Secondary endpoints included a change in blood eosinophil count, sputum eosinophil count, pre-bronchodilator FEV_1, and ACQ score. Mepolizumab produced no significant effect on asthma control in all three doses and had variable effects across doses on lung function, but positive results were seen for the reduction of eosinophils ($p<0.001$ versus placebo for blood eosinophil counts). Dose discrepancies were observed for sputum eosinophil count: 75 mg and 250 mg mepolizumab were not significantly effective, whereas 750 mg mepolizumab demonstrated a significant reduction ($p=0.0082$). The side effect profile of mepolizumab was similar across the three doses and not significantly different compared with placebo.

Benralizumab

Benralizumab is a humanised monoclonal antibody that binds with high affinity to the IL-5 receptor alpha subunit and depletes eosinophils through antibody-dependent cell-mediated cytotoxicity.[27] Various doses of benralizumab have been explored for the treatment of asthma, and in a Phase II study by Castro et al.[28] patients were stratified by eosinophil phenotype (based on the ratio of blood eosinophils [E] to lymphocytes [L], the ratio of blood eosinophils [E] to neutrophils [N] [ELEN index], and FeNO) into either eosinophilic or non-eosinophilic groups. Eosinophilic patients were randomised to either 2 mg, 20 mg, or 100 mg of benralizumab versus placebo, and non-eosinophilic patients were randomised to 100 mg benralizumab or placebo. Patients were followed >1 year and the primary endpoint looked at asthma exacerbations. Results showed that the 20 mg and 100 mg doses reduced exacerbations in the eosinophilic group, with an annual exacerbation rate reduction (AERR) of 36% ($p=0.173$) and 41% ($p=0.096$), respectively; the non-eosinophilic group had an AERR of 22% ($p=0.284$). The degree of eosinophilia in enrolled patients ranged from 50 cells/µL to ≥500 cells/µL and was mapped against AERR relative to placebo. Data showed a significant reduction in exacerbations for eosinophil levels ≥300 cells/µL; for 100 mg benralizumab 43% ($p=0.049$) and 70% ($p=0.002$) AERR was achieved for ≥300 cells/µL and ≥400 cells/µL, respectively. Treatment with anti-IL-5 confirmed that there was a significant reduction in exacerbations for patients with baseline eosinophil levels ≥300 cells/µL. The side effect profile of benralizumab was favourable with adverse events comparable across all three doses and placebo.

Reslizumab

Reslizumab is a humanised anti-human IL-5 monoclonal antibody that is licensed for the treatment of severe asthma in the USA and European Union (EU) at an IV dose of 3 mg/kg. A Phase II study of 106 patients with uncontrolled asthma and elevated eosinophil counts explored the effects of reslizumab 3 mg/kg (administered at baseline and at Weeks 4, 8, and 12) on blood eosinophils levels.[29] Reslizumab effectively reduced blood and sputum eosinophil levels to below baseline and reductions were observed as early as Week 4. At the end of the study, median percentage reductions in eosinophils in sputum were 95.4% in the treatment group and 38.7% in the placebo group ($p=0.0068$). Exacerbations occurred in 8% in the reslizumab group versus 19% in the placebo group ($p=0.083$). Reslizumab did not show a consistent effect on the primary endpoint, the ACQ score. Overall, 59% of patients in the reslizumab group achieved improvement of at least 0.5 in ACQ score compared with 40% in the placebo group (95% confidence interval: 2.06 [0.88–4.86], $p=0.0973$), which is the minimal clinically significant change. Significant improvement in lung function, measured by FEV_1 change from baseline, was seen after one dose of study drug ($p=0.0364$).[29] Patients with a history of nasal polyposis showed a marked improvement in ACQ score (-1.0 reslizumab versus

-0.1 placebo, p=0.012) compared with those with no history of nasal polyposis (-0.5 reslizumab versus -0.4 placebo, p=0.7176).

Two Phase III trials explored the effect of reslizumab 3 mg/kg administered over 52 weeks in patients with exacerbation-prone uncontrolled eosinophilic asthma. The studies met the primary endpoint, reduction of clinical exacerbation rate, demonstrating a pooled reduction rate of 54% compared with placebo (p<0.0001) (Figure 3). Secondary endpoints of lung function, quality of life score, ACQ score, and asthma symptom utility index were also met. Reslizumab was efficacious in reducing asthma exacerbations regardless of treatment received at baseline. Reslizumab was well-tolerated across the two studies and had slightly fewer discontinuations due to adverse events compared with placebo.[30]

Reslizumab had a greater effect on asthma exacerbation rate in adults aged ≥65 years (67% reduction compared with placebo) compared with younger adults (53% reduction compared with placebo).[31] Patients with late-onset disease (aged ≥40 years) have a preferential reduction rate in asthma exacerbations (75% reduction compared with placebo) when compared with those with early-onset disease (42% reduction compared with placebo).[32] Reslizumab demonstrated greater efficacy in reducing frequency of asthma exacerbations in patients with a history of chronic sinusitis and/or nasal polyposis.[33]

Other Biologic Therapies: Anti-Interleukin-4 and Anti-Interleukin-13

Targeting the IL-4 alpha receptor impacts IL-4 and IL-13 binding and leads to in-organ effects of mucous cell metaplasia, inflammation, and airway hyperactivity. Dupilumab, a monoclonal antibody against the IL-4 alpha receptor administered every 2 weeks at doses of 200 mg and 300 mg, was efficacious in reducing asthma exacerbations in the overall asthma population (70% reduction compared to placebo for both doses) and in the high eosinophil population (≥300 cells/μL) (71% and 81% reduction compared with placebo, respectively).[34]

Lebrikizumab, an anti-IL-13 drug, improved FEV_1 in patients with high pretreatment serum periostin.[35]

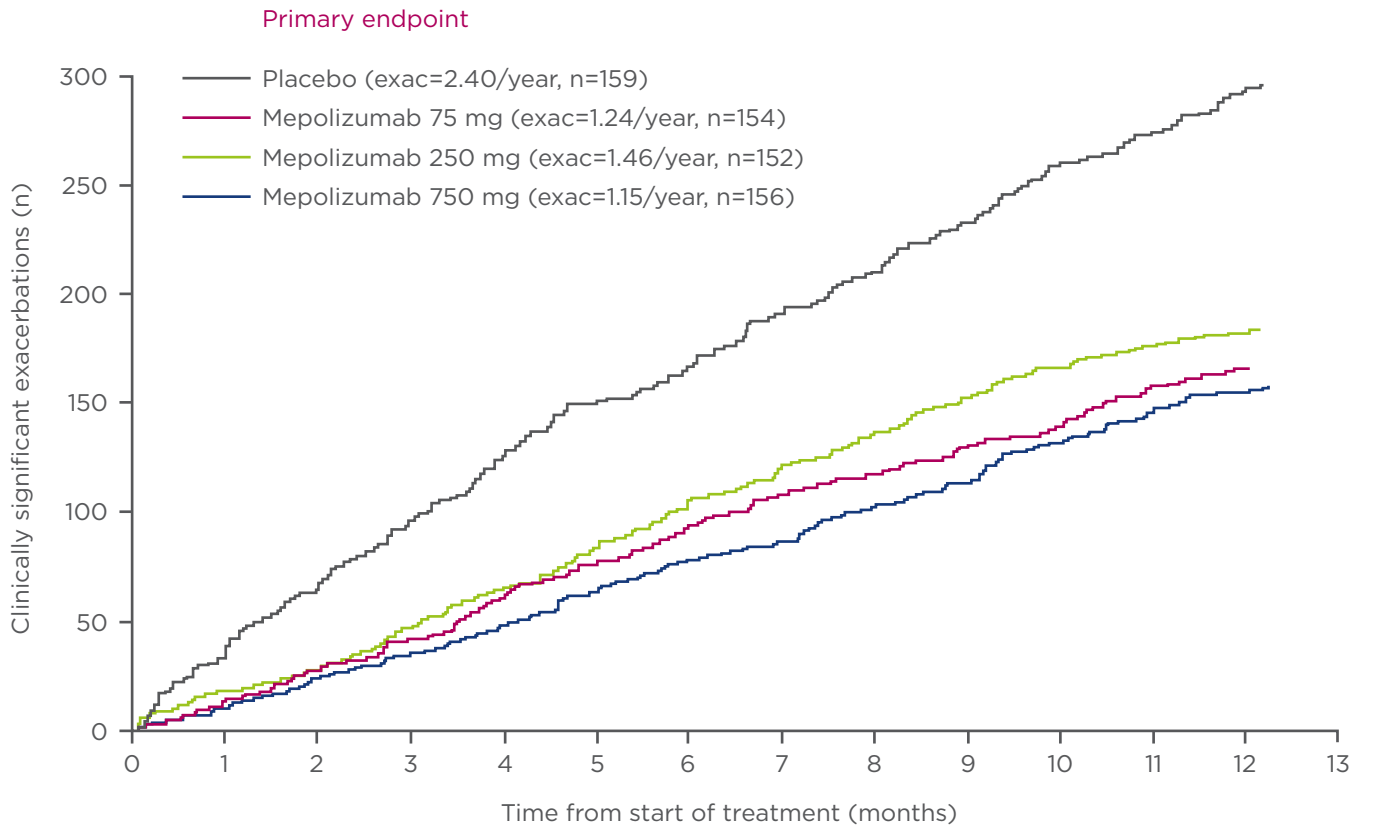


Figure 2: Efficacy of mepolizumab in reducing clinically significant asthma exacerbations in patients with severe eosinophilic asthma.[26]
exac: exacerbation rate.

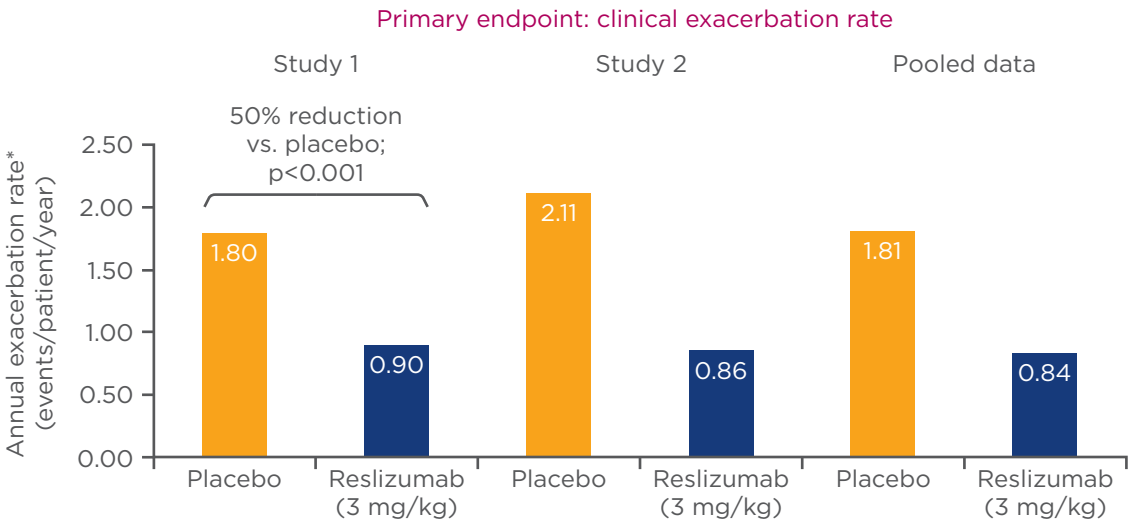


Figure 3: Data from two Phase III trials exploring the effect of reslizumab or placebo on annual exacerbation rate.[30]

*Exacerbations were defined as worsening asthma resulting in any of the following: use of systemic corticosteroids in steroid-naïve patients, a 2-fold increase in the dose of either inhaled corticosteroid or systemic corticosteroids for ≥3 days, or the need for asthma-related emergency treatment.

Tralokinumab is an anti-IL-13 drug that did not demonstrate significant reduction in asthma exacerbations in patients with severe asthma; however, patients with high serum dipeptidyl peptidase-4 levels showed improvements in FEV_1, ACQ score, and quality of life. Likewise, patients with high periostin concentrations showed improvements in asthma exacerbation rate, FEV_1, and ACQ score.[36] Omalizumab, an anti-IgE therapy, has retrospectively shown a 25% reduction in exacerbations compared with placebo in patients with high eosinophil and periostin levels.[37]

In conclusion, we are on the threshold of a new era for severe asthma. Anti-IL-5 treatment has demonstrated a positive effect on the reduction of asthma exacerbations and the requirement for oral corticosteroids in severe asthma. Biologic agents targeting IL-4, IL-13, and IgE show promise and are being explored in clinical studies. Blood eosinophil levels offer an excellent therapeutic and prognostic tool that help identify patient subgroups suitable for treatment with anti-IL-5 therapy. To further advance the field and make the most of anti-IL-5 and other biological treatments, new biomarkers and models of disease are necessary.

Question and Answer Session

Q: Is blood eosinophilia variable within patients, and if so, how many tests should be carried out before treatment is chosen?

Prof Pavord replied that blood eosinophilia can be triggered by viral infection of the upper airways. Therefore, a single measurement should never be relied on, instead, measurements should be taken over a period of 2–3 weeks. In patients taking systemic corticosteroids, a history of consistent eosinophilia is sufficient.

Q: Is there a need to reduce sputum eosinophils, as the clinical efficacy seems to be large with just a blood eosinophil reduction?

Prof Pavord replied that most clinicians do not measure sputum eosinophil levels in daily practice, although when it is used as a target the reduction in exacerbations is significant. Therefore, if sputum eosinophil levels are available they should be utilised to drive therapy.

Footnotes

Benralizumab was not approved at the time of the symposium and writing of this manuscript, and there may be other data available not covered by the faculty during the symposium. AstraZeneca published online in the Lancet on the 5th September 2016 two Phase III trials: CALIMA[38] and SIROCCO.[39] Benralizumab reduced annual exacerbation rates by 28% in CALIMA and 51% in SIROCCO (30 mg every 8 weeks). In conjunction with the DREAM trial, GSK published online 8th September 2014 in The New England Journal of Medicine the MENSA trial.[40] Asthma exacerbations were significantly alleviated by the administration of mepolizumab both IV and subcutaneously.

REFERENCES

1. Akinbami LJ et al. Asthma prevalence, health care use, and mortality: United States, 2005-2009. Natl Health Stats Report. 2011;12(32):1-14.

2. Masoli M et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004;59(5):469-78.

3. Rodrigo GJ et al. Acute asthma in adults: a review. Chest. 2004;125(3): 1081-102.

4. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2016. Available at: http://www.ginasthma.org. Last accessed: 13 September 2016.

5. Chung KF et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73.

6. Price D, Pearson M. What is success in asthma – the patient's view. Am J Respir Crit Care Med. 1998;157:A631.

7. Sarnes E et al. Incidence and US costs of corticosteroid-associated adverse events: a systematic literature review. Clin Ther. 2011;33(10):1413-32.

8. Elixhauser A et al. Health Cost Util Proj. 2007;1-12.

9. Haldar P et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008;178(3):218-24.

10. Green RH et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet. 2002; 360(9347):1715-21.

11. Haldar P et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009;360(10): 973-84.

12. Nair P et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009; 360(10):985-93.

13. Brusselle GG et al. Eosinophils in the spotlight: Eosinophilic airway inflammation in nonallergic asthma. Nat Med. 2013;19(8):977-9.

14. Robinson DS et al. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. N Engl J Med. 1992;326(5):298-304.

15. Bernink JH et al. The role of ILC2 in pathology of type 2 inflammatory diseases. Curr Opin Immunol. 2014;31: 115-20.

16. Wechsler ME. Combating the eosinophil with anti-interleukin-5 therapy. N Engl J Med. 2008;358(12):1293-4.

17. Zhang JY, Wenzel SE. Tissue and BAL based biomarkers in asthma. Immunol Allergy Clin North Am. 2007;27(4): 623-32.

18. Malinovschi A et al. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. J Allergy Clin Immunol. 2013;132(4):821-7.

19. Ali Z et al. Long-term mortality among adults with asthma: a 25-year follow-up of 1,075 outpatients with asthma. Chest. 2013;143(6):1649-55.

20. Price DB et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med. 2015;3(11):849-58.

21. Corren J et al. Phase 3 Study Of Reslizumab in Patients with Poorly Controlled Asthma: Effects Across a Broad Range Of Eosinophil Counts. Chest. 2016;150(4):799-810.

22. Thornton MA et al. Eosinophil recruitment to nasal nerves after allergen challenge in allergic rhinitis. Clin Immunol. 2013;147(1):50-7.

23. Costello RW et al. Localization of eosinophils to airway nerves and effect on neuronal M2 muscarinic receptor function. Am J Physiol. 1997;273(1 Pt 1):L93-103.

24. Filley WV et al. Identification by immunofluorescence of eosinophil granule major basic protein in lung tissues of patients with bronchial asthma. Lancet. 1982;2(8288):11-6.

25. Dunican E et al. Regional Ventilation Defects Measured On Hyperpolarized 3HE MRI Are Associated With Mucus Plugging Measured On CT In Asthma. Am J Respir Crit Care Med. 2016;A2004.

26. Pavord ID et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012; 380(9842):651-9.

27. Kolbeck R et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. J Allergy Clin Immunol. 2010;125(6):1344-53.

28. Castro M et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med. 2014;2(11):879-90.

29. Castro M et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011;184(10): 1125-32.

30. Castro M et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015; 3(5):355-66.

31. Bernstein D et al. Efficacy of Reslizumab in Older Patients (≥65 Years) with Asthma and Elevated Blood Eosinophils: Results from a Pooled Analysis of Two Phase 3, Placebo-Controlled Trials. J Allergy Clin Immunol. 2016;137(2):AB86.

32. Brusselle G et al. Reslizumab in patients with late-onset asthma with elevated blood eosinophils. Eur Resp J. 2015;46: OA287.

33. Weinstein SF et al. Efficacy of Reslizumab with Asthma, Chronic Sinusitis with Nasal Polyps and Elevated Blood Eosinophils. J Allergy Clin Immunol. 2016;137(2):AB86.

34. Wenzel S et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-

to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet. 2016;388(10039):31-44.

35. Corren J et al. Lebrikizumab treatment in adults with asthma. N Engl J Med. 2011; 365(12):1088-98.

36. Brightling CE et al. Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial. Lancet Respir Med. 2015;3(9): 692-701.

37. Hanania N et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med. 2013;187(8):804-11.

38. FitzGerald JM et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016; doi: 10.1016/S0140-6736(16)31322-8. [Epub ahead of print].

39. Bleecker ER et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016; doi: 10.1016/S0140-6736(16)31324-1. [Epub ahead of print].

40. Ortega HG et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014; 371(13):1198-207.

DOES ANAESTHESIA TYPE INFLUENCE THE QUALITY OF SMEARS OBTAINED DURING ENDOSONOGRAPHY IN PATIENTS WITH MEDIASTINAL ADENOPATHY?

***Ilya Sivokozov,[1,2,3] Irina Shabalina,[1] Galina Evgushenko,[1] Dmitry Dedushkin,[2] Eduard Artemkin,[2] Sergey Sokolov,[4] Boris Lensky,[4] Natalya Li,[5] Svetlana Pavlova,[6] Michael Burdyukov,[7] Ilya Yurichev,[7] Dmitry Sazonov,[3] Olga Lovacheva[1]**

1. Department of Endoscopy, Central TB Research Institute, Moscow, Russian Federation
2. Department of Endoscopy, Main Military Hospital, Moscow, Russian Federation
3. Department of Endoscopy, Federal Scientific & Clinical Center, Moscow, Russian Federation
4. Department of Endoscopy, Oncology Hospital #62, Moscow, Russian Federation
5. Department of Endoscopy, Regional Oncology Hospital, Tomsk, Russian Federation
6. Department of Endoscopy, Regional Oncology Hospital, Irkutsk, Russian Federation
7. Department of Endoscopy, Russian Oncology and Scientific Center, Moscow, Russian Federation
**Correspondence to grand63@yandex.ru*

RATIONALE

Until now, there has been controversy regarding the optimal anaesthesia protocol during endosonography in patients with mediastinal lesions. Nowadays, moderate or deep sedation is recommended by recent guidelines as the main anaesthesia procedure for endobronchial ultrasound (EBUS), but supporting evidence for that is minimal and local anaesthesia (LA) remains an option in certain cases. Several studies comparing deep versus moderate sedation in EBUS among this population of patients show conflicting results, thus leaving the question of optimal anaesthesia protocol unresolved.

METHODS

A dataset was extracted from the national web-based Registry of EndoBronchial UltraSound (REBUS), with further filters: isolated mediastinal adenopathy as an indication for endosonography and fine-needle biopsy of subcarinal lymph nodes via transbronchial or transoesophageal approach. A dataset comprising data for 87 predominantly male (61%) patients was retrieved. Data were structured as per each needle pass, reaching a total volume of 187 passes. Mean duration for each procedure type (endoscopic ultrasound-fine needle aspiration [EUS-FNA], EBUS-guided transbronchial needle aspiration [EBUS-TBNA], or EUS-guided bronchial fine-needle aspiration [EUS-b-FNA]), anaesthesia protocol, and proportion of passes with appropriate smear quality were analysed.

RESULTS

Patient groups were equal in numbers (29 per group) and comparable by age (53.5 years). Mean procedure duration for EUS-b-FNA was the shortest compared to other cohorts and reached 9.3 minutes in total, varying from 7.4 minutes under LA to 12.9 minutes under sedation, and reaching 21 minutes when using general anaesthesia (GA). The same data in the EUS-FNA cohort of patients reported 19 minutes in total, 18 minutes under LA, 17.8 minutes under sedation, and 20 minutes under GA. Among the EBUS-TBNA cohort, mean duration of procedure was expectedly longer at 23.9 minutes, 21.9 minutes under LA, 20.3 minutes under sedation, and 31.3 minutes under GA for the total group. In EBUS-TBNA patients, an appropriate quality of smears was retrieved in 77% of passes under LA, 57% using sedation, and all smears were of appropriate quality under GA. Among patients in the EUS-FNA cohort, LA led to even better results, with four out of five passes providing good material. Sedation provided a 60% chance

of obtaining a good smear, and as for the EBUS-TBNA cohort, GA in EUS-FNA gave the best results (100%). EUS-b-FNA presented the same quality of smears for LA (78%), but sedation led to a dramatically lower quality of smears at only 30%. The quality of smears obtained under GA in this group was also higher than in the EBUS or EUS cohorts, reaching 83%. Combining these data, the proportion of passes with appropriate smear quality (depending on anaesthesia protocol in patients with mediastinal adenopathy) was 79% using LA, 44% in the sedation cohort, and reached a maximum of 96% under GA.

CONCLUSION

Anaesthesia protocol definitely influences the quality of smears obtained during FNA in patients with mediastinal adenopathy. There is, however, still a place for LA in this situation. The unexpectedly low quality of smears obtained under sedation needs to be clarified in a larger cohort of patients, with research into possible underlying factors such as operator experience, needle type, and final diagnosis.

ASTHMA PATIENTS HOSPITALISED WITH INFLUENZA LACK MUCOSAL AND SYSTEMIC TYPE 2 INFLAMMATION

***Akhilesh Jha**

National Heart and Lung Institute, Imperial College London, St. Mary's Campus, London, UK
**Correspondence to a.jha@imperial.ac.uk*

RESEARCH OBJECTIVES

Globally, influenza is estimated to cause 3–5 million cases of severe illness and about 250,000–500,000 deaths annually.[1] Individuals with asthma have enhanced susceptibility to disease[2] and the H1N1 pandemic (swine flu) in 2009–2011 caused large numbers of admissions in this group, accounting for 29% and 31% of hospital admissions in the USA and Australia, respectively.[3,4] Surprisingly, asthmatics may have had a more favourable course of infection and a large UK-based study has found that inhaled corticosteroid use and earlier hospital admission was associated with less severe outcomes.[5] However, the mucosal and systemic immune response in asthma patients hospitalised with influenza has been less well-characterised.

RESEARCH PROCESS

The Mechanisms of Severe Acute Influenza Consortium (MOSAIC) was established to investigate the clinical and immunological profiles of patients presenting to hospitals across the UK with influenza-like illnesses. Detailed demographic information was collected and immune responses were measured in the nasal mucosa using nasosorption, and systemically in serum using a multiplex assay. Patients with asthma accounted for 30% of the MOSAIC cohort of which a large majority were females and had a very good prognosis relative to non-asthmatics. There were equivalent levels of nasal mediators among asthmatics but significantly less systemic inflammation. Interestingly, asthmatic patients did not show evidence of raised Type 2 inflammation compared with non-asthmatics.

CONCLUSION

The patients with asthma in the MOSAIC cohort were predominantly female with significantly reduced morbidity. They also had robust mucosal and systemic interferon responses, but no increase in Type 2 inflammation when compared with non-asthmatics. This raises the idea that those with a specific endophenotype of asthma (females with Type 2 low inflammation) are more predisposed to hospitalisation with influenza. This study emphasises the importance of studying the underlying immune response to viral infections in

hospitalised patients to understand how individual patients may be susceptible to disease. Large cohort studies with well-characterised subjects, such as the Severe Asthma Research Program (SARP)[6] and Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes (UBIOPRED)[7] project, are well placed to further explore these findings.

Acknowledgments

I would like to thank Prof Peter Openshaw, Dr Trevor Hansel, Dr Jake Dunning, Tanushree Tunstall, Dr Ryan Thwaites, and the MOSAIC investigators for their input in establishing the study and analysis of the results. I thank the Medical Research Council and Wellcome Trust for funding the study.

REFERENCES

1. World Health Organization. Influenza (Seasonal). 2016. Available at: http://www.who.int/mediacentre/factsheets/fs211/en/. Last accessed: 13 September 2016.

2. Yoo J-K et al. Viral infection of the lung: host response and sequelae. J Allergy Clin Immunol. 2013;132(6):1263-76.

3. McKenna JJ et al. Asthma in patients hospitalized with pandemic influenza A(H1N1)pdm09 virus infection-United States, 2009. BMC Infect Dis. 2013;13:57.

4. Denholm JT et al. Hospitalised adult patients with pandemic (H1N1) 2009 influenza in Melbourne, Australia. Med J Aust. 2010;192(2):84-6.

5. Myles P et al. Differences between asthmatics and nonasthmatics hospitalised with influenza A infection. Eur Respir J. 2013;41(4):824-31.

6. Jarjour NN et al. Severe asthma. Am J Respir Crit Care Med. 2012;185(4):356-62.

7. Shaw DE et al.; U-BIOPRED Study Group. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. Eur Respir J. 2015;46(5):1308-21.

THE EXPRESSION OF SUBSTANCE P AND THE LOCALISATION OF TACHYKININ NEUROKININ 1 RECEPTORS IN RAT PIAL ARTERIES FOLLOWING TOBACCO SMOKING

***Vera Nevzorova, Natalia Zakharchuk, Elena Gonchar**

Pacific State Medical University, Vladivostok, Russian Federation
**Correspondence to nevzorova@inbox.ru*

BACKGROUND AND AIM

An increasing production of substance P (SP) occurs at the pathogenic stage of many diseases, including those caused by chronic tobacco smoking (CTS). In the case of CTS, the increased SP leads to a higher penetrability of the haematoencephalic barrier, cerebral oedema, and ischaemia. SP acts through tachykinin neurokinin 1 (NK1) receptors previously discovered in neurons, glial cells, and capillary vessels. This paper aimed to study neurogenic inflammation markers (SP and NK1 receptors) in rat pial arteries, based on the comparison between CTS subjects and control animals.

MATERIALS AND METHODS

The study was conducted on pial branches (I–V order vessels) of the middle cerebral artery of male Wistar rats divided into a control and an experimental group, each with 10 animals. Control rats breathed regular atmospheric air while the experimental group was exposed to tobacco smoke for 6 months to recreate a CTS model, following the methodology of Zheng et al.[1] Histological samples of rat brain were produced after euthanasia. The serial sections (10 µm thick) were prepared and stained using antibodies to visualise morphological changes and conduct immunohistochemical analysis of SP and NK1 receptors. The sections were dewaxed and treated with primary antibodies to SP and NK1 receptors using a 1:500 ratio, secondary antibodies stained with horseradish peroxidase at a 1:200 ratio, and

chromogens. The percentage of immunopositive arteries was calculated based on the total amount of discovered vessels in at least 10 sections per animal.

RESULTS

CTS showed certain quantitative alterations in the arterial structure of the pia mater. The dominant type of reaction seen in all orders of vessel branches was dilation, but the most significant surplus in external diameter was detected in branches of the III–V orders directly involved in blood supply of the brain matter. Simultaneously, a significant increase in SP and NK1 receptors in brain vessels in the group of smoker rats was found compared with the control group ($p<0.05$). Despite not detecting any differences in NK1 receptor location in corresponding branches of pial vessels in either the control or experimental groups, the reaction intensity values differed significantly. Small pial arteries showed major differences in branches of the III–V orders, with intensity reaching 18–24%, while branches of the I order did not exceed 4–6%.

CONCLUSION

The results showed that CTS causes significant reorganisation of arterial vessels in the pia mater; the severity of those changes depended on the diameter of the vascular branches. Small pial branches should respond to external exposure with constriction to protect thin-walled intracerebral vessels from excessive blood flow, but in the case of CTS and an increased production of SP, consistent vasodilation developed. The arterial endothelium revealed an intensification of NK1 receptor expression, mediating the effects of SP and increasing the number of small branches. These effects may increase the risk of cerebrovascular events in current smokers.

REFERENCES

1. Zheng H et al. Development and characterization of a rat model of chronic obstructive pulmonary disease (COPD) induced by sidestream cigarette smoke. Toxicol Lett. 2009;189(3):225-34.

MATERNAL BUT NOT PATERNAL BMI IS ASSOCIATED WITH CHILDHOOD WHEEZE AND INFANT RESPIRATORY INFECTIONS

***Katy Pike,[1] Ashley Rajappan,[2] Hazel Inskip,[3] Keith Godfrey,[3,4] Graham Roberts,[5,6] Jane Lucas,[5,6] The Southampton Women's Survey Study Group[3]**

1. UCL Great Ormond Street Institute of Child Health, University College London, London, UK
2. UCL Medical School, University College London, London, UK
3. MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK
4. NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK
5. Academic Unit: Clinical and Experimental Sciences, University of Southampton, Southampton, UK
6. NIHR Southampton Respiratory Biomedical Research Unit, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK
**Correspondence to k.pike@ucl.ac.uk*

BACKGROUND

Children of mothers with a higher BMI have an increased risk of developing wheeze. *In utero* programming might explain this. This study uses paternal BMI to further investigate if a specifically maternal effect exists or whether confounding by shared postnatal environment can explain this association. Relationships between parental BMI and childhood atopy, infections, and lung function during infancy were also assessed.

METHOD

Data from the Southampton Women's Survey mother-offspring cohort were analysed. Of the 3,165 children born in this survey, 2,875 (91%) remained under follow-up at 1 year and 2,034 (64%) at 6 years. Exposures were maternal BMI measured at recruitment, reported maternal BMI pre-pregnancy, and reported paternal BMI during the mother's pregnancy. Measured paternal BMI was available for a small subset. Prospective questionnaires were used to record infections before 1 year and wheeze up to 6 years of age. Lung function was measured in 143 infants using the raised volume technique. Multivariable regression analysis was used to adjust for confounders and test for association using 5 BMI units as the unit of analysis.

RESULTS

Higher reported maternal pre-pregnancy BMI is significantly associated with children having ever wheezed (risk ratio [RR]: 1.07 per 5 BMI units, 95% confidence interval [CI]: 1.03–1.11) and transient wheeze (RR: 1.09 per 5 BMI units, 95% CI: 1.04–1.14). A similar association was found with persistent wheeze, although it was less significant (RR: 1.12 per 5 BMI units, 95% CI: 1.01–1.25). Higher maternal BMI was associated with a greater risk of cough (RR: 1.06 per 5 BMI units, 95% CI: 1.00–1.13) and of lower respiratory tract infection (LRTI) (RR: 1.10 per 5 BMI units, 95% CI: 1.03–1.17) before 1 year. Maternal BMI was not associated with atopy. Infant lung function analyses showed no associations, but they were underpowered. Paternal BMI was not significantly associated with any outcome. A Bland–Altman comparison of measured and reported BMI values demonstrated reasonable agreement in both mothers and fathers. Higher maternal BMI was associated with increased parity, lower maternal education, lower social class, higher birthweight, shorter duration of breastfeeding, and greater risk of maternal asthma, rhinitis, and smoking. Paternal BMI correlated with older maternal and paternal age, shorter paternal height, and decreased risk of maternal pregnancy smoking.

FEEDBACK AT CONFERENCE

The following points were raised and discussed at the ERS International Congress 2016. It is possible that lower vitamin D levels associated with maternal obesity may partly explain some of the associations with childhood outcomes; however, these associations persisted after adjusting for this. Whilst the infant lung function outcomes were underpowered, there may have simply been no association to be found with these outcomes. In this study, paternal obesity was used as a negative control for familial confounding. If we were specifically looking to assess the impact of paternal obesity on childhood outcomes, looking at paternal BMI earlier in life might be more representative of any transmitted intergenerational effect. Finally, we acknowledge that data may not have been reported from the natural father of each child.

CONCLUSION

Higher maternal pre-pregnancy BMI is significantly associated with ever and transient wheeze (RR: 7–9% per 5 BMI units) and higher maternal BMI is associated with a greater risk of cough and LRTI before 1 year. Whilst it was not possible to demonstrate an association between reduced lung function in the first weeks of life and wheeze later in childhood, the association between increased maternal BMI, increased LRTI, and cough recorded in the first year of life provide indirect evidence of reduced airway calibre via increased susceptibility to symptomatic respiratory infection. It is possible that differences in confounder structure might explain the differences in the maternal and paternal analyses. It is also possible that, given the absence of any association between paternal BMI and any outcome, a maternal mechanism (direct or indirect intrauterine) is more likely to be responsible for these findings than shared family and socioeconomic context or paternal factors (genetics).

SUMMARY OF GLOBAL LUNG FUNCTION INITIATIVE (GLI) REFERENCE EQUATIONS FOR THE CARBON MONOXIDE TRANSFER FACTOR

***Sanja Stanojevic on behalf of the European Respiratory Society (ERS) GLI TLCO Task Force**

Division of Respiratory Medicine, Hospital for Sick Children, Toronto, Canada
**Correspondence to sanja.stanojevic@sickkids.ca*

Lung function tests are routinely used to diagnose and monitor patients with respiratory disease; however, interpretation of results is complicated by the dependence of lung function on the size, age, sex, and ethnicity of the individual. To correctly interpret a patient's lung function results, physicians need to know what is expected of healthy individuals of a similar age, height, sex, and ethnicity. Until recently, each lung function laboratory used different sources to define what is expected in healthy individuals. The Global Lung Function Initiative (GLI) reference values for spirometry were created based on combining data from multiple sources to create a single set of predicted values, which can be applied universally across all ages and for multiple ethnic groups.

The single breath transfer factor of the lung for carbon monoxide (TLCO) is the second most commonly used lung function test, and while there are several predicted values available, there are marked differences between them. The aim of the study was to develop GLI all-age, multi-ethnic reference values for TLCO. Data from 19 centres in 14 countries from studies published after the year 2000 were combined. Reference equations based on 12,660 measurements in Caucasian, asymptomatic, lifetime non-smokers aged 4–91 years were derived for TLCO, carbon monoxide transfer coefficient, and alveolar volume. These values were corrected for the alveolar oxygen partial pressure at standard pressure (sea level) and a standard anatomic dead space volume was applied. This is the largest collection of normative TLCO data, and the first robust global reference equation available for TLCO. Importantly, the age-specific values for the lower limit of normal defined from the GLI TLCO data will improve the interpretation of results for patients. While this study represents a significant step forward, there is an urgent need for TLCO data in healthy non-Caucasian subjects.

17q21 VARIANTS ARE STRONGLY ASSOCIATED WITH PERSISTENCE OF SYMPTOMS IN YOUNG CHILDREN WITH WHEEZE

***Raquel Granell, Jonathan Sterne, John Henderson**

School of Social and Community Medicine, University of Bristol, Bristol, UK
**Correspondence to raquel.granell@bristol.ac.uk*

In 2008, a data-driven approach was used to identify six wheezing phenotypes using repeated measures of wheezing from birth to 7 years of age in more than 11,000 children in the Avon Longitudinal Study of Parents and Children (ALSPAC).[1] Later in 2013, it was reported that associations in the 17q21 susceptibility region for early childhood onset asthma were specific to persistent wheezing up to 7 years, but not to wheezing that remits before 3.5 years.[2]

Six new longitudinal wheezing phenotypes up to 16.5 years have been identified in 12,303 children in ALSPAC.[3] The largest phenotype, never or infrequent wheezing (59.9% of the sample),

includes children that never wheeze or had sporadic wheeze. Two phenotypes were identified with early onset wheeze: preschool onset remitting (18.7%) and mid-childhood onset remitting (7.5%). Finally, three phenotypes were characterised by persistence of wheeze up to adolescence: school-age onset persisting (4.3%), late-childhood onset persisting (4.7%), and continuous wheezing (4.9%) which was also characterised by early onset.

Associations with objective outcomes show that children with preschool onset remitting wheezing have no bronchodilator reversibility and normal fractional exhaled nitric oxide levels in adolescence, and are less likely to have allergy.

A *de novo* genome-wide association study of the identified wheezing phenotypes was performed to identify distinct genetic markers. Chromosome 17q21 region was confirmed as the main hit for early onset wheezing that persists to adolescence. A new region in chromosome 19q12, near the *VSTM2B* gene, was distinctively associated with preschool onset remitting wheezing. Replication will confirm this finding and, if successful, these variants might have the potential to discriminate between remitting and persisting childhood wheezing in genetic-based prediction tools.

REFERENCES

1. Henderson J et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. Thorax. 2008;63(11):974-80.

2. Granell R et al. Examination of the relationship between variation at 17q21 and childhood wheeze phenotypes. J Allergy Clin Immunol. 2013;131(3):685-94.

3. Granell R et al. Associations of wheezing phenotypes with late asthma outcomes in the Avon Longitudinal Study of Parents and Children: A population-based birth cohort. J Allergy Clin Immunol. 2016. [Epub ahead of print].

A POSITIVE VASODILATOR RESPONSE TO INHALED NITRIC OXIDE. DOES IT PREDICT SURVIVAL IN PULMONARY ARTERIAL HYPERTENSION?

***Geeshath Jayasekera, Colin Church, Andrew Peacock**

Scottish Pulmonary Vascular Unit, Glasgow, UK
**Correspondence to geeshath.jayasekera@nhs.net*

ABSTRACT

Right heart catheterisation with acute pulmonary vasodilator testing is recommended to enable the selection of appropriate medical treatment for patients with idiopathic pulmonary arterial hypertension (IPAH). In a previous study, long-term calcium channel blocker (CCB) responders represented <10% of IPAH and, during acute vasodilator testing, these patients showed significantly lower levels of both mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance which reached near-normal values.[1] Based on these findings, a decrease in mPAP by ≥10 mmHg to an absolute level of <40 mmHg is defined as a positive vasodilator response. This group of patients with IPAH should be considered for treatment with CCB.

Another study suggested that a reduction in mPAP and pulmonary vascular resistance during acute vasodilator testing may predict improved survival in the World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH), although no long-term data exist regarding survival in the group of patients defined as vasoreactive by current guidelines.[2] We conducted this study with the aim of determining whether vasoreactivity according to the current guidelines predict survival in Group 1 PAH or the specific subgroups of patients within. All new patients who were admitted to the Scottish Pulmonary Vascular Unit for diagnostic investigations from 1997–2015 were included, providing they met the criteria of PAH defined as mPAP ≥25 mmHg, pulmonary capillary wedge pressure ≤15 mmHg, and underwent acute vasodilator testing with inhaled nitric oxide

(40 ppm) at the time of diagnosis. Patients with pulmonary hypertension secondary to hypoxaemia and chronic thromboembolic pulmonary hypertension were excluded. Baseline demographics, clinical data, and changes in mPAP and cardiac output by thermodilution during acute vasodilator testing were recorded. In the study, 274 patients with Group 1 PAH (56.6±15.3 years, 179:9 female:male, mPAP 50.9±13 mmHg) were included. According to current criteria, 30 patients (60.9±13.9 years, 17:13 female:male, 48.3±6.5 mmHg) were acute responders. In the vasoreactive group, there were 24 IPAH and 6 connective tissue disease pulmonary hypertension (CTDPH) patients. The non-vasoreactive group (56.1±15.4 years, 162:82 female:male, mPAP 51.3±13.6) consisted of 132 IPAH patients, 66 CTDPH patients, and 46 other patients. The overall 5-year survival was 51.3%. The 5-year survivals in the vasoreactive group and the non-vasoreactive group were 43.3% and 52.3%, respectively. In a multivariate analysis, age ($p<0.005$, hazard ratio [HR]: 1.038, 95% confidence interval [CI]: 1.023–1.053) and right atrial pressure >10 mmHg (p=0.001, HR: 1.876, 95% CI: 1.276–2.758) were predictors of survival, while vasoreactivity (p=0.328, HR: 0.768, 95% CI: 0.452–1.303) was not. Perhaps surprisingly, acute vasoreactivity did not predict survival in either the IPAH (p=0.534, HR: 0.808, 95% CI: 0.412–1.584) or CTDPH subgroups. Vascular proliferation probably plays a larger role in PAH compared with vasoconstriction and the use of pulmonary hypertension disease-targeted therapy early in the event of insufficient response to CCB is recommended.

REFERENCES

1. Sitbon O et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111(23):3105-11.

2. Malhotra R et al. Vasoreactivity to inhaled nitric oxide with oxygen predicts long-term survival in pulmonary arterial hypertension. Pulm Circ. 2011;1(2):250-8.

SIMULTANEOUS SF_6 AND N_2 GAS MULTIPLE BREATH WASHOUT; UNDERSTANDING THE DIFFERENCE BETWEEN TEST GASES

***Katie J. Bayfield,[1,2] Eric W.F.W. Alton,[1] Samantha Irving,[1] Andrew Bush,[1] Alexander R. Horsley,[3,4] Jane C. Davies[1,2]**

1. Faculty of Medicine, National Heart & Lung Institute, Imperial College London; Royal Brompton & Harefield NHS Foundation Trust, London, UK
2. European Cystic Fibrosis Society-Clinical Trial Network (ECFS-CTN) Lung Clearance Index Core Facility, London, UK
3. Manchester Adult Cystic Fibrosis Centre, University Hospital of South Manchester, Manchester, UK
4. Institute of Inflammation and Repair, Education and Research Centre, University of Manchester, Manchester, UK
**Correspondence to k.bayfield@imperial.ac.uk*

The session 'The best is yet to come in Lung Function' presented at The European Respiratory Society (ERS) International Congress 2016, London, UK, gave a varied and interesting overview of different physiological measures currently used within respiratory medicine.

The presentation 'Simultaneous SF_6 and N_2 gas Multiple Breath Washout (MBW); understanding the difference between test gases' explored the hot topic of why two different test gases show dissimilar results when utilised in this technique.

MBW gives a readout of ventilation heterogeneity and gas mixing in patients with cystic fibrosis. The technique involves the clearance of a test gas to see how quickly it depletes, followed by analysis of the shape of the curve to understand disease progression. Within the literature, nitrogen (N_2) takes more breaths to reach the end target and consequently a longer time to clear when compared

to sulphur hexafluoride (SF_6). Here, a novel approach of washing out both SF_6 and N_2 simultaneously was applied, aiming to eliminate any potential confounders and study the difference in washout curves concurrently.

Results showed that despite completing the washout of both gases simultaneously, N_2 still finished after SF_6. The shapes of the washout curves were interesting, as both gases decayed similarly in the first instance, but eventually separated; the SF_6 curve declined linearly, whereas the N_2 readout continued in a curve, ultimately reaching a plateau. The author accounted for the results by inherent differences in gas properties, as well as a potential innate N_2 contribution from other body tissues, extending the N_2 washout and causing the plateau.

Discussions mentioned that the potential influence of equipment and an overestimation of N_2 may explain these differences. It was also highlighted that the results may genuinely be different and that this should therefore be explored further to understand the role of both set-ups. Finally, there was a show of hands from the audience indicating those who performed MBW at their centre and which gas they used: more sites employed N_2 but many also used SF_6. It was stated that there is a role for both gases, dependent on the enquiry posed, i.e. whether a technique that can give a readout and be used by multiple sites is needed (N_2), or if basic physiology outputs and a purer result are required (SF_6). The session was well received and explored many of the following steps required to improve the understanding of lung function measures and their relationship to disease.

TWENTY YEARS OF RESEARCH INTO BRONCHOPULMONARY DYSPLASIA

***Liudmila Zhelenina,[1] Alevtina Bogdanova,[2] Ilgar Mustafaev,[2] Svetlana Starevskaya,[2] Juriyi Gorelik,[2] Mariya Kuropatenko[3]**

1. Saint Petersburg State Pediatric Medical University, Saint Petersburg, Russian Federation
2. Research Institute of Pulmonology, Scientific Research Center, Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russian Federation
3. Federal State Budgetary Scientific Institution, Institute of Experimental Medicine, Saint Petersburg, Russian Federation
**Correspondence to zheleninarnf@gmail.com*

INTRODUCTION

Bronchopulmonary dysplasia (BPD) was first diagnosed 20 years ago in St. Petersburg, Russia. About 70,000 babies are born in St. Petersburg every year; 5–6% of them are born prematurely. Every year, approximately 300 children (280 children in 2015) are born with birth weights <1 kg. The incidence of BPD is inversely proportional to gestational age and birth weight; 84% had a birth weight of 0.75 kg, 64% had a birth weight of 0.751–1.0 kg, and 24% had a birth weight of 1.001–1.5 kg. Due to improvements in perinatal care, the incidence of the severe or classic form of BPD has decreased considerably. Thus in recent years, the clinical course of BPD has been less severe, representing a new BPD course.

AIM

Research was conducted in order to determine clinical and radiologic peculiarities to assess the severity of lesions in small bronchi and interstitial tissue, inflammatory characteristics, and long-term outcomes of the disease. A total of 143 children were born from 1998–2005 with the new form of BPD and were examined in this study. Of those born, 76.7% had an extremely low birth weight. The health of children with BPD was monitored. Assessment of respiratory function by spirometry, impulse oscillometry, and body plethysmography, as well as a computed tomography examination was performed.

RESULTS

Among our patients, 65% had recurrent wheezing episodes and 36% still showed these symptoms at preschool age. During the respiratory function examination, only one-third of the children had forced vital capacity and forced expiratory volume in 1 second results within the normal ranges. Obstructive changes were found in 66% of patients, residual lung volume was increased in 49% of patients, and restrictive changes did not exceed 6% of cases. Bronchial hyper-reactivity was found in 66% of patients. Only 21% of children with a history of BPD had normal computed tomography results. Most children retained heterogeneous pneumatisation, fibrosis lesions, atelectasis, and sometimes bullae.

CONCLUSION

The 'new' form of BPD could have severe consequences for the treatment of the disease especially with the presence of signs of the classic forms of clinical and radiological symptoms.

Follow-up observation showed the long-term preservation of obstructive disorders, specifically many more restrictive changes, which can lead to the formation of obstructive pulmonary disease.

THE IMPACT OF THE IMPACT STUDY ON HOMOGENEOUS EMPHYSEMA

***Arschang Valipour**

Ludwig-Boltzmann-Institute for COPD and Respiratory Epidemiology, Otto-Wagner Hospital, Vienna, Austria
**Correspondence to arschang.valipour@wienkav.at*

For patients with severe homogeneous emphysema, treatment options are limited. Lung volume reduction surgery is not recommended due to its invasiveness, variable success, and the increased mortality for homogeneous emphysema. Other minimally invasive therapies such as endoscopic coils have shown inconsistent and only modest benefits in lung function. One-way endobronchial valves (EBV) have emerged as a minimally invasive treatment for patients with severe emphysema, having been successfully used in clinical practice to improve lung physiology, exercise tolerance, and quality of life.

To date, EBV treatment has centred on patients with heterogeneous emphysema, since clinical studies in the past have focussed on the responder groups from lung volume reduction surgery. However, over the course of several major studies, it has become clear that a lack of collateral ventilation, and not the distribution of disease (heterogeneous and homogeneous), is a key indicator of success for EBV treatment. In fact, subgroup analyses from several recent studies have suggested that the therapy could also be effective in treating homogeneous emphysema.

The IMPACT study was the first major prospective trial to evaluate the efficacy and safety of EBV therapy in patients with homogeneous emphysema and the absence of collateral ventilation. In this prospective multicentre 1:1 randomised controlled trial of EBV therapy compared with standard of care (SoC) in 93 patients, the primary outcome was the percentage change in forced expiratory volume measured in 1 second (FEV_1) at 3 months, relative to the baseline in the EBV group compared with the SoC group. Secondary outcomes included further changes in FEV_1, St George's Respiratory Reponse Questionnaire (SGRQ) score, 6-minute walk distance (6MWD) test, and target lobe volume reduction. Collateral ventilation was assessed using the Chartis System.

Ninety-seven percent of patients experienced target lobe volume reduction, indicating effective occlusion of the target lobe following EBV placement. The results demonstrated statistically significant and clinically meaningful improvements in lung function, exercise capacity, and quality of life in EBV-treated patients versus the SoC group.

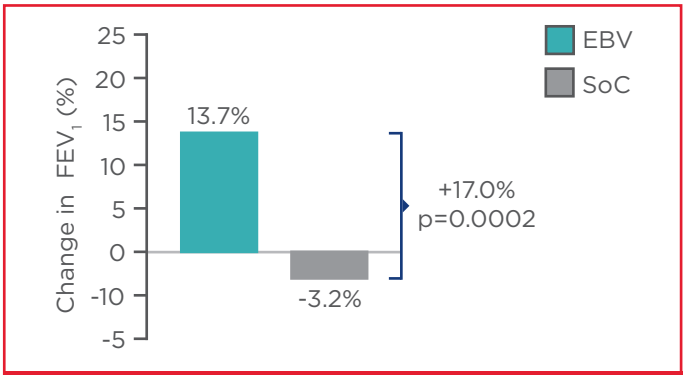


Figure 1: Primary outcome in the intention-to-treat population: percentage change in forced expiratory volume in 1 second from the baseline to 3 months.
FEV_1: forced expiratory volume measured in 1 second; EBV: endobronchial valves; SoC: standard of care.

Homogeneous patients with minimal or no collateral ventilation experienced a 17% higher FEV_1 compared with SoC patients (Figure 1), a 40-metre difference in the 6MWD, and a 10-point difference in SGRQ, both in favour of EBV patients. Significantly more patients in the EBV group had improvements that exceeded the minimal clinically important differences for FEV_1, the 6MWD, SGRQ, and residual volume at 3 months post-treatment (Figure 2).

The positive outcomes associated with EBV therapy in homogeneous emphysema were accompanied by a 25% incidence of pneumothorax. While the risk of pneumothorax should be considered when considering this therapy option, it has been closely associated with procedural success, and pneumothorax generally occurred within the first 48 hours of the procedure when patients were still hospitalised and could be appropriately managed. There was a very low incidence of valve migration that required replacement of the valves, and this could readily be accomplished because of the ease of removing and replacing the EBV.

We concluded that implanting EBV in patients with homogeneous emphysema without collateral ventilation results in clinically meaningful benefits of improved lung function, exercise tolerance, and quality of life. Follow-up of these patients is continuing and the long-term benefits will be assessed for up to 12 months. With a large number of diverse patients now showing improvement with EBV therapy across multiple trials, we now suggest that patient selection should focus more on hyperinflation and the absence of collateral ventilation as predictors of EBV therapy success, rather than on the homogeneity or heterogeneity of the disease.

While the magnitude of improvement is slightly less for homogeneous patients when compared to heterogeneous patients, because of the lack of treatment options, we suggest that EBV should be considered in these patients.

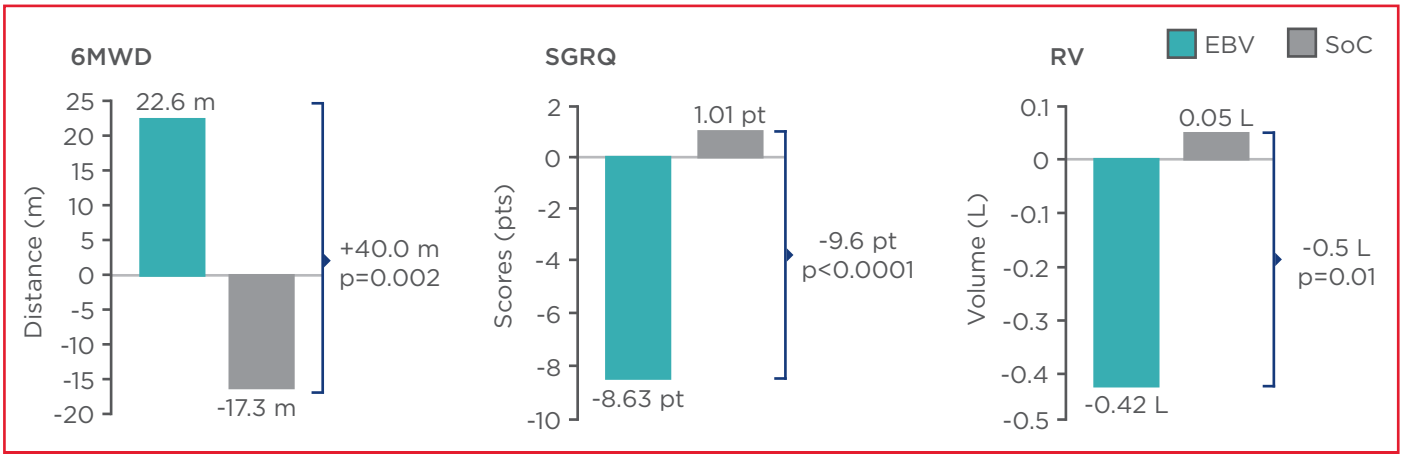


Figure 2: Secondary outcomes in the intention-to-treat population: change from baseline to 3 months.
SGRQ: St George's Respiratory Response Questionnaire Score; 6MWD: 6-minute walk distance; RV: residual volume; EBV: endobronchial valves; SoC: standard of care.

NURSES' KNOWLEDGE AND ABILITY GAPS CONCERNING HEALTHCARE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS: WINDOW FOR IMPROVEMENT

***Ilda de Godoy,[1] Duelene Ludmila Nogueira,[1] Irma Godoy[2]**

1. Department of Nursing, Botucatu Medical School, Botucatu Campus, University Estadual Paulista, Botucatu, Brazil
2. Department of Internal Medicine: Pneumology, Botucatu Campus, Botucatu Medical School, University Estadual Paulista, Botucatu, Brazil
**Correspondence to ildadegodoy@gmail.com*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic and progressive disease often complicated by episodes of exacerbation causing physical, emotional, and functional damage. Nurses have an important role in assessing each patient and promoting self-care by providing the necessary conditions in which adequate home care may be developed. Evaluating nurses' knowledge of COPD management is essential to be able to improve healthcare delivery.

OBJECTIVE

To evaluate nurses' knowledge of COPD from the healthcare network of Botucatu, Brazil.

METHODS

This is a quantitative study with cross-sectional, descriptive, and analytical design. From both primary and hospital care, 243 nurses were invited to participate in the study, and the data were collected between May and July 2015.

RESULTS

Within the study, 81.6% of the nurses defined COPD incorrectly; 76.1% considered spirometry unnecessary for diagnosis; 79% incorrectly answered questions related to bronchodilators; only 15.4% were sufficiently familiar with techniques for the use of inhaled medications; and 47% were unfamiliar with vaccines recommended for treating COPD. We conclude that there are considerable gaps in nurses' knowledge of COPD definition, the risk factors for the disease, diagnostic tools, management of stable or exacerbated disease, and guidance for and supervision of the treatment (mainly of inhaled drugs, vaccines, and long-term oxygen therapy). Nurses' abilities to define the line of care, to perform ongoing education for nurses, and to orchestrate health education activities for COPD patients and their families are simply insufficient.

CONCLUSIONS

This study shows that nurses are unprepared to care for COPD patients. However, they recognised that their knowledge about the disease is incomplete and expressed their desire to be trained in delivering effective prevention and management for patients with COPD.

EDITOR'S PICK

My choice is based on his recognised expertise around the study of chronic respiratory diseases potentially affecting employees in farms. Dr Stoleski and colleagues present, in the current journal, a cross-sectional study evaluating the incidence of respiratory symptoms and diseases among crop farmers. This study is very interesting, further underlining the expertise of Dr Stoleski in this setting.

Dr Antonio Rossi

RESPIRATORY SYMPTOMS, LUNG FUNCTION IMPAIRMENT, AND CHRONIC RESPIRATORY DISEASES AMONG CROP FARMERS: ASSESSMENT BY JOB EXPOSURE MATRICES

***Sasho Stoleski, Jordan Minov, Jovanka Karadzinska-Bislimovska, Dragan Mijakoski**

Center for Respiratory Functional Diagnostics, Institute for Occupational Health of Republic of Macedonia, Skopje, WHO Collaborating Center and GA²LEN Collaborating Center, Republic of Macedonia
**Correspondence to sstoleski@yahoo.com*

Disclosure: The authors have declared no conflicts of interest.
Received: 15.02.16 **Accepted:** 30.08.16
Citation: EMJ Respir. 2016;4[1]:72-80.

ABSTRACT

Objective: To evaluate the prevalence of chronic respiratory symptoms, lung function impairment, and chronic obstructive respiratory diseases in crop farmers. Our objective is to then examine their relation to exposure duration, and to explore the usefulness of job exposure matrices as tools for exposure assessment, and predictors for respiratory health impairment.

Methods: A cross-sectional study was performed, including 50 males (mean age: 45.4±10.7 years) employed as crop farmers (duration of exposure: 21.6±9.7 years) and 50 male office workers as a control group (mean age: 44.1±9.8 years) matched for age, smoking habits, and socioeconomic status. Methods of evaluating examined subjects included the completion of a questionnaire on respiratory symptoms in the last 12 months (cough, phlegm, dyspnoea, wheezing, chest tightness, and nasal symptoms), spirometry and histamine challenge (provocative concentration producing a 20% fall in forced expiratory volume in 1 second [FEV_1]: ≤8 mg/mL), as well as use of job exposure matrices.

Results: Crop farmers had a significantly higher prevalence of cough (29.4%), phlegm (16.7%), and wheezing (11.9%), than the control group ($p<0.05$). All spirometric parameters (forced vital capacity [FVC], FEV_1, FEV_1/FVC%, maximal expiratory flow (MEF) at 75%, 50%, and 25%) were lower in crop farmers compared to the control patients, but statistical significance was confirmed only for MEF at 25%, 50%, and 25–75% ($p=0.021$, $p=0.011$, and $p=0.003$, respectively). The prevalence of bronchial hyperresponsiveness, asthma, and chronic obstructive pulmonary disease was higher in crop farmers but without statistical significance. JEM were useful tools for exposure assessment and predictors of factors for asthma and COPD development.

Conclusion: The results suggest that occupational exposure among crop farmers is associated with a higher prevalence of respiratory symptoms, lung function impairment, and a higher prevalence of chronic respiratory diseases.

Keywords: Respiratory symptoms, farming, lung function, asthma, chronic obstructive pulmonary disease (COPD), job exposure.

INTRODUCTION

Respiratory hazards are one of the most prevalent occupational agents in agriculture, causing different types of respiratory disorders among exposed workers.[1] Such exposure occurs during soil processing, harvesting, treatment, and storage of corn and other plants.[2]

Despite exposure to respiratory hazards, smoking is also an important factor that leads to the development of chronic respiratory disorders among crop farmers. Many epidemiological studies that have analysed respiratory diseases in agriculture follow the effect of smoking, especially the 'joint effect' of smoking and occupational exposure among crop farmers.[3] Namely, the frequency of active smokers among farmers in France is 28%, and according to our previous research, the frequency of active smokers within agricultural workers in Macedonia is 40.2%.[4]

Most of the mineral soil fraction is predominantly of a silicate nature, i.e. respirable dust that contains quartz. The association between respirable quartz dust and silicosis has previously been established, but there is a special scientific interest in the pathological potential for quartz dust causing other chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD).[5] Organic dust exposure has qualitative and quantitative variations, and depends on the type of agricultural activity. Wheat dust includes mould spores, mycotoxins, bacteria and their components, excreta, dust mites, insects, animal products, particles of cotton, paper, flour, tobacco, and other types of dust.[6] Crop farmers are exposed to numerous plants (such as grains, grasses, weeds, and trees) and animal allergens (such as livestock hairs and poultry feathers).[7]

In the case of occupational exposure, skin absorption is more frequent than through the inhalation pathway for pesticides, but sometimes inhalation can be of great concern due to pesticides having high solubility and rapid evaporation rates.[1] Occupational exposure is most intensive in crop farmers involved in the mixing and loading of the pesticides; inhalation occurs while dealing with soluble liquids.[8] Exposure to aero-pollutants derived from welding, as well as the use of solvents, fuels, and disinfectants are considered as occupational hazards for crop farmers.[9] Disinfectants are used mostly in cattle breeding, and contain chloramine-T or quaternary ammonia compounds which are known to cause occupational asthma.[10]

Exposure to most respiratory hazards in agriculture are controllable and subsequently, work-related respiratory diseases in crop farmers caused by these agents are potentially preventable.[11]

In the present study we have compared the prevalence of chronic respiratory symptoms, lung function impairment, and chronic obstructive respiratory diseases between crop farmers and office workers. We have further examined this prevalence in relation to exposure duration, and explored the usefulness of job exposure matrices as tools for exposure assessment in crop farmers, as well as predictors for respiratory health impairment.

SUBJECTS AND METHODS

Study Design and Setting

Our team conducted a cross-sectional study at the Center for Respiratory Functional Diagnostics at the Institute for Occupational Health of Republic of Macedonia, Skopje, WHO Collaborating Center for Occupational Health and GA²LEN Collaborating Center, within the period March 2014–February 2015.

Study Sample

The representative study sample was calculated by the software program 'Programs for Epidemiologists version 4.04', with a 95% confidence level (0.05 significance) and a confidence interval ±5. In order to achieve the necessary sample size (with consideration for possible selection and response bias), we have taken a representative sample of 50 crop farmers and 50 matched office controls in a large scale agricultural enterprise.

Subjects

We have examined 50 male subjects (mean age: 45.4±10.7) employed as crop farmers (mean duration of exposure: 21.6±9.7). They were engaged in crop farming with main activities composed of cultivating crops and vegetables, planting, digging,

use of mechanised equipment, irrigation, and pesticide handling. They were exposed to various respiratory agents, including dust, inappropriate climate, fumes, vapours, and pesticides. The inclusion criteria for the examined group required employed males with an age range of 18–64 years, who were involved in crop farming and exposed to at least one occupational respiratory hazard (dust, gases, fumes, vapours, and pesticides).

Exclusion criteria for the examined group were subjects younger than 18 years, or older than 64 years, and subjects not engaged in crop farming. To avoid selection bias and results deviations, the study did not include subjects with exposure to respiratory hazards other than crop farming. Depending on the exposure duration, the examined subjects were divided into two subgroups: i) exposure <15 years; ii) exposure >15 years. In addition, a similar group of 50 male office workers (mean age: 44.1±9.8 years) matched for age, duration of employment, daily smoking, and socioeconomic status was studied as a control, with no data for occupational exposure to respiratory hazards.

The subjects in both groups who were diagnosed with a chronic respiratory disorder (asthma, COPD, bronchiectasis, sarcoidosis, etc.) by physicians, or were treated with bronchodilators and/or corticosteroids were not included in the study. Also, both groups did not comprise any subjects in whom either spirometry or bronchodilator reversibility testing was contraindicated.

Our institute's ethics committee has approved the content of our study protocol and each examined subject gave written informed consent before any involvement in the study.

Questionnaire

All study participants were interviewed by a physician and completed the standardised questionnaire (including questions on work history, respiratory symptoms in the last 12 months, and smoking habits). Chronic respiratory symptoms in the last 12 months (cough, phlegm, dyspnoea, wheezing, and chest tightness) were obtained using the European Community for Coal and Steel questionnaire (ECCS-87), and the European Community Respiratory Health Survey (ECRHS) questionnaire.[12,13]

Table 1: The prevalence of respiratory symptoms in the last 12 months in both examined groups and the prevalence of respiratory symptoms in the last 12 months in crop farmers with a duration of workplace exposure of more and less than 15 years.

Respiratory symptoms in the last 12 months	Crop farmers (n=50)	Office workers (n=50)	p-value*
Any respiratory symptom	17 (34%)	13 (26%)	0.383
Cough	14 (28%)	6 (12%)	0.045
Phlegm	8 (16%)	2 (4%)	0.045
Dyspnoea	7 (14%)	3 (6%)	0.182
Wheezing	8 (16%)	2 (4%)	0.046
Chest tightness	5 (10%)	3 (6%)	0.461
Crop farmers			
Respiratory symptoms in the last 12 months	**Exposed >15 years (n=27)**	**Exposed <15 years (n=23)**	**p-value***
Any respiratory symptom	12 (44.4%)	4 (17.4%)	0.041
Cough	8 (29.6%)	3 (17.4%)	0.158
Phlegm	6 (22.2%)	2 (8.7%)	0.193
Dyspnoea	7 (25.9%)	1 (4.3%)	0.042
Wheezing	6 (22.2%)	2 (8.7%)	0.193
Chest tightness	3 (11.1%)	2 (8.7%)	0.578

Data are expressed as a number and percentage of study subjects with certain variables.
*Tested by chi-square test or Fisher's exact test where appropriate.

Classification of smoking status was determined according to the World Health Organization (WHO) guidelines on definitions of smoking status.[14] A 'daily smoker' was defined as a subject who, at the time of the field survey, smoked at least once a day, except on days of religious fasting. Among daily smokers, lifetime cigarette smoking and daily mean of cigarettes smoked were also assessed. Pack-years smoked were calculated according to recommendations.[15] An 'ex-smoker' was defined as a former daily smoker, who no longer smokes. Passive smoking or exposure to environmental tobacco smoke was defined as the exposure of a person to tobacco combustion products from smoking by others.[16]

Spirometry

All study subjects underwent spirometry testing performed by the spirometer Ganshorn SanoScope LF8 (Ganshorn Medizin Electronic GmbH, Niederlauer, Germany), measuring forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, and maximal expiratory flow (MEF) at 50%, 75%, and 25–75% of FVC (MEF_{50}, MEF_{75}, and MEF_{25-75}, respectively), by recording the best result from three measurements of the values of FEV_1 within 5% of each other. The spirometry results were given as a percentage of their predicted values, according to the current European Respiratory Society (ERS) and American Thoracic Society (ATS) recommendations, including reproducibility and acceptability.[17]

Histamine Challenge

Bronchial hyperresponsiveness (BHR) was assessed by the histamine challenge test performed according to the ERS/ATS recommendations.[18,19] Namely, concentrations of 0.5, 1.0, 2.0, 4.0, and 8.0 mg/mL histamine (Torlak, Beograd, Serbia) were prepared by dilution with buffered saline.

Table 2: Mean values of spirometric parameters in examined groups and mean values of spirometric parameters in crop farmers, with a duration of workplace exposure of more and less than 15 years.

Spirometric parameter	Crop farmers (n=50)	Office workers (n=50)	p-value*
FVC (% pred)	85.3±8.2	86.1±8.5	0.633
FEV_1 (% pred)	83.2±7.9	85.6±8.3	0.142
FEV_1/FVC%	72.9±4.3	74.2±4.7	0.152
MEF_{25} (% pred)	57.7±6.1	60.5±5.9	0.021
MEF_{50} (% pred)	56.7±5.4	59.3±6.2	0.011
MEF_{75} (% pred)	59.3±6.9	61.5±5.8	0.087
MEF_{25-75} (% pred)	58.3±7.1	62.9±8.1	0.003
Crop farmers			
Spirometric parameter	**Exposed >15 years (n=27)**	**Exposed <15 years (n=23)**	**p-value***
FVC (% pred)	83.6±8.1	84.9±8.7	0.587
FEV_1 (% pred)	80.9±5.9	81.3±6.2	0.816
FEV_1/FVC%	72.3±3.9	74.1±4.3	0.127
MEF_{25} (% pred)	55.2±5.2	57.8±4.9	0.076
MEF_{50} (% pred)	53.2±5.3	56.2±4.9	0.044
MEF_{75} (% pred)	49.5±5.5	52.6±5.1	0.045
MEF_{25-75} (% pred)	58.2±6.1	61.1±7.3	0.132

Data are expressed as a mean value with standard deviation.
*Tested by independent-sample T-test.
FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; MEF_{25}, MEF_{50}, MEF_{75}, MEF_{25-75}: maximal expiratory flow at 25%, 50%, 75%, and 25-75% of FVC, respectively; % pred: percentage of predicted value.

Table 3: Risk of developing asthma and chronic obstructive pulmonary disease due to occupational exposure to respiratory agents, according to the matrices for job exposure among crop farmers.

	OR (95% CI)	
	Asthma	COPD
Qualitative job exposure matrix		
Dust	1.78 (0.34–3.59)	1.82 (0.41–3.86)
Gases/fumes/vapours	1.83 (0.41–3.90)	1.75 (0.30–3.72)
Pesticides	1.45 (0.21–3.02)	1.34 (0.17–3.24)
Matrix with exposure intensity		
Dust exposure		
Low	1.63 (0.21–3.76)	1.75 (0.35–3.82)
Intermediate	1.76 (0.29–3.91)	1.84 (0.42–4.01)
High	2.25* (1.12–4.17)	2.34* (1.23–4.45)
Gases/fumes/vapours exposure		
Low	1.87 (0.67–4.02)	1.63 (0.39–3.46)
Intermediate	2.37* (1.22–4.30)	1.78 (0.56–3.89)
High	3.12* (1.56–5.97)	2.36* (1.34–4.78)
Pesticide exposure		
Low	1.21 (0.17–2.68)	1.17 (0.09–2.56)
Intermediate	1.42 (0.31–2.90)	1.38 (0.23–2.87)
High	1.73 (0.54–3.45)	1.64 (0.45–3.21)
Matrix with exposure frequency		
Dust exposure		
Rare	1.54 (0.39–3.04)	1.63 (0.43–3.12)
Sporadic	1.76 (0.62–3.79)	2.04* (1.03–4.11)
Regular	2.18* (1.04–4.05)	2.45* (1.38–4.23)
Gases/fumes/vapours exposure		
Rare	1.65 (0.41–3.12)	1.59 (0.33–3.09)
Sporadic	1.73 (0.52–3.32)	1.66 (0.43–3.21)
Regular	3.28* (1.63–6.25)	2.67* (1.41–4.15)
Pesticide exposure		
Rare	1.17 (0.12–2.45)	1.12 (0.06–2.32)
Sporadic	1.36 (0.24–2.86)	1.32 (0.20–2.75)
Regular	1.69 (0.43–3.35)	1.58 (0.41–3.17)

Data are given as ORs with 95% CIs.
*p<0.05
*Tested by logistic regression after adjustment for age and smoking habit.
OR: odds ratio; CI: confidence interval; COPD: chronic obstructive pulmonary disease.

Afterwards, the doses of aerosol generated by a Pari LC® nebuliser, with an output rate 0.17 mL/min, were inhaled by mouthpiece. Subjects inhaled increasing concentrations of histamine using a tidal breathing method, until FEV_1 fell by more than 20% of its base value (provocative concentration $[PC]_{20}$) or until the highest concentration was reached. According to ATS recommendations, BHR was categorised as moderate-to-severe BHR (PC_{20} <1.0 mg/mL), mild BHR (PC_{20}=1.0–4.0 mg/mL), and borderline BHR (PC_{20}=4.0–8.0 mg/mL).[19]

Job Exposure Matrices

In order to assess occupational exposure to respiratory agents among crop farmers, we have used job exposure matrices recommended by the

European Association of Schools of Occupational Medicine (EASOM), including both a qualitative and quantitative matrix, with exposure intensity and exposure frequency.[20]

Diagnostic Criteria for Asthma and Chronic Obstructive Pulmonary Disease

According to the current recommendations of the Global Initiative for Asthma (GINA), asthma in subjects with normal spirometry findings is defined as symptomatic BHR with PC_{20} ≤4 mg/mL, whereas in subjects with respiratory impairment a positive bronchodilator test is sufficient.[21] According to the current recommendations by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is defined by a post-bronchodilator FEV_1/FVC ratio <0.70 in subjects with dyspnoea, chronic cough, and/or cough with phlegm.[22]

Statistical Analysis

We have analysed the data using STATISTICA for Windows® version 7. Continuous variables were expressed as mean values, with standard deviation and categorical variables as numbers and percentages. The chi-square test (or Fisher's exact test) was used for testing differences in the prevalence of respiratory symptoms, while the comparison of spirometric measurements was performed by an independent-samples T-test. A p-value of <0.05 was considered statistically significant. Logistic regression analysis was used to assess the risk of chronic respiratory symptoms, asthma, and COPD development within job exposure matrices, adjusted for age and smoking habits. Study variables were checked for normality by the Kolmogorov–Smirnov and Shapiro–Wilk W tests.

RESULTS

Demographic characteristics of the study subjects were similar in both crop farmers and office controls. Crop farmers had a higher prevalence of respiratory symptoms in the last 12 months than office workers, with significant differences for cough (29.4%), phlegm (16.7%), and wheezing (11.9%). The prevalence of respiratory symptoms in the last 12 months was higher in crop farmers exposed for >15 years than in those with workplace exposure <15 years, being significantly different for overall respiratory symptoms and dyspnoea (Table 1).

All spirometric parameters (FVC, FEV_1, FEV_1/FVC%, MEF_{75}, MEF_{50}, and MEF_{25}) were lower in crop farmers compared to the office controls, but statistical significance was reached for MEF_{25}, MEF_{50}, and MEF_{25-75} (p=0.021, p=0.011, and p=0.003, respectively). Mean values of spirometric parameters were lower in crop farmers exposed <15 years, than in those exposed for <15 years, with statistical significance for MEF_{50} and MEF_{75} (Table 2).

Restrictive and obstructive spirometric changes were more frequent in crop farmers compared to controls, but a significant difference was found only for small airway obstruction. The prevalence of non-specific BHR was higher in exposed crop farmers, but statistical significance was not reached (22% versus 12%). Prevalence of mild and borderline BHR was higher in crop farmers, but was not statistically significant. Asthma and COPD were more prevalent in crop farmers compared with office workers, but without reaching statistical significance.

Occupational exposure to respiratory agents among crop farmers was assessed by the job exposure matrices, providing conformity of occupational exposure to respiratory agents with their specific job activities. In order to prevent the influence of possible confounding factors on the results obtained by job exposure matrix, we have used logistic regression analyses, adjusted by age and smoking habit. The association of asthma and COPD, with the exposure to respiratory agents according to the job exposure matrices in crop farmers, is shown in Table 3.

The data obtained show that a high degree of dust exposure on a regular basis significantly increases the asthma risk in crop farmers. The same statement is valid for an intermediate and high degree of exposure to gases, fumes, and vapours on a regular basis. On the other hand, sporadic and regular dust exposure with high intensity significantly increases COPD risk. Concerning exposure to gases, fumes, and vapours, COPD risk is significantly associated with a high degree of exposure on a regular basis. Pesticide exposure does not influence the risk of asthma and COPD development in crop farmers.

DISCUSSION

Chronic respiratory symptoms, lung function impairment, and respiratory disorders remain important clinical and public health issues for farmers worldwide.[23] This study compares the prevalence of chronic respiratory symptoms,

lung function impairment, and chronic obstructive respiratory diseases between crop farmers and office workers, and introduces job exposure matrices as tools for exposure assessment.

The prevalence of chronic respiratory symptoms among crop farmers in this study is 34%, with 70% of them reporting work-related exposure. Office workers, on the other hand, report a frequency of 26%, and no workplace association. The prevalence is higher among exposed workers, and is a significant cause of cough, phlegm, and wheezing symptoms. According to European studies, the prevalence of chronic respiratory symptoms range between 25% and 35%,[24] whereas Stoleski et al.[25] report a prevalence of 26.6% for overall respiratory symptoms among agricultural workers. A frequency of 8.3% is reported for chronic cough with phlegm, similar to our previous research,[26] but also by studies from Slovenia and Croatia.[27] According to the Croatian study, the prevalence of cough with phlegm among agricultural workers is 2–12%, being highest among cattle breeders.[24] The frequency of cough with phlegm among Finnish farmers is 7.5%,[28] and up to 23% according to research from Manitoba, Canada.[29] The Danish study among 834 elderly males reveals that the highest prevalence of cough with phlegm is among retired agricultural workers.[30] A study in France shows the highest frequency of dyspnoea in farmers (37%), while the lowest is recorded in school teachers (15%).[31]

A study in Poland shows a prevalence of 44.7% for overall chronic respiratory symptoms in crop farmers, and the highest rates are registered for chronic cough (26.3%) and dyspnoea (19.7%).[32] Other studies confirm a higher frequency of wheezing in agricultural workers compared with office workers.[33] This study suggests the risk of developing respiratory symptoms increases with >15 years of job exposure. A significant association between exposure duration and chronic bronchitis is reported in the study by Omland et al.[34] with 1,691 farmers exposed to organic and inorganic dust. Many surveys report a higher frequency of chronic respiratory symptoms among agricultural workers with longer occupational exposure,[35] while those examining respiratory effects of organic dust show a significant association between smoking habits and respiratory symptoms.[36] A study among French farmers shows a synergistic effect of occupational exposure and smoking, especially for chronic cough and phlegm.[37]

Our research shows a significant difference for small airways indices in crop farmers compared to controls. The average values of spirometric parameters are lower in crop farmers exposed for >15 years, with significant differences in MEF_{50} and MEF_{75}. The results confirm a higher prevalence of restrictive and obstructive types of ventilatory insufficiency among exposed workers compared to controls, while small airways obstruction is significantly higher in crop farmers. The research on agricultural workers by Stoleski et al.[25] reports lower average values of all spirometric parameters compared to controls, with significant differences in MEF_{50} and MEF_{75}. Ventilatory insufficiency is associated with those aged >60 years, having a job exposure duration of >20 years, a smoking habit, and open to dust and pesticide exposure. Dosman et al.[38] report significantly lower values of all spirometric parameters among Danish crop farmers compared to the control group, despite associations with age and pesticide exposure.

Similar results concerning the effect of grain dust over values of the spirometric parameters in exposed farmers are presented by Huy et al.,[39] Corey at al.,[40] and Enarson et al.[41] Dalphin et al.[42] reported significantly lower values of FVC and FEV_1 among cattle breeders compared to controls. Recent studies show that an increase in the annual decline of lung function is usually associated with job exposure, but also smoking habit.[43] Our previous research confirms lung function decline by exposure duration, significant for MEF indices in farmers exposed for more than 15 years.[44] Leuenberger et al.[45] report a significantly higher prevalence of BHR in subjects exposed to dust, vapours, and fumes compared to those who are not exposed.

The prevalence of asthma in crop farmers in the present study is 10%, which is not significantly higher than office workers (6%). In a cross-sectional study among farmers in Denmark, Iversen et al.[46] detected a prevalence of 27% for chronic bronchitis and 8% for asthma, while Dalphin et al.[37] reported a lower asthma prevalence (5.3%) in French farmers. Previous studies worldwide show that occupational exposure to toxic gases and grain dust on farms, as well as dust and fumes from industrial facilities,[47] are strongly associated with COPD. The ATS performed a large epidemiological survey in 2013 which showed that 15% of COPD cases are connected to occupational exposure,[48] and consequently reports similar estimates.[49]

The prevalence of COPD in the present study is non-significantly higher in crop farmers (8%) compared to office controls (4%). The prevalence of chronic bronchitis and COPD in crop farmers and cattle breeders, assessed by Eduard et al.,[50] confirmed the association between dust exposure on farms with COPD development. Epidemiological surveys in France, Netherlands, and Norway show significant associations between occupational exposure assessed by specific job exposure matrices, and lung function in the rural population.[51]

Occupational exposure to respiratory agents in the actual study beside the questionnaire on job exposure is assessed also by job exposure matrices (qualitative, matrix on exposure intensity, and matrix on exposure frequency). According to the matrix data in this study, a high degree of dust exposure on a regular basis significantly increases the asthma risk among crop farmers. The same fact is reported for a medium and high degree of exposure to gases, fumes, or vapours on a regular basis, while sporadic and regular high intensity dust exposure significantly increases the risk of COPD development. Concerning job exposure to gases, fumes, or vapours, the risk of COPD development is significantly associated with a high degree of exposure on a regular basis. Le Moual et al.[52] evaluated risk factors for COPD development and reported associations between occupational exposure assessed by specific population matrix and lung functional impairment.

Job exposure matrices are relatively easily designed, are not restricted by the number and categories of examined subjects, and have better characteristics and performances compared with the self-reported method, especially when optimal conditions for practical implementation are fulfilled. Matrices should be widely used for occupational exposure assessment and hypothesis deriving, especially in large groups of examinees, and in cases with a lack of adequate questionnaires on workplace exposure. Despite some expected weaknesses, the matrices offer great opportunities in exposure assessment of occupational respiratory hazards. Nevertheless, additional research is also needed in order to improve their performance and predictive values.

This study has certain limitations, namely, the relatively small number of subjects in the study groups, and an absence of ambient monitoring, which could aggravate a clear relationship between occupational exposure and respiratory impairment in crop farmers.

In conclusion, we found a higher prevalence of respiratory symptoms, significantly lower values of small airways indices, and a higher prevalence of asthma and COPD in crop farmers compared to controls, also related to exposure duration. The results recognised the role of job exposure matrices in farming exposure assessment and characterisation, their potential to be a predictive factor in the development of respiratory diseases, and promotes their applicability within the diagnostic algorithm for respiratory health assessment.

REFERENCES

1. American Thoracic Society. Respiratory health hazard in agriculture. Am J Respir Crit Care Med. 1998;158(Suppl 1):S1-76.

2. Kurppa K et al. Sectoral network on occupational health and safety in agriculture to support enterprises and family farms in Estonia. Ind Health. 2006; 44(1):3-5.

3. Stellman SD et al. Smoking habits of 800,000 American men and women in relation to their occupations. Am J Ind Med. 1988;13(1):43-58.

4. Minov J et al. Smoking among Macedonian workers five years after the anti-smoking Campaign. Arh Hig Rada Toksikol. 2012;63(2):207-13.

5. Popendorf W, Donham KJ., "Agricultural hygiene," Clayton GD, Clayton FE (eds.), Patty's Industrial Hygiene and Toxicology (1991) 4th edition, New York: John Wiley & Sons, Inc, pp.721-61.

6. Faria NM et al. Farm work, dust exposure and respiratory symptoms among farmers. Rev Saude Publica. 2006; 40(5):827-36.

7. Rautiainen M et al. Nasal sensitization of dairy farmers to bovine epithelial and urinary antigens. Rhinology. 1992; 30(2):121-7.

8. Cole D, "Occupational Health Hazards of Agriculture," Hawkes C, Ruel MT (eds.), Understanding the links between agriculture and health (2006), Washington DC: International Food Policy Research Institute, pp.17-8.

9. Shaver CS, Tong T. Chemical hazards to agricultural workers. Occup Med. 1991; 6(3):391-413.

10. Bernstein JA et al. A combined respiratory and cutaneous hypersensitivity syndrome induced by work exposure to quaternary amines. J Allergy Clin Immunol. 1994; 94(2):257-9.

11. Schenker MB. Farming and asthma. Occupational and Environmental Medicine 2005;62(4):211-2.

12. Minette A. Questionnaire of the European Community for Coal and Steel (ECSC) on respiratory symptoms. 1987 - Updating of the 1962 and 1967 questionnaires for studying chronic bronchitis and emphysema. Eur Respir J. 1989;2(2):165-77.

13. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Respiratory

Health Survey (ECRHS). Eur Respir J. 1996;9(4):687-95.

14. World Health Organization. Guidelines for controlling and monitoring the tobacco epidemic (1998), Geneva: WHO.

15. Smoking Pack-Years. 2013. Available at: http://smokingpackyears.com/calculate. Last accessed: 15 November 2014.

16. US Department of Health and Human Services. The Health Consequences of Smoking: Chronic Obstructive Pulmonary Disease. A report of the Surgeon General. 1984. Available at: http://profiles.nlm.nih.gov/ps/access/NNBCCS.pdf. Last accessed: 16 February 2016.

17. Quajner Ph.H et al. Lung Volumes and Forced Ventilatory Flows: Official Statement of the European Respiratory Society. Eur Respir J. 1993;16(1):1-100.

18. Sterk PJ et al. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working Party for the Standardization of Lung Function Tests. European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J. 1993;6(S16):53-83.

19. Crapro RO et al. Guidelines for Metacholine and Exercise Challenge Testing - 1999. Official Statement of the American Thoracic Society. Am Respir Crit Care Med. 2000;161(1):309-29.

20. Semple S. Exposure matrices: how to create them, how to use them, and what they can tell us. 2016. Available at: www.easom.org/data/summerschools/Semple.ppt. Last accessed: 15 February 2016.

21. National Institutes of Health, National Heart, Lung, and Blood Institute. "Definition, description, and diagnosis of asthma", Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention (2015), pp.1-11.

22. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2013 Update. Available at: http://www.goldcopd.org/uploads/users/files/WatermarkedGlobal%20Strategy%202016(1).pdf. Last accessed: 15 February 2016.

23. Linaker C, Smedley J. Respiratory illness in agricultural workers. Occup Med. 2002;52(8):451-9.

24. Bongers et al. Lung function and respiratory symptoms in pig farmers. Br J Ind Med. 1987;44(12):819-23.

25. Stoleski S et al. Chronic Respiratory Symptoms and Lung Function in a Sample of Agricultural Workers in Skopje Region. Maced J Med Sci. 2014;2(2):327-34.

26. Karadzinska-Bislimovska J et al. Respiratory symptoms, atopic status and lung function tests in agricultural workers. Allergy. 2007;62(83):283.

27. Annesi-Maesano I et al. Relationship of upper airway disease to tobacco smoking and allergic markers: a cohort study of men followed up for 5 years. Int Arch Allergy Immunol. 1997;114(2):193-201.

28. Terho EO. Work-related respiratory disorders among Finnish farmers. Am J Ind Med. 1990;18(3):269-72.

29. Warren CPW, Manfreda J. Respiratory symptoms in Manitoba farmers: association with grain and hay handling. Can Med Assoc J. 1980;122(11):1259-64.

30. Heederik D et al. Chronic non-specific lung disease and occupational exposures estimated by means of a job exposure matrix: the Zutphen study. Int J Epidemiol. 1989;18(2):382-9.

31. Kauffmann F et al. Occupational exposure and 12 year spirometric changes among Paris area workers. Br Ind Med. 1982;39(3):221-32.

32. Skórska C et al. Effects of exposure to grain dust in Polish farmers: work-related symptoms and immunologic response to microbial antigens associated with dust. Ann Agric Environ Med. 1998;5(2):147-53.

33. Chan-Yeung M et al. Five cross-sectional studies of grain elevator workers. Am J Epidemiol. 1992;136(10):1269-79.

34. Omland O et al. The shape of the maximum expiratory flow-volume curve reflects exposure in farming. Ann Agric Environ Med. 2000;7(2):71-8.

35. Zock JP et al. Occupation, chronic bronchitis, and lung function in young adults. An international study. Am J Respir Crit Care Med. 2001;163(7):1572-7.

36. Ulvestad B et al. Cumulative exposure to dust causes accelerated decline in lung function in tunnel workers. Occup Environ Med. 2001;58(10):663-9.

37. Dalphin JC et al. Prevalence of asthma and respiratory symptoms in dairy farmers in the French province of the Doubs. Am J Respir Crit Care Med. 1998;158:1493-8.

38. Dosman JA et al. Respiratory symptoms and pulmonary function in farmers. J Occup Med. 1987;29(1):38-42.

39. Huy T et al. Grain dust and lung function: dose response relationships. Am Rev Respir Dis. 1991;144(6):1314-21.

40. Corey P et al. Grain elevator workers show work-related pulmonary function changes and dose-effect relationships with dust exposure. Br J Ind Med. 1981; 39(4):330-7.

41. Enarson DA et al. Rapid decline in FEV1 in grain handlers. Am Rev Respir Dis. 1985;132(4):814-7.

42. Dalphin JCH et al. Etiologic factors of chronic bronchitis in dairy farmers. Case control study in the Doubs region of France. Chest. 1993;103(2):417-21.

43. Omland O. Exposure and respiratory health in farming in temperate zones - a review of the literature. Ann Agric Environ Med. 2002;9(2):119-36.

44. Stoleski S et al. Chronic Respiratory Symptoms and Lung Function in Agricultural Workers - Influence of Exposure Duration and Smoking. OA Maced J Med Sci. 2015;3(1):158-65.

45. Leuenberger P et al. Occupational exposure to inhalative irritants and metacholine responsiveness. Scand J Work Environ Health. 2000;26(2):146-52.

46. Iversen M et al. Respiratory symptoms in Danish farmers: An epidemiological study of risk factors. Thorax. 1998;43(11): 872-7.

47. Becklake MR. Occupational exposures: evidence for a causal association with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1989;140(2):S85-91.

48. Balmes J et al. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med. 2003;167(5):787-97.

49. Blanc PD, Toren K. Occupation in chronic obstructive pulmonary disease and chronic bronchitis: an update. Int J Tuberc Lung Dis. 2007;11(3):251-7.

50. Eduard W et al. Chronic bronchitis, COPD, and lung function in farmers: the role of biological agents. Chest. 2009; 136(3):716-25.

51. Bouyer J, Hémon D. Comparison of three methods of estimating odds ratios from a job exposure matrix in occupational case-control studies. Am J Epidemiol. 1993;137(4):472-81.

52. Le Moual N et al. Performance of population specific job exposure matrices (JEMs): European collaborative analyses on occupational risk factors for chronic obstructive pulmonary disease with job exposure matrices (ECOJEM). Occup Environ Med. 2000;57(2):126-32.

RADIOMETER

TCM5 BASIC monitor

Awake during sleep

The TCM5 transcutaneous monitor has a dedicated sleep mode allowing it to operate in complete silence and with a dark screen. It allows patients to sleep undisturbed as it continuously records key data. As it provides easy connectivity to polysomnography systems, information can be stored, shared and managed simply, making it ideal for sleep diagnostics.

NO LIGHT

NO NOISE

ADVANCED CONNECTIVITY

For more information on the TCM5 monitor, please contact your local Radiometer representative

www.radiometer.com

A CONFOUNDING CASE: PNEUMOCOCCAL PNEUMONIA UNMASKING SYSTEMIC LUPUS ERYTHEMATOSUS

***Ashok Arbat, Sneha Tirpude, Mitesh K. Dave, Sukhant Bagdia, Sameer Arbat**

Department of Pulmonology, KRIMS Hospitals, Nagpur, Maharashtra, India
**Correspondence to ashok_arbat@yahoo.com*

Disclosure: The authors have declared no conflicts of interest.
Received: 21.04.16 **Accepted:** 26.08.16
Citation: EMJ Respir. 2016;4[1]:82-85.

ABSTRACT

We report a case of systemic lupus erythematosus in a 27-year-old female complicated with pneumonia and severe respiratory failure, requiring treatment in an intensive care unit and non-invasive ventilation. Symptoms developed in an otherwise healthy female with no comorbidities except recurrent oral ulcers. Despite evidence of pulmonary infection, response was noted only after early introduction of intensive immunosuppressive treatment. Differential diagnosis and treatment of this condition represent a real challenge but close co-operation between the intensive care unit, pulmonology, and rheumatology departments reduce the risk of a fatal outcome.

Keywords: Systemic lupus erythematosus (SLE), pneumococcal pneumonia, acute lupus pneumonitis (ALP).

INTRODUCTION

Lupus ranges from mild to severe symptoms and many people have long periods with few or no symptoms before a sudden flare-up. In a person who is genetically susceptible to develop systemic lupus erythematosus (SLE), multiple environmental factors such as air pollution, smoking, exposure to toxins and gases, and infections can act as triggers to develop the clinical features of SLE. Tissue chimerism also plays an important role in producing lung disease in SLE.[1] Chimerism refers to cells from one individual in another individual. Kremer Hovinga et al.[2] performed a postmortem investigation for chimerism in SLE and normal controls. It was found that chimerism occurred more commonly in SLE organs and in those who had an evidence of injury. During pregnancy, fetal cells enter the maternal circulation, making the mother chimeric.

The incidence of SLE is higher amongst non-Caucasians,[3] although finding the true prevalence of lung involvement with SLE is complicated by high rates of pulmonary infections. Reported prevalence of pulmonary involvement in SLE varies from 14–100%. Pulmonary manifestations may be the presenting symptom in 4–5% of patients, and the lungs are involved in almost half of patients during the disease course.[4] SLE most commonly affects females of childbearing age.[5] In India, the reported prevalence of SLE ranges from 14–60 people per 100,000.[6] This case report shows an otherwise asymptomatic female presenting with pulmonary infection but eventually diagnosed with SLE.

CASE REPORT

A 27-year-old female had complaints of fever for 3 months and cough with mucoid expectoration for 1.5 months. She was privately hospitalised for 7 days but did not respond to the empirical treatment. After 15 days she followed up with us and, except for fever, her observations were stable. Her chest radiograph showed persistent left lower zone opacity (Figure 1). We performed bronchial washings and gave her cefuroxime and awaited her reports.

The next month, her bacterial culture yielded *Streptococcus pneumoniae*, and she was then hospitalised in the intensive care unit, with a temperature of 38.3˚C, respiratory rate of 24 breaths

per minute with use of accessory muscles, and oxygen saturation of 84%. She had a rash over her faucial pillars and soft palate, and coarse-end inspiratory crackles in all zones on auscultation. She was treated with injectable vancomycin followed by linezolid, according to the antibiotic sensitivities report, and oxygen supplementation with non-invasive ventilator support was provided. She was still febrile and her chest radiograph worsened, now involving bilateral mid and upper zones. She had three absence seizures to which her neurological assessment yielded no abnormality. A complete blood count showed a white blood cell count of 2,500/mm^3, lymphocytes of 13% (absolute lymphocyte count 325/mm^3), and haemoglobin of 9.4 g/dL. There was proteinuria and serum creatinine of 0.7 mg/dL. The patient did not consent to spirometry with diffusion capacity of lung for carbon monoxide. On computed tomography, the thorax showed bilateral patchy alveolar opacities with ground glass opacification and superimposed tiny nodular opacities. The anti-nuclear antibody test was positive, along with anti-double stranded DNA and perinuclear anti-neutrophil cytoplasmic antibodies. Complement C3 (36.5 mg/dL) and C4 (<6.3 mg/dL) were low, rheumatoid factor was negative, and a transbronchial lung biopsy on repeat bronchoscopy showed evidence of diffuse alveolar damage (organising phase).

DISCUSSION

The most immediate concern was the progressive worsening of the patient despite several courses of antibiotics, with the backdrop of difficult communication due to language barriers. There was an initial bronchial washings report suggesting infection due to *S. pneumoniae* after which she started on appropriate antibiotics. Despite this, she continued to have fever and radiological progression of her condition. Her oral ulcers, faucial pillar rash, and reports of anaemia, lymphopenia, proteinuria, and diffuse alveolar damage led to serology tests that confirmed the diagnosis of SLE. Pulse steroid, mycophenolate mofetil, and hydroxychloroquine were then started. She showed improvement clinically and radiologically. Her symptoms and chest radiograph after 4 weeks of treatment significantly improved (Figure 2).

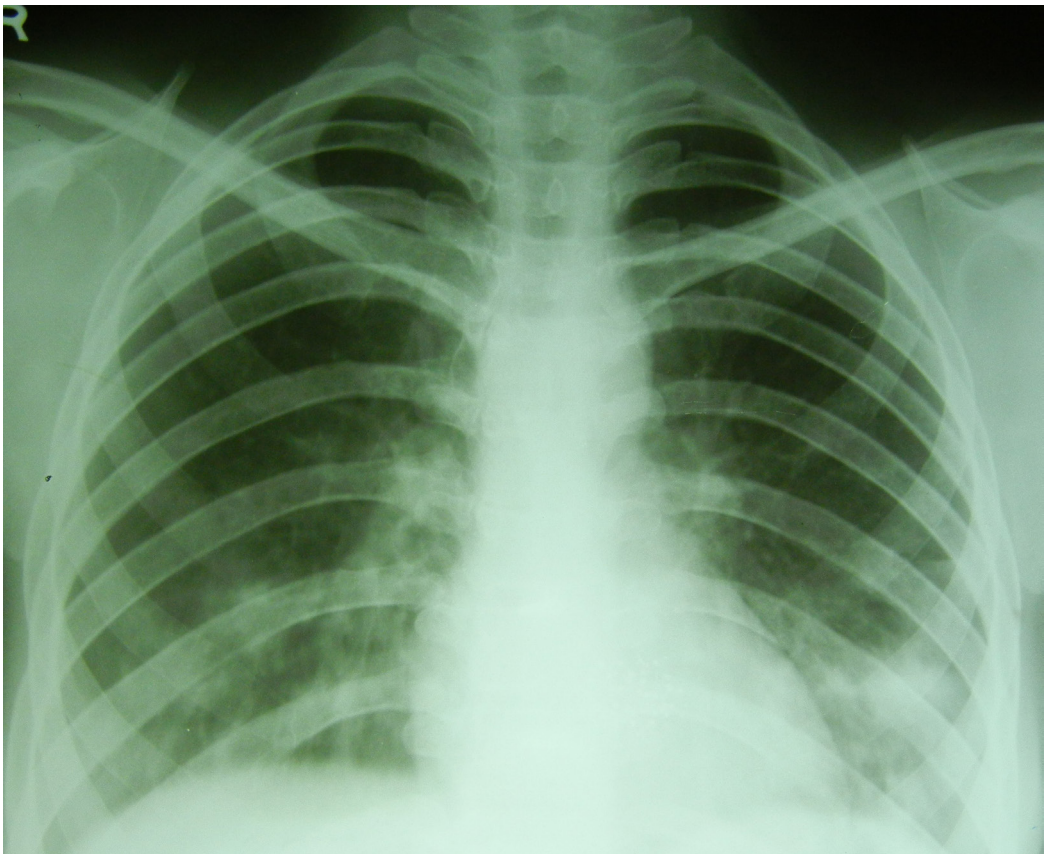


Figure 1: Chest radiograph showing progressive increase in opacities bilaterally in the mid and lower zones.

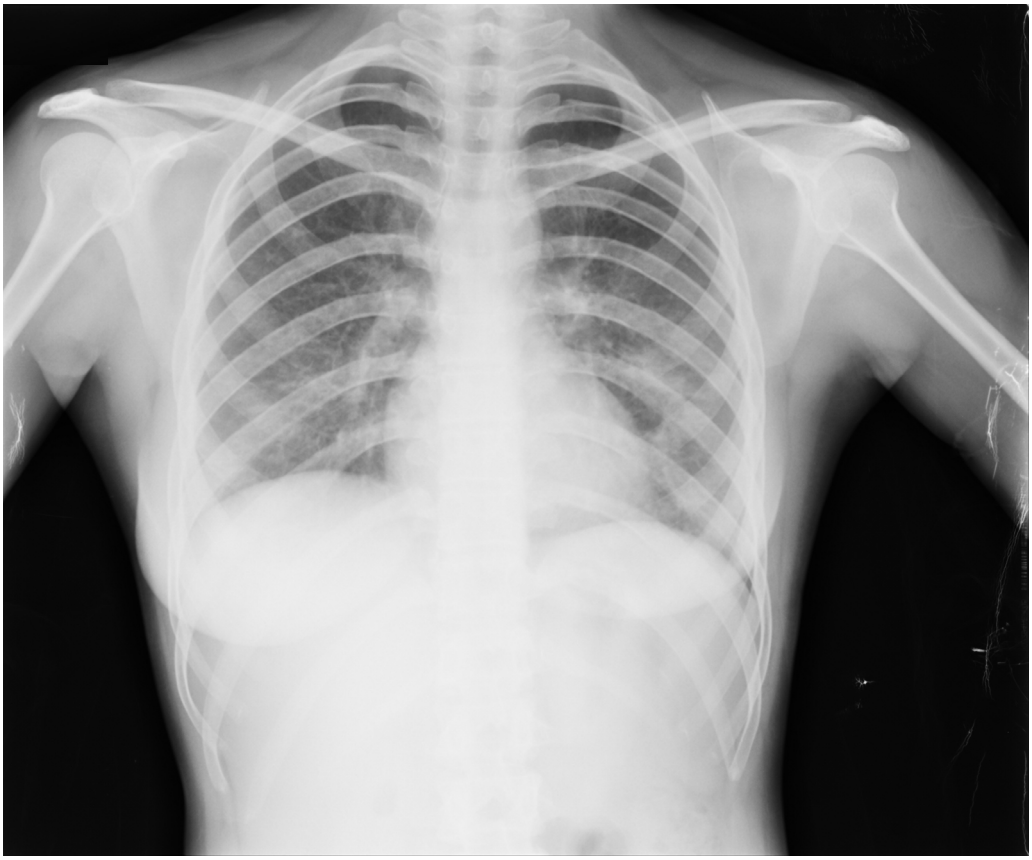


Figure 2: Chest radiograph showing resolution of opacities.

SLE has various pulmonary manifestations ranging from pleurisy, obstructive lung disease, and diaphragmatic dysfunction (shrinking lung syndrome) to acute lupus pneumonitis (ALP), diffuse alveolar haemorrhage (DAH), and chronic interstitial pneumonia. The rate of infection in SLE appears to exceed that of any other autoimmune diseases and immuno-compromised states by as much as 8-fold.[7] The clinical presentation of ALP is non-specific and is characterised by the sudden onset of fever, cough, and dyspnoea with hypoxaemia and hypocapnia, pleuritic chest pain, and patchy alveolar infiltrates on chest radiograph without clinical and laboratory evidence of an underlying infection.[8] If the bronchial washings had been negative to culture, this patient would have been a case of ALP versus DAH. ALP can be difficult to differentiate from infectious pneumonia because of similar clinical and radiological presentation. Their differentiation is important for treatment, but in this patient both antibiotics and immuno-suppressive treatment were required. The underlying SLE in the form of ALP became apparent with this infection. We may call this acute lupus 'pneumonia' instead of acute lupus 'pneumonitis'.

Bacterial DNA can promote several of the autoimmune abnormalities observed in SLE through molecular mimicry and has a possible pathogenic role in activating immune cells.[9-11] Bacteria and viruses produce toxins called superantigens that bind to the major histocompatibility complex Class II proteins on antigen-presenting cells and to the specific T cell receptors on activated T cells. The ability to stimulate polyclonal B (immunoglobulin G) as well as T cell responses raises the possibility of a role for superantigens in the induction of autoimmune diseases.[12] In the framework of autoimmune diseases, antibodies developed against bacterial antigens during infection are supposed to recognise self-antigens, inducing formation of immune complexes. The infections are particularly due to encapsulated organisms.[13] Pulmonary tuberculosis is the most common infection seen in India in patients with SLE. A 2009 study showed that individuals on hydroxychloroquine are 16-times less likely to get a major infection when taking the drug, regardless of whether or not corticosteroids are also taken.[14] Lupus patients' immune systems need to receive bactericidal rather than bacteriostatic drugs;[15] non-live vaccines are useful.[13]

This is a novel case, in which the patient had an ongoing fever for 3 months due to pneumonia that triggered the expression of SLE. We arrived at this conclusion because the increased opacities resolved only after the addition of treatment of ALP.

REFERENCES

1. Kamen DL, Strange C. Pulmonary manifestations of systemic lupus erythematosus. Clin Chest Med. 2010;31(3): 479-88.

2. Kremer Hovinga IC et al. Tissue chimerism in systemic lupus erythematosus is related to injury. Ann Rheum Dis. 2007;66(12):1568-73.

3. Somers EC et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. Arthritis Rheumatol. 2014;66(2):369-78.

4. Vitali C et al. Disease activity in systemic lupus erythematosus: report of the Consensus Study Group of the European Workshop for Rheumatology Research. I. A descriptive analysis of 704 European lupus patients. European Consensus Study Group for Disease Activity in SLE. Clin Exp Rheumatol. 1992;10(5):527-39.

5. Weckerle CE, Niewold TB. The unexplained female predominance of systemic lupus erythematosus: Clues from genetic and cytokine studies. Clin Rev Allergy Immunol. 2011;40(1):42-9.

6. Malaviya AN et al. Prevalence of systemic lupus erythematosus in India. Lupus. 1993;2(2):115-8.

7. Skare TL et al. Infections and systemic lupus erythematosus. Einstein (São Paulo). 2016;14(1):47-51.

8. Torre O, Harari S. Pleural and pulmonary involvement in systemic lupus erythematosus. Presse Med. 2011;40(1Pt2): e19-29.

9. Tomita H et al. Systemic lupus erythematosus-like autoimmune abnormalities induced by bacterial infection. Clin Exp Rheumatol. 2003; 21(4):497-9.

10. Sheybani F et al. Sometimes there is more than one puzzle on the table: Pneumococcal bacteremia as a new systemic lupus erythematosus presentation. Case Rep Infect Dis. 2015; 970289.

11. Sánchez B et al. Interaction of Intestinal Microorganisms with the Human Host in the Framework of Autoimmune Diseases. Front Immunol. 2015;20(6):594.

12. Acha-Orbea H. Bacterial and viral superantigens: Roles in autoimmunity? Ann Rheum Dis. 1993;52(Suppl 1):S6-16.

13. Abu-Shakra M. Safety of vaccination of patients with systemic lupus erythematosus. Lupus. 2009;18(13): 1205-8.

14. Medscape Medical News; Barclay L. Hydroxychloroquine use may be safe in systemic lupus erythematosus. 15 June 2009. Available at: http://www.medscape.com/viewarticle/704385. Last accessed: 26 August 2016.

15. Lupus Society of Illinois. Managing Infections for Lupus Patients - Highlights from Dr. Curran's Presentation. 411 S. Chicago, Illinois, 9 August 2012. Available at: http://www.lupusil.org/managing-infections-for-lupus-patients---highlights-from-dr-currans-presentation.html. Last accessed: 26 August 2016.

SMOKING CESSATION WITH LUNG CANCER: NOT TOO LITTLE, NEVER TOO LATE!

***Rachel Gemine,[1] Keir Lewis[2]**

1. Research and Development, Hywel Dda University Health Board; College of Medicine, Swansea University, Swansea, UK
2. Department of Respiratory Medicine, Prince Philip Hospital, Hywel Dda University Health Board; College of Medicine, Swansea University, Swansea, UK
**Correspondence to Rachel.Roberts3@wales.nhs.uk*

Disclosure: The authors have declared no conflicts of interest.
Received: 01.03.16 **Accepted:** 29.06.16
Citation: EMJ Respir. 2016;4[1]:86-91.

ABSTRACT

Smoking is the leading cause of lung cancer (LC) worldwide, however any continuing effects of smoking or cessation following a diagnosis are less well known. With around 40% of patients with LC smoking at the time of diagnosis and the majority presenting with an incurable/progressive disease, should clinicians be strongly recommending smoking cessation programmes? The evidence proposes that they should be. Current literature suggests that stopping smoking following a diagnosis of LC can lead to better treatment responses, fewer treatment complications, and less recurrence or new tumours. These benefits translate into reduced mortality and importantly, better quality of life. This review will look at the growing body of evidence that suggests smoking cessation should be prioritised in patients who have been diagnosed with LC.

Keywords: Lung cancer (LC), smoking cessation, mortality, treatment complications, quality of life.

INTRODUCTION

Lung cancer (LC) has the highest mortality rate of any cancer,[1] with >1.6 million new cases and 1.4 million deaths per year worldwide.[2] The current 1, 5, and 10-year survival rates of patients with LC remain poor despite advances in treatment and diagnostic techniques.[3,4] Worldwide, smoking prevalence is increasing.[5] Smoking causes around 85% of LC and the impact of LC and other smoking-related diseases, especially on low and middle-income countries, is rising.

Aside from the rate of LC caused by smoking (80–85%),[6,7] less is known about the effect of continuing to smoke versus cessation on prognosis and survival in patients already diagnosed with LC. This review examines the current evidence for the effects of continued smoking and smoking cessation on clinical outcomes following LC diagnosis, providing some recommendations for a tailored smoking cessation service specifically for this vulnerable group.

Most studies report that ~40% of patients are smoking at the time of their LC diagnosis;[8-10] this represents a considerable number of people, e.g. at least 18,000 in the UK alone[11] and 164,000 individuals across Europe per annum.[12] Moreover, some ex-smokers may restart under the stress of diagnosis or treatments. Therefore, even small clinical effects may have public health implications. Continued smoking is likely to adversely affect outcomes in several ways.

IMPACT OF TOBACCO SMOKE ON TUMOUR CELLS

It is biologically plausible that continuing to smoke affects cancer cells. The 2014 Surgeon General Report stated that 69 carcinogens in tobacco smoke (TS) had been identified;[13] these include polycyclic aromatic hydrocarbons and nicotine-specific nitrosamines, and continued exposure to TS has been shown to increase the rate of tumour growth by further increasing cellular damage, mainly by causing more genetic mutations and by

suppressing the body's defenses.[14] TS affects the integrity of DNA by alkylation, which can facilitate the development of existing and new cancer. In addition, *in vitro* studies have shown that smoking was significantly related to more chemo-resistant tumours.[15,16] Continuing to smoke following a diagnosis of LC can lead to an increased risk of recurrence or subsequent primary malignancies.[17-19]

Nicotine itself may also directly accelerate the development of the tumour by increasing capillary and collateral growth. Enhanced tissue perfusion has been observed in mouse models of LC,[20] but this has not been confirmed in human studies, and the benefits of nicotine replacement therapy in helping people quit and reduce TS exposure far outweigh any direct potential carcinogenic effects of the compound itself.

IMPACT OF SMOKING ON IMMUNE-SURVEILLANCE

Within humans, TS can affect the immune system and response, leading to reduced defences such as natural killer cells and, subsequently, further cancer.[14] Application of TS to lung tumours has certainly caused faster growth in animal studies.[17] It also depresses the immune system's response to malignant growths and increases the risk of metastatic development.[21]

IMPACT OF TOBACCO SMOKE ON TREATMENT FOR LUNG CANCER

Surgery

A systemic review highlighted the association between smoking at the time of any surgery and increased surgical and especially respiratory complications in smokers compared with non-smokers, producing an odds ratio (OR) of 5.5 (95% confidence interval [CI]: 1.9–16.2).[22]

More interestingly, quitting smoking even for short periods prior to any type of surgery is associated with reduced postoperative risks, including pulmonary and respiratory complications,[23,24] as well as better wound healing,[25] shortened bone fusion time,[26] and decreased time in hospital following the procedure.[27] However, the evidence suggests that longer periods of abstinence have greater effectiveness at reducing surgical complications.[23]

Between 14% and 40% of patients who undergo surgery for lung or colorectal cancer smoke;[28,29] observational studies again suggest that cancer patients in general who smoke are also independently at higher risk of surgical complications and mortality.[30]

In particular, patients with LC were significantly more likely to develop complications such as pneumonia after surgery if they were currently smoking (OR: 1.62, 95% CI: 1.25–2.11).[30] A retrospective cohort study comparing smokers with those who had abstained or had never smoked showed a decrease in survival at 120 weeks following surgical resection, from 60–70% to 25%.[31] This difference in fatality could be due to the increased risk of postoperative complications, increased recurrence, or presence of new malignancies in smokers.[32] Even following potentially curative resection for head and neck cancers, smokers are also at a higher risk of recurrence or secondary cancers.[33,34] Smokers are also more likely to have or develop comorbid conditions, such as chronic obstructive pulmonary disease (COPD) or chronic heart disease, which may also contribute to this mortality rate.

Slatore et al.[35] estimated that providing smoking cessation prior to surgery for LC could result in a monetary saving by reducing postoperative complications and recovery times. This value should however be regarded with speculation, as quitting smoking may be a marker of other positive health behaviours that may contribute to recovery time.

Chemo-Radiotherapy

In addition to surgery, there is also a notable effect of smoking status on those receiving chemotherapy and radiotherapy. Smoking induces the hepatic cytochrome P450 system, potentially reducing blood/tissue levels of chemotherapeutic agents.[36] Preclinical studies show that smoking increases carboxyhaemoglobin levels, which impairs tumour oxygenation and in turn reduces the effectiveness of radiotherapy,[37,38] increasing treatment complications.[39] Following radiation therapy, those with LC who did not smoke had a median survival of 27.9 months, compared with 13.7 months in those who smoked (p=0.01).[40]

Smoking tobacco directly affects drug metabolism, which can impact responses to targeted therapy and chemotherapy. TS can also impact responses to targeted therapy directed at the estimated glomerular filtration rate. An early phase intervention study found that doubling the dosage in those who smoked only led to a similar incidence

of diarrhoea and skin toxicity, compared with non-smokers taking the standard dose.[41] This indicates that smokers clear their therapeutic agents more quickly, and so are less likely to respond.

A retrospective study of 285 patients found that non-responders (n=191) had smoked significantly more than responders (67.8±35.1 versus 38.7±27.1 pack-years; p<0.001). Multivariate analysis confirmed that heavy tobacco consumption (≥40 pack-years) was the most important independent negative predictor of response (adjusted OR: 10.4; 95% CI: 5.1–21.3).[42] This may be because those who smoke may have a faster systemic clearance, meaning that to be effective they would require a larger dose of treatment or because the tumours are more resistant to treatment due to their previous exposure to carcinogenics from tobacco. In addition, among patients with LC, retrospective studies suggest that continuing to smoke[8] independently increases treatment-related complications such as radiation pneumonitis and neutropenic sepsis.[28] Further research is needed in this area to look at the effects of increasing chemotherapy dose in patients who continue to smoke but current evidence suggests these higher doses of chemotherapy and radiotherapy are very likely to lead to additional complications and greater side effects in this population.

Despite this evidence, many trials of new therapeutic agents neglect to even record smoking status or assess any impact of smoking on outcome.[43] Those that do record smoking usually rely on self-reported measures and therefore lack validation. The benefits of smoking cessation for patients receiving chemotherapy are equally biologically plausible, but any survival advantage will in part be mitigated by the poorer overall survival of people with more advanced cancers selected for these treatments.

IMPACT OF TOBACCO SMOKE ON COMORBIDITIES IN PEOPLE WITH LUNG CANCER

Smoking can adversely affect outcome by causing and accelerating other illnesses in people with LC. Smokers are more likely to be diagnosed with COPD, heart disease, cerebrovascular disease, high blood pressure, diabetes, thrombosis, and many other conditions.[44] Continued smoking worsens any comorbid condition, which can lead to an increased risk of infections and result in delays or interruptions to LC treatment.

For those with head and neck cancer, patients who stopped smoking following diagnosis had double the survival rate than those who continued to smoke, whilst those who continued to smoke had a 4-times higher chance of recurrence.[45] In patients with breast cancer, recurrence in smokers increased by 15% (p=0.039) compared with those who quit.[46] This finding has been replicated in patients with prostate cancer.[47]

OVERALL IMPACT OF TOBACCO SMOKING ON MORTALITY IN PEOPLE WITH LUNG CANCER

Smoking and Early Stage Lung Cancer

In a study comparing 215 patients with limited disease small-cell lung cancer (SCLC) treated with radio-chemotherapy, 5-year survival was improved in those who quit smoking prior to treatment commencing. Patients who abstained from smoking had a median survival time of 18.0 versus 13.6 months compared with those who continued to smoke. This indicates that smoking cessation is an important factor when advising on long-term survival and day-to-day treatment.[48] This is further supported by a meta-analysis of 10 randomised controlled trials and longitudinal studies that examined the effect of quitting smoking after a diagnosis of LC on outcomes. Continued smoking was associated with a significantly increased risk of all-cause mortality (hazard ratio [HR]: 2.94, 95% CI: 1.15–7.54) and recurrence (HR: 1.86; 95% CI: 1.01–3.41) in early stage non-SCLC (NSCLC) and of all-cause mortality (HR: 1.86, 95% CI: 1.33–2.59), development of a second primary tumour (HR: 4.31, 95% CI: 1.09–16.98), and recurrence (HR: 1.26, 95% CI: 1.06–1.50) in limited stage SCLC. In limited stage SCLC, an estimated 29% of continuing smokers survive for 5 years versus 63% of quitters.[49]

A recent meta-analysis by Parsons et al.[49] highlighted the effect on survival in patients with early stage LC who quit smoking after diagnosis. This review found that the 5-year survival in continued smokers was 33%, compared with 70% survival in LC patients who quit.

Benefit of Smoking Cessation in all Patients with Lung Cancer

A recent study by Dobson Amato et al.[50] observed the impact of telephone smoking cessation advice in 250 recently diagnosed patients with LC. Survival data indicated that the 102 patients who had reportedly quit by the time of last contact had a median survival of 29 months compared with 20 months in the 148 continued smokers (HR: 1.79, 95% CI: 1.14–2.82). Continued smoking has also been associated with decreased survival in a variety of cancers, including head and neck cancers[51] and prostate cancer.[52] With almost half of all LC patients smoking at the time of diagnosis,[10] it is important to look at the continued risk of continuing to smoke following a diagnosis of LC.

Smoking status is likely to affect overall mortality. The Mayo Clinic, Rochester, USA, studied a large cohort of patients (N=5,229) with any stage of either NSCLC or SCLC to prospectively evaluate any potential relationship between duration of smoking abstinence and survival.[53] Among NSCLC patients, the median survival was progressively worse among never (1.4 years), former (1.3 years), and current smokers (1.1 years), respectively ($p<0.01$), whilst no effect of smoking abstinence was observed among SCLC patients. Most recently, in a retrospective analysis of 284 patients with limited SCLC treated in the Mayo Clinic, Chen et al.[54] found that patients who actually quit at or after diagnosis reduced their risk of death by 45% (HR: 0.55, 95% CI: 0.38–0.79) and patients who quit before LC diagnosis also experienced survival benefit (HR: 0.72, 95% CI: 0.52–1.00). They recommended that "clinicians and all care providers should strongly encourage smoking cessation at diagnosis of limited stage SCLC."[54]

Benefit of Smoking Cessation in Advanced Lung Cancer

Despite the evidence for smoking cessation following a diagnosis of limited or early stage LC,[55] the evidence is less clear in patients with advanced LC.[56] A retrospective analysis of patients with advanced NSCLC showed a 5-month difference in survival between smokers and those who had never smoked, however due to the low number of participants this was not statistically significant.[57] Tsao et al.[56] found that continuing smoking during chemotherapy for Stage III and IV LC did not impact prognosis. This could be due to the poor survival following diagnosis in this group which does not allow for a benefit of cessation to be seen, or because previous exposure to carcinogens has a long-lasting effect.

PROBLEMS WITH CURRENT LITERATURE

Most current research is based on retrospective studies that are open to selection and especially reporting bias. Moreover, in the majority of studies smoking is self-reported and not validated. Smoking status may also be indicative of other prognostic factors. Those who quit smoking are more likely to be of higher socioeconomic status and could have better diet, reduced alcohol consumption, or be more compliant in taking medication and attending appointments. In this context, cessation is merely a marker for other good health behaviours.

The 2011 National Institute for Health Care and Excellence (NICE) guidelines for the treatment of LC highlight the importance of smoking cessation after diagnosis, including the specific recommendation to "advise patients to stop smoking as soon as the diagnosis of LC is suspected."[58] NICE calls for more research investigating the benefits of cessation on pulmonary complications, quality of life, and survival.

Based on the current evidence it is clear that quitting smoking is the best thing that any hospitalised patient can do to improve their health[59] and a combination of pharmacotherapy and counselling should be offered.[60] There is clear biological plausibility and increasing observational evidence that continued smoking after a diagnosis of LC increases tumour recurrence along with the risk of secondaries and new primaries. Continued smoking also increases resistance to, and complications from, all current modes of treatment. It is probably also a marker for other poor health behaviours. For all these reasons, continued smoking after a diagnosis is associated with or will directly worsen quality of life, and lower survival.

Combining this growing evidence with all the other (non-cancer related) known benefits of smoking cessation, we believe that a randomised, controlled, intervention trial is unethical. However, we believe that adequately powered prospective, observational, cohort studies validating smoking status are important and are relatively easy to do. People with cancer have unique needs and are receiving many treatments. The next practical step

is working with those who have been diagnosed with LC to examine their motivations and barriers to smoking cessation to build a responsive and convenient smoking cessation service. With integration of this service directly into ongoing treatment plans, perhaps a smoking cessation specialist may even be part of the LC multidisciplinary team in the future.

REFERENCES

1. Molina JR et al. Non-small cell lung cancer: Epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc. 2008;83(5): 584-94.

2. World Health Organization; International Agency for Research on Cancer. GLOBOCAN 2008: Cancer Incidence and Mortality Worldwide, IARC CancerBase No. 10. 2010. Available at: http://www.iarc.fr/en/media-centre/iarcnews/2010/globocan2008.php. Last accessed: 1 March 2016.

3. Youlden DR et al. The International Epidemiology of Lung Cancer: Geographical distribution and secular trends. J Thorac Oncol. 2008;3(8):819-31.

4. Janssen-Heijnen MLG, Coebergh JW. The changing epidemiology of lung cancer in Europe. Lung Cancer. 2003;41(3): 245-58.

5. Ng M et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. JAMA. 2014;311(2):183-92.

6. Centers for Disease Control and Prevention. 2004 Surgeon General's Report – The Health Consequences of Smoking. 2004. Available at: http://www.cdc.gov/tobacco/data_statistics/sgr/2004/index.htm. Last accessed: 1 March 2016.

7. Pesch B et al. Cigarette smoking and lung cancer--relative risk estimates for the major histological types from a pooled analysis of case-control studies. Int J Cancer. 2012;131(5):1210-9.

8. Garces YI et al. The relationship between cigarette smoking and quality of life after lung cancer diagnosis. Chest. 2004;126(6):1733-41.

9. Cavichio BV et al. [Duration of smoking cessation for the prevention of surgical wound healing and complications]. Rev Esc Enferm USP. 2014;48(1)170-80.

10. Roberts R, Lewis K. Comparing smokers and non-smokers attending a rapid access lung cancer clinic. Eur Respir J. 2014;44(Suppl 58):327.

11. Cancer Research UK. Lung cancer incidence statistics. 2013. Available at: http://www.cancerresearchuk.org/health-professional/lung-cancer-incidence-statistics. Last accessed: 4 February 2016.

12. Ferlay J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013:49(6):1374-403.

13. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health.; Atlanta (GA): Centers for Disease Control and Prevention (US). The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. 2014.

14. Stämpfli MR, Anderson GP. How cigarette smoke skews immune responses to promote infection, lung disease and cancer. Nat Rev Immunol. 2009;9(5): 377-84.

15. Volm M et al. Relationship between chemoresistance of lung tumours and cigarette smoking. Br J Cancer. 1990; 62(2):255-6.

16. Volm M et al. Angiogenesis and cigarette smoking in squamous cell lung carcinomas: an immunohistochemical study of 28 cases. Anticancer Res. 1999; 19(1A):333-6.

17. Hecht SS. Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst. 1999; 91(14):1194-210.

18. Richardson GE et al. Smoking cessation after successful treatment of small-cell lung cancer is associated with fewer smoking-related second primary cancers. Ann Intern Med. 1993;119(5):383-90.

19. Levi F et al. Second primary cancers in patients with lung carcinoma. Cancer. 1999;86(1):186-90.

20. Heeschen C et al. Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. Nat Med. 2001;7(7): 833-9.

21. McAllister-Sistilli CG et al. The effects of nicotine on the immune system. Psychoneuroendocrinology. 1998:23(2): 175-87.

22. Bluman LG et al. Preoperative smoking habits and postoperative pulmonary complications. Chest. 1998;113(4):883-9.

23. Theadom A, Cropley M. Effects of preoperative smoking cessation on the incidence and risk of intraoperative and postoperative complications in adult smokers: A systemic review. Tob Control. 2006;15(5):352-8.

24. Møller AM et al. Effect of smoking on early complications after elective orthopaedic surgery. J Bone Joint Surg Br. 2003;85(2):178-81.

25. Sorensen LT et al. Abstinence from smoking reduces incisional wound infection: A randomized control trial. Ann Surg. 2003;238(1):1-5.

26. Ishikawa SN et al. The effect of cigarette smoking on hindfoot fusions. Foot Ankle Int. 2002;23(11):996-8.

27. Møller AM et al. Effect of preoperative smoking intervention on postoperative complications: A randomised clinical trial. Lancet. 2002;359(9301):114-7.

28. Monson JM et al. Clinical radiation pneumonitis and radiographic changes after thoracic radiation therapy for lung carcinoma. Cancer. 1998;82(5):842-50.

29. Park ER et al. A snapshot of smokers following lung and colorectal cancer diagnosis. Cancer. 2012;118(12)3153-64

30. Gajdos C et al. Adverse effects of smoking on postoperative outcomes in cancer patients. Ann Surg Oncol. 2012; 19(5):1430-8.

31. Sardari Nia P et al. Prognostic value of smoking status in operated non-small cell lung cancer. Lung Cancer. 2005;47(3): 351-9.

32. Mason DP et al. Impact of smoking cessation before resection of lung cancer: A Society of Thoracic Surgeons General Thoracic Surgery Database study. Ann Thorac Surg. 2009;88(2):362-71.

33. Wein RO. Preoperative smoking cessation. Arch Otolaryngol Head Neck Surg. 2009;135(6):597-601.

34. Schwartz LH et al. Synchronous and metachronous head and neck carcinomas. Cancer. 1994;74(7):1933-8.

35. Slatore CG et al. Cost-effectiveness of a smoking cessation program implemented at the time of surgery for lung cancer. J Thorac Oncol. 2009;4(4):499-504.

36. Dresler CM. Is it more important to quit smoking than which chemotherapy is used? Lung Cancer. 2003;39(2):119-24.

37. Grau C et al. Effect of carbon monoxide breathing on hypoxia and radiation response in the SCCVII tumor in vivo. Int J Radiat Oncol Biol Phys. 1994;29(3): 449-54.

38. Siemann DW et al. Smoking: The influence of carboxyhemoglobin (HbCO) on tumor oxygenation and response to radiation. Int J Radiat Oncol Biol Phys. 1978;4(7-8):657-62.

39. Nieder C, Bremnes RM. Effects of smoking cessation on hypoxia and its potential impact on radiation treatment effects in lung cancer patients. Strahlenther Onkol. 2008;184(11):605-9.

40. Fox JL et al. The effect of smoking

status on survival following radiation therapy for non-small cell lung cancer. Lung Cancer. 2004;44(3):287-93.

41. Hughes AN et al. Overcoming CYP1A1/1A2 mediated induction of metabolism by escalating erlotinib dose in current smokers. J Clin Oncol. 2009; 27(8):1220-6.

42. Duarte RL et al. The cigarette burden (measured by the number of pack-years smoked) negatively impacts the response rate to platinum-based chemotherapy in lung cancer patients. Lung Cancer. 2008;61(2):244-54.

43. Baser S et al. Smoking cessation after diagnosis of lung cancer is associated with a beneficial effect on performance status. Chest. 2006;130(6):1784-90.

44. NHS choices. What are the health risks of smoking? 2015. Available at: http://www.nhs.uk/chq/Pages/2344.aspx?CategoryID=53&SubCategoryID=536. Last accessed: 1 February 2016.

45. Stevens MH et al. Head and neck cancer survival and life-style change. Arch Otolaryngol. 1983;109(11):746-9.

46. Bishop JD et al. Smoking and breast cancer recurrence after breast conservation therapy. Int J Breast Cancer. 2014;2014:327081.

47. Daniell HW. A worse prognosis for smokers with prostate cancer. J Urol. 1995; 154(1):153-7.

48. Videtic GM et al. Continued cigarette smoking by patients receiving concurrent chemoradiotherapy for limited-stage small-cell lung cancer is associated with decreased survival. J Clin Oncol. 2003; 21(8):1544-9.

49. Parsons A et al. Influence of smoking cessation after diagnosis of early-stage lung cancer on prognosis: Systematic review of observational studies with meta-analysis. BMJ. 2010;340:b5569.

50. Dobson Amato KA et al. Tobacco cessation may improve lung cancer patient survival. J Thorac Oncol. 2015; 10(7):1014-9.

51. Jensen AR et al. Tumour progression in waiting time for radiotherapy in head and neck cancer. Radiother Oncol. 2007: 84(1):5-10.

52. Pickles T et al. The effect of smoking on outcome following external radiation for localized prostate cancer. J Urol. 2004; 171(4):1543-6.

53. Ebbert JO et al. Duration of smoking abstinence as a predictor for non-small-cell lung cancer survival in women. Lung Cancer. 2005;47(2):165-72.

54. Chen J et al. Prognostic factors for limited-stage small cell lung cancer: A study of 284 patients. Lung Cancer. 2010; 67(2):221-6.

55. Tammemagi CM et al. Smoking and lung cancer survival: The role of comorbidity and treatment. Chest. 2004; 125(1):27-37.

56. Tsao AS et al. Smoking affects treatment outcome in patients with advanced nonsmall cell lung cancer. Cancer. 2006;106(11):2428-36.

57. Toh CK et al. The impact of smoking status on the behavior and survival outcome of patients with advanced non-small cell lung cancer: A retrospective analysis. Chest. 2004;126(6):1750-6.

58. Nice guidelines [CG121]. Lung cancer: Diagnosis and management. 2011. Available at: https://www.nice.org.uk/guidance/cg121. Last accessed: 3 February 2016.

59. Rigotti NA et al. Smoking cessation interventions for hospitalized smokers: A systematic review. Arch Intern Med. 2008; 168(18):1950-60.

60. Stead LF, Lancaster T. Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation. Cochrane Database Syst Rev. 2012;12: CD009670.

THORACIC SURGERY AND TRANSPLANTATION

***Marcello Migliore**

Division of Thoracic Surgery, Department of Surgery and Medical Specialties, University of Catania, Catania, Italy
**Correspondence to mmiglior@unict.it*

Disclosure: The author has declared no conflicts of interest.
Received: 20.06.16 **Accepted:** 27.09.16
Citation: EMJ Respir. 2016;4[1]:92-96.

ABSTRACT

Major changes are bringing a new dimension to thoracic surgery and lung transplantation. This article reports the foremost recent advancements within the field. The most important advancement in thoracic surgery is certainly the widespread use of uniportal video-assisted thoracic surgery in the common practice of most thoracic operations, including major resections for lung cancer. In oncological thoracic surgery, to avoid unnecessary operations in the future, prospective randomised trials are ongoing to demonstrate why some patients with a 'resectable' malignancy within the chest will not survive as long as expected. Lung transplantation has progressed on multiple fronts but a significant advancement is the possibility to perform minimally invasive techniques to insert the lung into the chest of the recipient.

In conclusion, the search for minimal invasiveness has a prominent role in thoracic surgery but further research is essential to demonstrate the real advantages of technological surgical innovations. Worldwide co-operation will permit the collection of data faster and allow the completion of randomised controlled studies to this end.

Keywords: Thoracic surgery, lung cancer, lung transplantation, video-assisted thoracic surgery (VATS), uniportal, minimally invasive surgery.

INTRODUCTION

Major changes are bringing a new dimension to the future of thoracic surgery and there is no doubt that as technology is evolving so rapidly, it is sometimes difficult to follow all of the true advancements. In this brief article, the author analyses modern, major advancements within the field of thoracic surgery and lung transplantation, and the possible impact that some of these advancements will have inthe future.

THORACIC SURGERY

The most important recent advancement in thoracic surgery is certainly the widespread use of uniportal video-assisted thoracic surgery (VATS) in common practice. The concept of uniportal VATS was introduced in Europe (Catania, Italy) in 1998 and the first results were published between 2000 and 2003,[1-6] but only recently is the technique becoming known worldwide.[7-11] Briefly, uniportal VATS permits the execution of many thoracic operations, from pleural biopsy to major lung resection, through a single, small skin incision. It is performed by a team of one or, at a maximum, two surgeons. Some authors have also been able to perform more sophisticated operations using this technique, such as bronchial sleeve resection.[12]

Robotic-assisted thoracic surgery is performed in only a few European centres with high-quality results,[13] but controversy remains regarding the application of robotic surgery because of the lack of well-established evidence.[14-16] Robotic-assisted thoracic surgery is still too expensive for the majority of hospitals, mainly because of the cost of the 'robot' and the long length of operating room usage reported.[13]

Awake thoracic surgery has successfully been used to perform wedge resections of the lung for diagnostic purposes, pneumothorax, and tracheal resections,[17] but recently its use for major lung resection has brought about ethical concerns;[18,19] on the contrary, the concept of enhanced recovery

('fast-track') after thoracic surgery and anaesthesia has allowed an increased number of video-assisted parenchymal lung resections to be performed in managing primary lung cancer.[20]

Surgery for oesophageal cancer, one of the most complex operations, is nowadays more frequently performed using minimally invasive techniques, becoming the preferred method of approach to reduce postoperative complications and help patients to recover from surgery quickly. Scientists are trying to establish which extended surgery techniques patients are more likely to benefit from. The Society of Thoracic Surgeons (STS) recently published practice guidelines on 'the role of multimodality treatment for cancer of the esophagus and gastroesophageal junction'.[21] It is important that surgeons and physicians fully understand that evidence-based guidelines are recommendations, not absolutes, and are intended to assist healthcare providers in clinical decision-making by reviewing a range of acceptable approaches for the management of specific conditions. The most important messages included in the guidelines are that patients without metastatic disease, in whom surgical resection can be safely performed, should receive oesophageal resection.[21]

Recent publications in thoracic surgery, including important scientific messages, are not yet widespread. This is becoming problematic as personal surgical experience operating on patients with extended malignant disease is starting to count less than before, and this is because patients are asking for evidence of survival, and not just an opinion based on difficult past experiences. On this subject, Treasure et al[22] recently wrote that the 'E' in EBM (evidence-based medicine) stands for evidence, not for eminence, experience, expertise, eloquence, or any words that have been used to give authority to one or a group of surgeons.

In the last few years it has become evident, for example, that indications for the surgery of mesothelioma and pulmonary metastasectomy are very weak, and based on case series instead of prospective randomised trials.[23-25] Moreover, few meta-analyses have been published.[26] Rigorous scientists agree that to answer heavily disputed topics such as surgery for mesothelioma or lung metastases, only prospective randomised trials will help.[27] Regarding mesothelioma, only two prospective randomised papers have been published.[28,29] The first demonstrated that extended surgery for mesothelioma does not prolong survival and is possibly harmful to patients,[28] while the second showed that pleurectomy/decortication and talc pleurodesis have similar long-term results. In a few words, it seems that for mesothelioma in particular, the less the patient is put through, the better.[29] Although morally, surgeons give 'hope' but not 'false hope' to patients with mesothelioma,[30] some studies have been initiated with the intention to report results of pleurectomy/decortication with hyperthermic intraoperative intrathoracic chemotherapy (HITHOC) versus talc pleurodesis alone.[31,32] The rationale to use HITHOC is justified by the fact that under *ex vivo* hyperthermic conditions, cisplatin diffuses into human lung tissue with a median penetration depth of approximately 3–4 mm.[33]

Around lung metastases, only one prospective randomised trial exists: the PulMiCC trial.[34] Launched in 2010, this trial investigated lung metastases of colorectal cancer, with the main goal of giving a definitive answer to whether or not surgical resection of pulmonary metastases from colorectal cancer lengthens survival. Although the trial was initiated in the UK, it is now open internationally and is recruiting patients in both Europe and China.[35,36] Recently, a staging system for lung metastases has been proposed to the scientific community.[36] It is difficult to obtain data on the long-term survival rates of 'rare' and complex surgeries, and therefore the need to include these patients in a worldwide collaborative, prospective multicentre trial has become mandatory, otherwise their best treatment options remain uncertain. An ethical approach in thoracic oncologic extended operations (but not only) when long-term survival is uncertain should probably stay between patient and surgeon needs, always keeping in mind the oath to do no harm.[37] In the future, efforts must be made to demonstrate evidence that the surgical practice used for every oncological disease remains effective at prolonging survival and improving quality of life. For example, the progression of metastasis is still not well known, but it seems that it is mainly caused by a small fraction of tumour cells with the capability to navigate away from primary tumour cells to result in end-organ metastasis.[38] For this reason it is possible that in the future, the so called liquid biopsy could be used to detect the presence of circulating tumour DNA in the blood of patients with lung metastasis burden.[38]

MOBILE TECHNOLOGY AND THORACIC SURGERY

The use of mobile technology, such as smart phones or tablets, is also influencing daily practice of thoracic surgery; the surgeon is able to see images from home or wherever he/she is, and consequently, medical opinions can be delivered to the junior doctor without the need to reach the hospital, as was required 20 years ago.[39-42] There are several advantages of this method, such as the possibility to simultaneously inform all members of the team regarding the clinical situation and decisions taken about every single patient in the unit; and the ability to connect with remote colleagues who work where there is not, for example, a thoracic unit. The most important possible limitation of this form of communication is the possibility to change the relationship between the doctor and patients, and between doctors themselves, and that it may challenge patient privacy; consequently, medico-legal issues could arise.[42] Nevertheless, the use of this technology needs a well-documented study to demonstrate its effectiveness.

LUNG TRANSPLANTATION

Following the first transplant performed in 1963,[43] the lung probably remains a difficult organ to transplant because of its fragility, which easily facilitates injuries and infections. Several questions remain unresolved, and between them, the shortage of lung donors is a chronic problem worldwide. In 2015, the International Society for Heart and Lung Transplantation (ISHLT) published guidelines to help physicians and surgeons in their decision making, writing that: "in the absence of high-grade evidence to support decision making, these consensus guidelines remain part of a continuum of expert opinion based on available studies and personal experience. Some positions are immutable. Although transplant is rightly a treatment of last resort for end-stage lung disease, early referral allows proper evaluation and thorough patient education. Subsequent waiting list activation implies a tacit agreement that transplant offers a significant individual survival advantage. It is both the challenge and the responsibility of the transplant community globally to ensure organ allocation maximises the potential benefits of a scarce resource, thereby achieving that advantage."[44] Recently, sophisticated devices have been introduced to recondition sub-lobar donor lungs to make the organs suitable for transplant. Machines have been designed to enhance lung function by ventilating and perfusing the organ for up to 6 hours after the lungs' retrieval from a donor.[45] This permits an extended assessment and provides time for the lungs to recover from the inflammatory shock following brain death. Another emerging innovation in lung transplantation includes the possibility to perform minimally invasive techniques to insert the lung into the chest of the recipient. A recent study from Harefield Hospital, UK, evaluated 194 bilateral sequential lung transplant patients between April 2010 and November 2013, compared with 124 patients who underwent clamshell incision and 70 patients who underwent bilateral anterior thoracotomies.[46] Results showed that minimally invasive techniques have early postoperative and mid-term clinical benefits compared with the traditional approach of clamshell operations.[46] These observations warrant larger definitive studies to further evaluate the impact of minimally invasive lung transplantation on physiological, clinical, and patient-reported outcomes.[46] Only a few months ago, some authors reported experience on the impact of cell death signals at 24 hours and 48 hours following lung transplantation on short and long-term clinical outcomes of 60 bilateral lung transplant recipients. They demonstrated that recipient plasma concentration of epithelial cell death markers after lung transplantation negatively correlated with early graft performance and long-term survival.[47]

THE FUTURE

From what it is possible to determine from recently published papers, it appears bizarre that although the use of uniportal VATS was born in Europe, nowadays it is less used in Europe and the USA compared with China, where two major hospitals including the Shanghai Pulmonary Hospital perform over 8,000 anatomic and sub-anatomic lung resections per year. Although there is not a clear explanation for this behaviour, the common feeling is that uniportal VATS will be more frequently used worldwide in the near future.[48] The use of smaller incisions to treat cancer should never place patients at risk, and therefore the use of uniportal VATS will require approval by scientific societies following evidence of improvement, or at least maintenance, of similar outcomes for both benign and malignant diseases. Moreover, the next generation of thoracic surgeons should receive formal training for all the available VATS techniques (single incision, multiple

port, and robotic-assisted), and after training, the surgeon should be able to decide to operate according to the approach that suits him/her best.[49] To note, if in the next decade the indications and the number of operations for lung cancer remain the same, fewer surgeons will be needed because uniportal VATS and robotic surgery are performed by a single surgeon.[50]

No less important is the future of lung transplantation, which appears bright with progress on multiple fronts.[51] Indications for surgery in malignant diseases with uncertain postoperative long-term survival will have an answer after prospective randomised trials are completed. To avoid the possibility of unnecessary operations,[52] more efforts need to be executed to demonstrate why some patients with a 'resectable' malignant disease in the chest will not survive as long as expected, and therefore the completion of further research is essential to demonstrate that surgical innovations given by technology are true advantages for both patients and surgeons.[53] Worldwide co-operation will permit the collection of data promptly and finishing randomised controlled studies will ultimately benefit humanity.

REFERENCES

1. Migliore M et al. Video assisted thoracic surgery through a single port. Proceedings of Thoracic Surgery and Interdisciplinary Symposium on the Threshold of the Third Millenium. 11-13 May 2000, Naples, Italy.

2. Migliore M et al. A single-trocar technique for minimally invasive surgery of the chest. Surg Endosc. 2001;15(8): 899-901.

3. Migliore M et al. Four-step local anesthesia and sedation for thoracoscopic diagnosis and management of pleural diseases. Chest. 2002;121(6):2032-5.

4. Migliore M. Efficacy and safety of single-trocar technique for minimally invasive surgery of the chest in the treatment of noncomplex pleural disease. J Thorac Cardiovasc Surg. 2003;126(5):1618-23.

5. Migliore M. Initial History of Uniportal Video-Assisted Thoracoscopic Surgery. Ann Thorac Surg. 2016;101(1):412-3.

6. Migliore M et al. Uniportal video assisted thoracic surgery: summary of experience, mini-review and perspectives. J Thorac Dis. 2015;7(9):E378-80.

7. Gonzalez D et al. Single-port video-assisted thoracoscopic lobectomy. Interact Cardiovasc Thorac Surg. 2011; 12(3):514-5.

8. Rocco G et al. Uniportal VATS wedge pulmonary resections. Ann Thorac Surg. 2004;77(2):726-8.

9. Ocakcioglu I et al. A 3-cm Single-port Video-assisted Thoracoscopic Lobectomy for Lung Cancer. Surg Laparosc Endosc Percutan Tech. 2015;25(4):351-3.

10. Kamiyoshihara M et al. A 3.5-cm Single-Incision VATS Anatomical Segmentectomy for Lung Cancer. Ann Thorac Cardiovasc Surg. 2015;21(2): 178-82.

11. Zhu Y et al. Single-port video-assisted thoracoscopic surgery lung resection: experiences in Fujian Medical University Union Hospital. J Thorac Dis. 2015;7(7):1241-51.

12. Gonzalez-Rivas D et al. Uniportal video-assisted thoracoscopic sleeve lobectomy and other complex resections. J Thorac Dis. 2014;6(Suppl 6):S674-81.

13. Veronesi G. Robotic lobectomy and segmentectomy for lung cancer: results and operating technique. J Thorac Dis. 2015;7(Suppl 2):S122-30.

14. Yamashita S et al. Robotic Surgery for Thoracic Disease. Ann Thorac Cardiovasc Surg. 2016;22(1):1-5.

15. Louie BE et al. Comparison of Video-Assisted Thoracoscopic Surgery and Robotic Approaches for Clinical Stage I and Stage II Non-Small Cell Lung Cancer Using The Society of Thoracic Surgeons Database. Ann Thorac Surg. 2016;102(3):917-24.

16. Migliore M. Robotic surgery for lung resection in search of evidence. J Thorac Dis 2016. [In press].

17. Gonzalez-Rivas D et al. Non-intubated (tubeless) uniportal video-assisted thoracoscopic lobectomy. Ann Cardiothorac Surg. 2016;5(2):151-3.

18. Zhong JS. Professor Takashi Suda: we should not compromise the safety and precision of a thoracic surgery. Ann Transl Med. 2015;3(10):144.

19. Nakanishi R et al. Awake thoracoscopic surgery under epidural anesthesia: is it really safe? Chin J Cancer Res. 2014;26(4):368-70.

20. Loop T. Fast track in thoracic surgery and anaesthesia: update of concepts. Curr Opin Anaesthesiol. 2016;29(1):20-5.

21. Little AG et al. The Society of Thoracic Surgeons practice guidelines on the role of multimodality treatment for cancer of the esophagus and gastroesophageal junction. Ann Thorac Surg. 2014;98(5):1880-5.

22. Treasure T et al. If no difference in effectiveness is found between two treatments it may be because the treatments are similarly ineffective. Ann Transl Med. 2015;3(14):201.

23. Lee YC. Surgical resection for mesothelioma: an evidence-free practice. Lancet. 2014;384(9948):1080-1.

24. Treasure T. Extrapleural pneumonectomy for malignant pleural mesothelioma: is this an operation that should now be consigned to history? Future Oncol. 2015;11(24 Suppl):7-10.

25. Mineo TC, Ambrogi V. Lung metastasectomy: an experience-based therapeutic option. Ann Tansl Med. 2015;3(14):194.

26. Migliore M et al. Wider implications of video-assisted thoracic surgery versus open approach for lung metastasectomy. Future Oncol. 2015;11(Suppl 2):25-9.

27. Datta A et al. Surgery in the treatment of malignant pleural mesothelioma: recruitment into trials should be the default position. Thorax. 2014;69(2):194-7.

28. Treasure T et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol. 2011; 12(8):763-72.

29. Rintoul RC et al. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. Lancet. 2014;384(9948):1118–27.

30. Maat AP et al. Is the patient with mesothelioma without hope? Future Oncol. 2015;11(Suppl 24):11-4.

31. Migliore M et al. Pleurectomy/ decortication and hyperthermic intrapleural chemotherapy for malignant pleural mesothelioma: initial experience. Future Oncol. 2015;11(24 Suppl):19-22.

32. Sugarbaker DJ et al. Hyperthermic intraoperative pleural cisplatin chemotherapy extends interval to recurrence and survival among low-risk patients with malignant pleural mesothelioma undergoing surgical macroscopic complete resection. J Thorac Cardiovasc Surg. 2013;145(4): 955-63.

33. Ried M et al. Assessment of cisplatin concentration and depth of penetration in human lung tissue after hyperthermic exposure. Eur J Cardiothorac Surg. 2015; 47(3):563-6.

34. Treasure T et al. Pulmonary metastasectomy in colorectal cancer: the PulMiCC trial. J Thorac Oncol. 2010; (6):S203-6.

35. Migliore M et al. Finding the evidence for pulmonary metastasectomy in colorectal cancer: the PulMicc trial. Future Oncol. 2015;11(2 Suppl):15-8.

36. Migliore M, Gonzalez M. Looking forward lung metastasectomy -do we need a staging system for lung metastases? Ann Transl Med. 2016;4(6):124.

37. Wancata LM, Hinshaw DB. Rethinking autonomy: decision making between patient and surgeon in advanced illnesses. Ann Transl Med. 2016;4(4):77.

38. Lancet Oncology. Liquid cancer biopsy: the future of cancer detection? Lancet Oncol. 2016;17(2):123.

39. Migliore M. How surgical care is changing in the technological era. Future Sci OA. 2016;2(2): doi: 10.4155/fsoa-2016-0010.

40. Prgomet M et al. The impact of mobile handheld technology on hospital physicians' work practices and patient care: a systematic review. J Am Med Inform Assoc. 2009;16(6):792-801.

41. Migliore M. Smartphones or tablets for a better communication and education between residents and consultant in a teaching hospital. J Surg Educ. 2013; 70(4):437-8.

42. Migliore M. The use of smartphones or tablets in surgery. What are the limits? Ann Ital Chir. 2015;86(2):185-6.

43. Hardy JD et al. LUNG HOMOTRANSPLANTATION IN MAN. JAMA. 1963;186:1065-74.

44. Weill D et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015;34(1):1-15.

45. Sauerwein K. Surgeons test technology with potential to expand lung transplant donor pool, 2016. Available at: https://medicine.wustl.edu/news/surgeons-test-technology-potential-expand-lung-transplant-donor-pool/. Last accessed: 27 September 2016.

46. Marczin N et al. Outcomes of minimally invasive lung transplantation in a single centre: the routine approach for the future or do we still need clamshell incision? Interact Cardiovasc Thorac Surg. 2016;22(5):537-45.

47. Hashimoto K et al. Circulating Cell Death Biomarkers May Predict Survival in Human Lung Transplantation. Am J Respir Crit Care Med. 2016;194(1):97-105.

48. Gonzalez-Rivas D. Uniportal thoracoscopic surgery: from medical thoracoscopy to non-intubated uniportal video-assisted major pulmonary resections. Ann Cardiothorac Surgery. 2016;5(2):85-91.

49. Migliore M. Will the widespread use of uniportal surgery influence the need of surgeons? Postgrad Med J. 2016;92(1086):240.

50. Migliore M. VATS surgery for Anatomical lung resection: a different approach for every surgeon. VATS 2016. DOI: 10.21037/vats.2016.10.01.

51. Nathan SD. The future of lung transplantation. Chest. 2015;147(2): 309-16.

52. Migliore M et al. Extending surgery for pulmonary metastasectomy: what are the limits? J Thorac Oncol. 2010;5(6 Suppl 2): S155-60.

53. Treasure T. What is the best approach for surgery of malignant pleural mesothelioma? It is to put our efforts into obtaining trustworthy evidence for practice. J Thorac Cardiovasc Surg. 2016;151(2):307-9.

LÖWENSTEIN medical

BreathCaring Simplicity.
prisma VENT.

brilliant display

easy handling

360° easy turn

allover compatibility

low noise

prismaVENT.com

Completely intuitive use.

THERAPEUTIC EFFECT OF WHOLE LUNG LAVAGE ON PNEUMOCONIOSIS

Hongmei Zhang,[1] *Pei Liu,[2] Hongmei Zheng,[3] Deng Chunyan,[2] *Yanjun Zeng[4]

1. Department of Respiratory medicine, Taihe Hospital , Hubei University of Medicine, Hubei, China, Hongmei Zhang email: houyu791614@sina.com
2.Department of Intensive Care Unit, Taihe Hospital ,Hubei University of Medicine, Hubei, China, Pei Liu email: lpwelcom0545@sina.com,
Deng Chunyan email: 15272297386@139.com
3. Department of Skill Training Center, Taihe Hospital , Hubei University of Medicine, Hubei, China, Hongmei Zheng email: zhm197702@163.com
4. Biomechanics and Medical Information Institute, Beijing University of Technology, Beijing, China, Yanjun Zeng email: yjzeng@bjut.edu
**Correspondence to lpwelcom0545@sina.com, yjzeng@bjut.edu.cn*
Yanjun Zeng conceived the initial idea and the study design. Pei Liu designed the study and contributed to data analysis. Chunyan Deng collected data. Hongmei Zhang collected data and drafted the manuscript.

Disclosure: The authors have declared no conflicts of interest.
Ethics Statement: Written consent was obtained from the family members of all patients and the study was approved by the Medical Ethics Committee of the Affiliated Taihe Hospital at Hubei University of Medicine.
Received: 18.02.16 **Accepted:** 19.09.16
Citation: EMJ Respir. 2016;4[1]:98-103.

ABSTRACT

Pneumoconiosis as an occupational disease is a serious threat to the health of workers. Patients with pneumoconiosis are mainly engaged in dust-related work such as gold, coal, or iron mining, electric welding, or road work, and present with miliary nodules, fuse mass-like opacities, and cavity lesions on chest imaging. Clinical manifestations of pneumoconiosis include progressive chest tightness, dyspnoea, chest pain, coughing, expectoration, fever, and hypodynamia. Pneumoconiosis patients are prone to respiratory tract infections (including bacterial pneumonia and tuberculosis) because of poor disease resistance and will eventually lose the ability to work and fully function in daily life completely. Patients can lose their life because of complications such as pulmonary heart disease and respiratory failure. Disease prevention is the main method to control pneumoconiosis.

We retrospectively analysed 516 cases of pneumoconiosis patients receiving whole lung lavage (WLL) procedure from May 2009–January 2015. The symptoms, pulmonary function, chest computed tomography manifestations, and living status were reviewed carefully. The improvement rate of chest tightness, chest pain, and dyspnoea was 99%, 90%, and 98%, respectively, 7 days after WLL procedure. The symptoms had improved in 235 patients at 3–6 months postoperatively. The therapeutic effect remained stable in 56 cases after 4–5 years. Chest tightness, chest pain, and dyspnoea were improved significantly, and pulmonary diffusion function and small airway resistance also improved. There was no progress in 62 patients 4–5 years postoperatively, as indicated by the chest computed tomography examination. Overall, WLL treatment is an effective method for treating pneumoconiosis.

Keywords: Whole lung lavage (WLL), pneumoconiosis, therapeutic effect.

INTRODUCTION

Pneumoconiosis as an occupational disease is a serious threat to the health of workers.[1] Clinical manifestations of pneumoconiosis include progressive chest tightness, dyspnoea, chest pain, cough, and expectoration.[2] Pneumoconiosis patients are prone to respiratory tract infection because of

poor disease resistance and can ultimately lose the ability to work and engage in daily life. Patients may lose their lives because of such complications as pulmonary heart disease and respiratory failure. Disease prevention is the main method by which pneumoconiosis is controlled.[3] Once symptomatic pneumoconiosis develops, only a few therapies are available,[4] including drug treatment (such as tetrandrine), whole lung lavage (WLL), and avoiding work in a dusty environment. Therapies can also treat the various complications associated with pneumoconiosis, for example infection control, oxygen therapy, and ventilator support.

In this study, we reported on 582 patients with pneumoconiosis who were treated at our hospital from May 2009–January 2015. Of these, 38 patients had severe restrictive pulmonary dysfunction, 16 patients complicated with pneumothorax, 10 patients complicated with tuberculosis infection, and 2 patients complicated with bacterial pneumonia. After the exclusion of 66 patients who could not undergo WLL, a total of 516 cases of pneumoconiosis were treated with WLL in our hospital from May 2009–January 2015.

METHODS

General Information

Study patients were selected from the inpatients of our hospital; all were male (22–68 years) with an average age of 54.6±5.8 years. Of these cases of pneumoconiosis, 322 were coal worker's pneumoconiosis, 150 were gold mining-induced pneumoconiosis, 3 were cement-induced pneumoconiosis, 8 were foundry worker's pneumoconiosis, 2 were electric welder's pneumoconiosis, 27 were turquoise-induced pneumoconiosis, and 4 were mixed pneumoconiosis.

Diagnosis and Staging of Pneumoconiosis

The diagnosis of pneumoconiosis was made by the Occupational Disease Diagnosis Agency of the local Disease Control Center. In our study, 482 patients were suffering with Stage I pneumoconiosis, 24 with Stage II pneumoconiosis, and 10 with Stage III pneumoconiosis. Chest X-ray was the main test to diagnose pneumoconiosis and its stages.

Stage I pneumoconiosis

a) I: Small round opacities at profusion Level 1 which are distributed in at least one zone of each lung and the size is ≥2 cm in diameter, or small irregular opacities with profusion Level 1 and the distribution reaches at least two lung zones
b) I^{+}: Small opacities are significantly increased but the intensity or distribution of opacities are not sufficient to classify as Stage II pneumoconiosis

Stage II pneumoconiosis

a) II: Small round or irregular opacities at profusion Level 2 and the distribution range exceeds four lung zones, or small irregular opacities at profusion Level 3 and the distribution range reaches four lung zones
b) II^{+}: Small irregular opacities at profusion Level 3 and the distribution range exceeds four lung zones, or large opacities that are not enough to be diagnosed as Stage III pneumoconiosis

Stage III pneumoconiosis

a) III: Large opacities appear which are ≥2 cm long and 1 cm wide
b) III^{+}: One large opacity area, or the sum of several large opacities, exceed the area of the right upper lung zone

There were 135 cases complicated by chronic bronchitis, 68 cases by pulmonary emphysema, and 32 cases by hypertension. All included patients had smoked.

Indications for Whole Lung Lavage

WLL was considered for patients with coal worker's pneumoconiosis, silicosis, and other pneumoconiosis caused by various inorganic dusts. For patients with complications before the procedure, WLL was not performed until the complications were under control and conditions became stable. Pulmonary function test results were used as an indicator for WLL, with lung function indices determined for 155 patients before and after lavage. Results indicative of WLL being an appropriate procedure were:

- Vital capacity (VC) and maximal voluntary ventilation (MVV) reaching 70% of predicted values
- Peak expiratory flow, forced expiratory flow at 25–75% of forced VC (FEF_{25-75}), forced expiratory volume in 1 second (FEV_1), and diffusing capacity of the lung for carbon monoxide (DL_{CO}) reaching 70% of predicted values
- Partial pressure of oxygen in arterial blood exceeding 9.3 kPa (70 mmHg)

- Heart, liver, kidney function, and relevant test indices all normal

For patients >55 years old:

- VC and MVV reaching 70% of predicted values
- FEF_{25-75}, FEV_1, and DL_{CO} reaching 80% of predicted values
- The partial pressure of oxygen in arterial blood exceeding 10.0 kPa (75 mmHg)

WHOLE LUNG LAVAGE THERAPY

Treatment Before Anaesthesia

It is necessary to visit patients before anaesthesia to fully determine their state of illness. Full consideration should be given to anaesthesia-related risks and the anaesthesia should be meticulously prepared. The left-sided double-lumen endotracheal tubes, which can pass through the glottis and have a large enough diameter, were selected for intubation. This will help reliable management during WLL. The depth of the double-lumen endotracheal tube was determined by referring to a 170 cm adult male, for whom the front end of the double-lumen endotracheal tube is 29 cm off the incisor. The depth should increase by 1 cm for every 10 cm increase in height. Ensuring the accurate insertion of the endotracheal tube is a critical step in anaesthetising patients for WLL. Bilateral lungs must be effectively isolated and the isolation effect should be examined repeatedly by listening to respiratory sounds. WLL can be conducted when the location of the endotracheal tube and the isolation of bilateral lungs are satisfactory. It is recommended that the left lung with a smaller capacity or the lung with poor compliance should be lavaged first. Ventilation pressure is generally 4–5 kPa and it should be controlled <4 kPa for patients with pulmonary bullae. During the negative pressure suction, the silicone tube should be marked to indicate the length of the suction tube. For patients with pulmonary bullae, the negative pressure suction should be <4 kPa. Clinically, a mode of alternating positive pressure ventilation and negative pressure suction, which is synchronous with the ventilated lung, has been developed for the lavaged lung.

Table 1: Symptom improvement of pneumoconiosis patients at 7 days, 3–6 months, and 4–5 years after whole lung lavage.

	7 days postoperatively (n=516)		3–6 months postoperatively (n=235)		4–5 years postoperatively (n=56)	
Symptom	Improvement (n)	Improvement rate (%)	Improvement (n)	Improvement rate (%)	Improvement (n)	Improvement rate (%)
Chest tightness	511	99.1	219	93.2	51	90.5
Dyspnoea	507	98.3	215	91.4	50	89.2
Chest pain	465	90.4	208	88.5	48	86.3
Physical strength changes	464	89.9	190	80.7	39.0	70.5

Table 2: Lung function changes of 56 pneumoconiosis patients at 4–5 years after whole lung lavage (measured value/expected value, %).

	FVC	FEV_1	MVV	FEF_{25}	FEF_{50}	DL_{CO}
Pre-treatment	90.6±7.2	87.3±5.2	89.4±6.2	53.7±4.9	59.4±5.3	80.7±6.3
Post-treatment	80.3±6.7†	79.3±7.1†	73.8±5.9†	59.4±4.8†	69.0±6.9†	88.6±5.2†

†indicates $p<0.05$ compared with the pre-treatment condition.
FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; MVV: maximal voluntary ventilation; FEF_{25}: forced expiratory flow at 25% of forced vital capacity; FEF_{50}: forced expiratory flow at 50% of forced vital capacity; DL_{CO}: single breath diffusing capacity of the lungs for carbon monoxide.

This study adopted a high-frequency jet ventilation mode. The ventilation mode with low tidal volume not only achieves a certain ventilation, but also maintains low intratracheal and intrathoracic pressure. Additionally, this mode can prevent pulmonary overexpansion and improve the oxygenation of patients, and has less influence on circulation.

Method of Anaesthesia

All participants received combined intravenous–inhalational general anaesthesia under rapid induction and double-lumen endotracheal intubation. Each patient was intramuscularly injected with 10.0 mg of diazepam and 0.5 mg of atropine 30 minutes before the procedure. The following anaesthetics were then administered successively: 3–5 mg of midazolam, 10 mg of dexamethasone, 1.5–2 mg/kg of propofol, 25 mg of atracurium besilate, and 0.1–0.2 mg of fentanyl. After 3 minutes of oxygen supply by mask, the left-sided double-lumen endotracheal tube was inserted. The tube location and the isolation of both lungs were examined by respiratory sound auscultation, silicone tube detection, fibrobronchoscopy, and airway pressure observation. If the examination result was satisfactory, propofol was continuously pumped at the dosage of 4–12 mg/kg/hour to maintain anaesthesia. Meanwhile, atracurium besilate and fentanyl were administered intermittently and isoflurane inhalation was also provided. The depth of anaesthesia was adjusted according to surgical requirements and the patient's vital signs. One-lung ventilation parameters are as follows: pure oxygen inhalation, tidal volume 8–12 mL/kg, 12–14 times/min, end-tidal carbon dioxide 35–45 mmHg, airway pressure <40 cm H_2O. One side of the double-lumen endotracheal tube was connected with the anaesthesia machine for one-lung ventilation. The other side was connected with the WLL device. After vital signs became stable WLL was conducted, during which a multifunction electrocardiogram monitor was used.

Method of Whole Lung Lavage

The patient lay supine on the operating table to receive the intravenous anaesthesia combined with the double-lumen endobronchial intubation (Robertshaw tube). After it was confirmed that two lungs were effectively isolated, WLL began. Generally, the lung with more serious lesions would be lavaged first, with 37˚C normal saline. At first, the normal saline of the volume equivalent to single-lung functional residual capacity (around 1,000 mL for adults) was injected. If the patient kept calm, with no obvious variations of electrocardiogram and oxygen saturation, repeated lavages were allowed to begin. In the following lavages, ~500–1,000 mL of normal saline was injected each time, and then the bronchoalveolar lavage fluid of the same volume was sucked out at a negative pressure of 4–5 kPa. At the end of the third, sixth, and ninth drainage, pressurised ventilation was performed with the maximum pressure kept below 4 kPa. WLL was performed repeatedly until the recovered bronchoalveolar lavage fluid became clear. However, WLL would not exceed 12 times for a single lung in general. Oxygen supply continued for another 12 hours after operation. The patients should be kept warm to avoid hypothermia. Routine antibiotics and potassium supplementation were given for 1 day. Hypokalaemia may occur in some patients after the WLL procedure, which can cause serious complications, so prevention of hypokalaemia requires particular attention after WLL. Supplementation of potassium after catheterisation during the operation and 1–2 g potassium supplementation after operation can prevent the occurrence of hypokalaemia.

Observation of Therapeutic Effect

The clinical symptoms of all patients were analysed after 7 days of treatment. The clinical characteristics were analysed of 235 patients were analysed for 3-6 months postoperatively and 56 patients 4–5 years postoperatively, including clinical symptoms, physical strength, physical changes, pulmonary function, and chest computed tomography (CT) manifestations. The changes in chest CT manifestations of 62 patients receiving WLL treatment were analysed for 4–5 years postoperatively.

Statistical Methods

Lung function data are shown as x±SD and treated by t-test. The difference in incidence rate was evaluated using the chi-square test, where $p<0.05$ was considered statistically significant.

RESULTS

Improvement in Symptoms

Dyspnoea was eased immediately after single lung lavage. Chest tightness was found in 496 patients, chest pain in 482 patients, and

dyspnoea in 502 patients. The improvement rate of these symptoms 7 days after WLL was 99%, 90%, and 98%, respectively. Symptoms improved in 235 patients 3–6 months postoperatively and the therapeutic effect remained stable in 56 patients 4–5 years postoperatively (Table 1). The pulmonary function and chest CT findings had no significant changes on 235 cases 3–6 months postoperatively. The pulmonary function examination showed improvements in both small airway resistance and dispersion function, and the decline in ventilatory function on 56 patients 4–5 years postoperatively (Table 2). As indicated by the chest CT examination, pneumoconiosis presented with interlobular septal thickening, nodules, round or irregular large mass-like opacities, and pulmonary emphysema. There was no obvious progress in 62 patients 4–5 years postoperatively compared with their preoperative conditions. A comparison of chest CT manifestations showed that 56 patients (90.3%) remained unchanged and 6 patients (9.7%) showed progress.

Complications

In recent years, complications in WLL procedures have decreased gradually following the development of WLL technology and the introduction of a standardised operation procedure. The complication rate was as high as 47% in 134 patients receiving WLL before 2012, including 28 cases of hypoxaemia, 10 cases of bronchospasm, 8 cases of postoperative fever, 10 cases of hypokalaemia, 5 cases of atelectasis, and 1 mortality. The complication rate was 2.8% in 382 patients receiving WLL from 2012–2015, including 7 patients with hypoxaemia, 2 patients with postoperative fever, and 2 patients with atelectasis. The complication incidence has shown an obvious decrease.

DISCUSSION

Pneumoconiosis is the most common occupational disease in China that has definite aetiology. WLL was first successfully applied to a patient with mixed pneumoconiosis in 1982 by Mason et al.[5] WLL was applied to a basic experimental and clinical research in 1986 in China.[6] The WLL procedure can physically remove residual dust in alveoli and phagocytose alveolar macrophages to improve clinical symptoms and lung function.[7] Research shows that the occurrence of silicosis and dust concentration had an obvious dose-response relationship and the severity of silicosis and the amount of dust deposition had a dose-effect relationship.[8] So the occurrence of pulmonary fibrosis can be reduced by a WLL procedure removing dust from the lungs. As an effective supplement to aetiological treatment WLL can remove the dust deposits, dust cells in the lungs, and a variety of fibrosis-related active substances.[9] WLL can eliminate silicon dioxide and macrophages not only in the alveoli but also within the pulmonary interstitial tissue, so as to improve the patient's clinical symptoms and delay the development of pneumoconiosis, as demonstrated in a study by Morgan et al.[10]

In our study, the symptoms of chest tightness, chest pain, and dyspnoea were significantly alleviated after the WLL, and chest CT manifestations and pulmonary function had no obvious change after 3–6 months. The improvements were still maintained 4–5 years after the WLL. There was no further development of disease shown in the chest CT examination. The pulmonary function examination showed that both small airway resistance and diffusion function improved, and pulmonary ventilation declined. WLL can improve pulmonary diffusing capacity because it can wash out a lot of dust and reduce diffusion distance. The reason for pulmonary ventilation decline may be relative to natural lung hypofunction and ageing. Our study showed that WLL does improve symptoms and delays the deterioration of patients with pneumoconiosis.

The safety of WLL has always been a concern. The key to ensuring safety is good control of anaesthesia and the effective separation between ventilated lung and lavaged lung. Leaking of the ventilated lung is the main cause of hypoxaemia. In recent years, we have used an ultrafine bronchoscope which was inserted by double-lumen catheter to ensure the catheter gasbag was in place. This improvement reduced gasbag leaks after displacement and the occurrence of hypoxaemia.

Complications of WLL were significantly reduced from 2012–2015 in our hospital, which was due to continuous technological improvement in the practice, careful consideration of the indications and contraindications, complete preparation of the preoperative examination, and standardisation of the operation procedure. At the time we used furosemide, anisodamine, dexamethasone, aminophylline, and other drugs to promote residual liquid discharge and absorption according to the intraoperative situation. The indication of second

lung lavage was strictly selected. The anaesthesia duration was extended and the indication of stopping anaesthesia and extubation was selected carefully. At the same time, we strengthened the intraoperative and postoperative nursing care, expectorant treatment, and the respiratory function exercise.

CONCLUSION

WLL, as a safe and effective treatment for pneumoconiosis, can remove the dust and alveolar macrophages in the respiratory tract and alveolar cavity, improve symptoms, and delay disease development. Strict conformation to the operation procedures, as well as strengthening of the anaesthetic, intraoperative, and postoperative care is necessary in its application. As to further research, a multicentre, large sample investigation is needed to accurately evaluate the effects of WLL because of the small sample size and short observation duration at present. Pneumoconiosis therapy should also include the avoidance of dusty work environments, tetrandrine administration (which can be administered orally), and the treatment of various complications such as active infection control, oxygen therapy, and ventilator support.

Acknowledgements

The authors would like to thank all participating patients and the staff from their respiratory department.

REFERENCES

1. Cáceres-Mejía B et al. [Development of pneumoconiosis and outsourcing work in peruvian miners]. Rev Peru Med Exp Salud Publica. 2015;32(4):673-9.
2. Cullinan P, Reid P. Pneumoconiosis[J]. Prim Care Respir J. 2013;22(2):249-52.
3. Cohen RA et al. Lung Pathology in U.S. Coal Workers with Rapidly Progressive Pneumoconiosis Implicates Silica and Silicates. Am J Respir Crit Care Med. 2016; 193(6):673-80.
4. Méndez-Vargas MM et al. [Acute silicosis. An infrequent pneumoconiosis]. Rev Med Inst Mex Seguro Soc. 2015;53(4):524-7.
5. Mason GR et al. Treatment of mixed-dust pneumoconiosis with whole lung lavage. Am Rev Respir Dis. 1982;126(6):1102-7.
6. Guangxin T. Whole lung Lavage as an Effective Treatment of Silicosis and other Pneumoconioses. Chinese Journal of Industrial Hygiene and Occupational Diseases. 1990;8(4):220-2.
7. Begin R et al. Carborundum pneumoconiosis. Fibers in the mineral activate macrophages to produce fibroblast growth factors and sustain the chronic inflammatory disease. Chest. 1989;95(4):842-9.
8. Chen Z et al. Standard treatment of pneumoconiosis with whole lung lavage. National Medical Journal of China. 2005; 85(40):2856-8.
9. Mossman BT, Churg A. Mechanisms in the pathogenesis of asbestosis and silicosis. Am J Respir Crit Care Med. 1998; 157(5 Pt 1):1666-80.
10. Morgan WK et al. The "middling" tendency: a possible source of bias in the interpretation of chest films for pneumoconiosis. Arch Environ Health. 1974;29(6):334-7.

NON-INTUBATED VIDEO-ASSISTED THORACIC SURGERY FROM MULTI TO UNIPORT APPROACHES: SINGLE-CENTRE EXPERIENCE

***Tommaso Claudio Mineo,[1] Vincenzo Ambrogi,[1,2] Francesco Sellitri[1]**

1. Official Awake Thoracic Surgery Research Group, Policlinico Tor Vergata, Department of Thoracic Surgery, University of Rome Tor Vergata, Rome, Italy
2. Chief of the Minimally Invasive Thoracic Surgery Unit, Policlinico Tor Vergata, Rome, Italy
**Correspondence to mineo@uniroma2.it*

Disclosure: The authors have declared no conflicts of interest.
Received: 24.06.16 **Accepted:** 07.09.16
Citation: EMJ Respir. 2016;4[1]:104-112.

ABSTRACT

The success and evolution of video-assisted thoracic surgery (VATS) renewed the interest for thoracoscopic operations in awake patients. Non-intubated, or tubeless, procedures found progressive credit and uptake. In particular, non-intubated uniportal VATS represents the latest stage in its evolution. An increasing number of more complicated procedures have been successfully carried out with this combined modality.

In the early 2000s, the Awake Thoracic Surgery Research Group at the University of Rome Tor Vergata started an investigational programme of thoracic operations performed without general anaesthesia and one-lung ventilation. Since that date >1,000 operations have been successfully carried out. Initially, non-intubated anaesthesia was successfully employed in non-oncologic conditions such as pneumothorax, emphysema, pleural infection, and interstitial lung disease. Oncologic conditions such as malignant pleural effusion, peripheral lung nodules, and mediastinal tumours were successively approached. Major operations are now being performed in this way. Uniportal access was progressively adopted with significant positive outcomes in postoperative recovery, patient acceptance, and economical costs. Operations of this kind overcome many anatomical and technical challenges satisfying the patient, surgeon, physician, nurse, and economical administrator. The hindrance caused by operating with a breathing lung is that it requires a particular set of skills but experience demonstrates that the learning curve is no longer than that required for any other new endoscopic procedure.

Other investigations have involved the biological impact of the procedure, demonstrating lower concentrations of inflammatory and stress mediators with a lower degree of immune-depression. Psychological preselection of the most suitable patients for non-intubated surgery is one of our fields of investigation. Non-intubated thoracic surgery is projected towards the future and still represents a nearly unexplored and potentially fruitful field.

Keywords: Thoracic surgery, video-assisted thoracic surgery (VATS), thoracic epidural anaesthesia (TEA), intercostal block.

INTRODUCTION

The entry of video-assisted thoracic surgery (VATS) in the field of thoracic surgery represented the watershed between the classic open surgery and new methods. The initial three-port technique rapidly evolved into uniportal access.[1] A small single-port incision was used to perform VATS operations, assuring adequate mobility of the instruments and the valid surgical access.[2-5] In 2000 Migliore et al.[6,7] applied this approach in 58 patients, safely performing a variety of minor procedures. In 2004 Rocco et al.[8] published an article about the use of the uniportal VATS to perform wedge pulmonary resection and subsequently a multiplicity of other operations.[4,9] Minor and major

procedures such as carinal resection, bronchial sleeve, and vascular reconstruction[10,11] have more recently been successfully carried out both for diagnostic and curative intent.

At the same time, VATS resuscitated interest in thoracic operations in awake patients. Indeed, non-intubated thoracic surgery is not a new strategy; it was developed early in the 20th century and was employed for a long time with variable results until the advent of general anaesthesia (GA) with one-lung ventilation. However, this anaesthetic modality produced several important adverse effects. Indeed, mechanical ventilation-related lung injuries occur in 4% of major lung resections carrying a mortality rate as high as 25%.[12] Sugasawa et al.[13] found that single-lung ventilation could induce inflammatory responses during lung resections, which may be associated with postoperative complications.

Thus, non-intubated VATS techniques were progressively proposed and investigated.[14-21] The term 'awake' was used as many patients remained fully alert during the procedure.[15-18] Subsequently more technically demanding operations were faced in more sedated patients while conserving spontaneous ventilation, thus the definition of non-intubated or tubeless surgery.[22] Thoracic epidural anaesthesia (TEA), intercostal nerve block, and paravertebral block are the most commonly employed techniques for non-intubated anaesthesia.[23-29] Nowadays, a non-intubated technique has been shown to be a feasible approach for a number of procedures, even under uniportal access.[22] It is particularly suitable for patients excluded from conventional surgery by elderly age, comorbidity, and respiratory disease.[30,31]

In 2014 Rivas et al.[22] published the first non-intubated single-port VATS lobectomy in a patient with middle lobe cancer. The patient was discharged 36 hours after with excellent postoperative outcome. To date, many groups have reported good results of major pulmonary resections.[17,19,32]

EXPERIENCE OF RESEARCH GROUP AT TOR VERGATA UNIVERSITY

In the early 2000s, after a consolidate experience in multiport VATS with intubated GA, we started an investigational programme of thoracic operations performed without GA and one-lung ventilation. This programme was approved by our Institutional Review Board and encompassed the whole body of thoracic pathologies treated by surgery. Within this project, a multidisciplinary group named the Awake Thoracic Surgery Research Group was founded by one of our members, Dr Tommaso Claudio Mineo, who remains co-ordinator of the group. This group included thoracic surgeons, anaesthesiologists, pneumologists, cardiologists, physiotherapists, infectologists, psychologists, and administrators.

Initially, non-intubated anaesthesia was successfully employed in non-oncologic conditions such as pneumothorax, emphysema, pleural infection, and interstitial lung disease. Oncologic conditions such as malignant pleural effusion, peripheral lung nodules, and mediastinal tumours were approached with TEA. As the familiarity with this surgical practice has increased, we progressively shifted from a multiportal to a uniportal approach and now the majority of operations are being performed in this way (Table 1).

THE EVOLUTION OF THE ANAESTHESIOLOGICAL SUPPORT

Initially, our standard anaesthetic protocol was based on TEA.[24] Nevertheless, in some operations the use of this form of regional anaesthesia looked exaggerated compared with the potential risks, which included severe hypotension, respiratory depression, bleeding, epidural haematoma, and intracranial hypertension. With this purpose, the paravertebral and the intercostal blocks were introduced for shorter and less elaborate operations.

However in some circumstances TEA appeared to be inadequate. This was the case for operations requiring a considerable amount of time and conducted in proximity of hilar structures, thus triggering the cough reflex. The most remarkable improvements in this field were the introduction of vagal blockade, the development of new opioids (sufentanil and remifentanil), and the employment of bispectral index monitoring for the regulation of sedation level during the operation. These techniques have consistently facilitated non-intubated major lung resections.[26-28]

THE EVOLUTION OF THE SURGICAL TECHNIQUE

When we began 15 years ago, the approach was typically through three ports placed according to the 'baseball diamond', with the camera port at the 'home base' pointing to the lesion sited at 'second

base'. The other two ports were placed at the 'first base' and 'third base' positions to allow the right and left-hand instruments to be placed and triangulated forwards towards the target. The use of these two ports was very useful at the beginning because they allowed for the introduction of gauze pad sticks to enable some control over the inevitable movements of a breathing lung.

Following the natural evolution of the VATS technique under GA, we progressively tried to omit the posterior port also in awake patients. In fact, it was possible to achieve adequate surgical retraction and manipulation using a wider utility port. The restriction of the number of access points proved effective in decreasing both intraoperative discomfort and postoperative pain.

The natural passage was the insertion of the camera port through the unique anterior port, thus carrying out the whole procedure through a single-port access protected by a plastic sleeve-shaped retractor to avoid instrument impingement. This further step of progress was possible with the development of the new anaesthesiological technique that allowed operations in nearly 'numb' patients with minimal respiratory movements. The initial difficulties in reaching the operatory field with the correct angle following a unique direction and the crowding problem created by a single port were resolved by the development of dedicated instruments.

Current efforts are aimed at the development of non-intubated surgery through a subxiphoid approach[33,34] that we pioneered for a long time under GA.[35-38] This route proved safe and tolerable for the awake patient, reasonably pain free in the postoperative period, and easy for the surgeon as it allows the introduction of one entire hand in the chest cavity. Its location allows a superb exposure of the lower lobes and a more perpendicular direction of the stapling devices towards the structures of the hilum. Nowadays our group has employed this approach in non-intubated modality for lung metastasectomy, undetermined lung nodules, and pulmonary and mediastinal biopsies.[39] The development of new dedicated instruments and the increment of surgical skill in uniportal VATS may open new intriguing perspectives.

PRIMARY AND SECONDARY SPONTANEOUS PNEUMOTHORAX

Our attention was primarily directed to the treatment of primary and secondary pneumothorax in awake VATS under sole TEA (Table 1). We assessed in a randomised study the technical feasibility, efficacy, and acceptance of the procedure.[40] Awake two or three-port VATS bullectomy and pleurodesis proved to be technically feasible. In this experience only one patient had recurrence within 12 months. Reduction of procedure-related costs are impressive.

Currently we prefer non-intubated single-port access that proved both safe and more acceptable. With this access we have not yet experienced surgical conversion or need of orotracheal intubation. The same technique was used for the treatment of secondary spontaneous pneumothorax which is often a challenging condition because of the underlying disease and deteriorated general status of the patients.[41] Awake procedures were initially performed through a classic three-port and now through a uniport approach with better results in terms of postoperative pain and hospital stay. We did not find any difference in conversion rate between the two approaches.

EMPHYSEMATOUS BULLAE

We treated emphysematous bullae by awake multiportal (n=48) and uniportal (n=27) introflexive non-resection bulloplasty (Table 1), of which 27 were giant. According to our previous classification, we removed 44 Grade I, 28 Grade II, and 3 Grade III bullae.[42] There was no mortality. A mini anterior thoracotomy was necessary in four patients without tracheal intubation. Severe and diffuse adhesions required GA in another four patients. In the uniport approach, conversion to GA was required in one patient only. No patient needed GA because of excessive hypercapnia or panic attack. This technique allowed a shorter air leakage period, and in all instances satisfaction of patients was excellent, especially in those with comorbidities.[43]

EMPYEMA THORACIS

Awake VATS procedures under TEA or paravertebral block were used for localised empyema, achieving an almost complete lung re-expansion in nearly all patients (Table 1).[44] We have now accomplished the procedure through a single port along the maximum diameter of the fluid collection. We experienced a shorter hospital stay compared with patients undergoing classic operation. Conversion was only due to surgical reasons, and no difference was found between multi and uniport groups.

Table 1: Awake Thoracic Surgery Research Group at Tor Vergata University of Rome. Cumulative experience with non-intubated video-assisted thoracic surgery from 2000–2016.

Non-intubated procedure	Multiport		Uniport	
	Number	Failures	Number	Failures
Primary pneumothorax	69	2	44	-
Secondary pneumothorax	31	7	20	3
Emphysematous bullae	48	4	27	1
Empyema thoracis	26	7	18	2
Interstitial lung disease	20	6	30	2*
LVRS	77	13	31	4
Redo LVRS	13	6	11	-
Malignant pleural effusion	16	-	451	-
Benign nodules	48	2	32	-
Malignant nodules	23	2	22	4
Lung metastases	14	4	55 (7 subxiphoid)	5*
Anterior mediastinal biopsies	68	-	126	-
Lung cancer anatomical resections	32	17	11 (4 subxiphoid)	5

*p<0.05 for failures multi versus uniport.
LVRS: Lung volume reduction surgery.

INTERSTITIAL LUNG DISEASE BIOPSY

The correct diagnosis of interstitial lung disease is considered the mainstay of the therapeutic approach. The non-intubated modality has become fundamental in all these forms since one-lung ventilation carries a mortality rate.[45] Initially, we operated under TEA. Ultimately the procedures are carried out under intercostal block through a unique access (Table 1).[46] Conversion rate was lower in this subset of patients (Table 1). These patients presented a lesser reduction of intraoperative oxygenation and postoperative respiratory function. We observed a shorter hospital stay and a reduction in costs without affecting diagnostic yield and pneumonologists' satisfaction.

LUNG VOLUME REDUCTION SURGERY

Lung volume reduction surgery (LVRS) implies anatomical resection of the most severely emphysematous target area. We originally performed the procedure under multiportal VATS with intubation GA. In properly selected patients, this technique allowed improvements in exercise capacity, respiratory function, survival, and quality of life.[47,48]

In 2001, one of our members, Dr Mineo, introduced a novel personal technique of LVRS, entailing the plication of the most emphysematous lung regions (Figure 1). This technique was used under conventional awake TEA multiport VATS in a pilot study with faster recovery, minimal acute postoperative pain, and satisfactory 6-month functional outcomes (Table 1).[49-51]

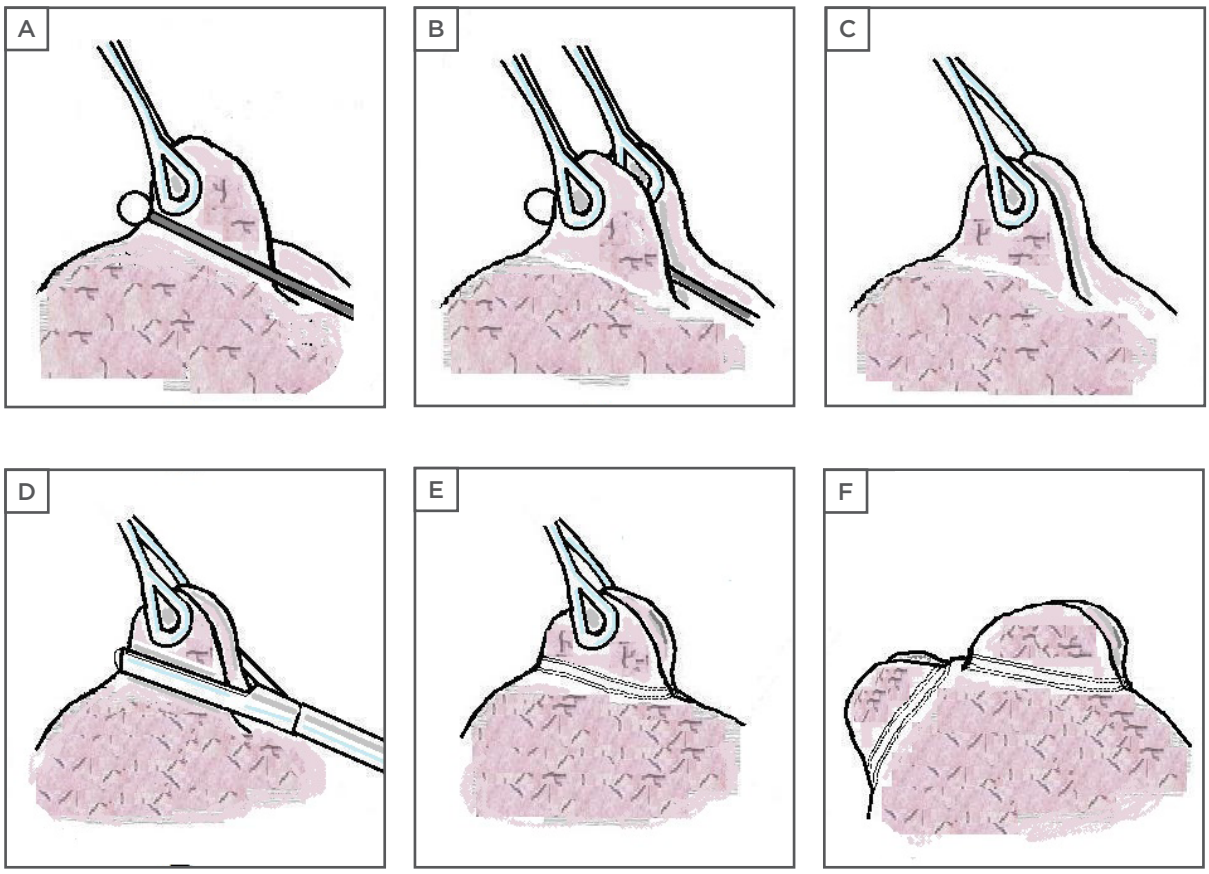


Figure 1: Surgical steps in non-resectional lung volume reduction.
A) A wide plication is created in the most emphysematous area of the upper lobe with the help of a sponge stick and ring forceps; B) a second plication is created adjacent to the previous one; C) the two plications are included in the same bite with unique ring forceps; D) a no-knife 45 mm stapler is positioned at the bases of the plicated areas; E and F) the stapler fires a unique triple-staple suture line, creating the lung volume reduction. This method respects the basic concept of resectional lung volume reduction surgery, including a reduction of 30% of the lung volume, thus favouring the immediate postoperative re-expansion and reducing the risk of prolonged air leaks.

More recently, the same change to process was accomplished by uniport technique with satisfactory early clinical results, costs, and nursing patient care. Four patients required intubation for adhesions (n=2) and panic (n=2). Open surgery was necessary in two patients due to firm adhesions. We also use uniportal non-intubated VATS in redo LVRS. In some cases, a second port is utilised when tenacious adhesions are present. Early results were impressive especially regarding the postoperative recovery and functional improvement (unpublished data). No patient required intubation due to panic attack.

MALIGNANT PLEURAL EFFUSION

Patients with recurrent malignant pleural effusion and scheduled for VATS represent an optimal group for non-intubated anaesthesia (Table 1). From the beginning we perform a single-port access under intercostal block and sedation during incidental pleural biopsy and talc pleurodesis. To evaluate the efficacy of the non-intubated procedure we recently presented a case-matched study (intercostal versus GA) in which patients were paired by computer according to their clinical features.[52] In this series, the procedure was safe and effective in relieving dyspnoea. The success rate for non-intubated VATS talc pleurodesis was 85.7%, which is similar to the rates observed in operations performed under GA. No intubation was necessary, and shorter operative theatre and hospital stay were consistently observed. In selected patients we accomplish this procedure in a one-stop day ambulatory setting. With the exception of explicit request from the patient, we now treat pleural effusion with a non-intubated approach on a routine basis.

RESECTION OF NODULES

In 2004 Dr Mineo began a randomised study concerning the feasibility of awake VATS resection of solitary pulmonary nodules. Awake TEA multiport VATS resection proved safe and feasible.[53-56] Single-port access has now been employed (Table 1). We detected 58 early-stage unexpected lung cancers because of their shape and low uptake at positron emission tomography. Better patient satisfaction was associated with faster recovery and less nursing care.[57,58] No surgical conversion was observed and intubation was required in two patients with benign tumour for cardiac impairment, and in six patients with malignant tumour for surgical reasons.

LUNG METASTASES

We dedicated specific attention to the awake resection of lung metastases. Awake multiport thoracoscopic resection under sole TEA proved feasible and safe with a significant reduction of global operating theatre time and hospital stay.[59] We treated 45 patients using the uniportal local anaesthesia approach. These patients had comparable long-term survival to those performed under GA but with lower postoperative morbidity and reduced cost. A significant lower failure rate was found in the uniportal subset (Table 1). We have begun a programme of non-intubated lung metastasectomy through a subxiphoid approach, which was our preferred route for many years.[35-38,60] We accrued a total of seven patients, who manifested significantly lesser postoperative pain and greater satisfaction compared with any transthoracic approach (Table 1). We identified some limitations, such as difficulties in performing a complete lymphnode dissection and controlling major bleeding. However, this approach provides significant advantages such as minimal pain and good cosmesis.

ANTERIOR MEDIASTINAL MASSES BIOPSY

Our group boasts a long experience with the acute diagnosis of bulky mediastinal masses provoking a superior vena cava syndrome.[61] VATS or mediastinotomy under non-intubated anaesthesia were performed and achieved a diagnostic accuracy of 96%.[62] The majority of these procedures were performed in supine patients with single-port anterior access under intercostal block (Table 1). No failure was experienced.

LUNG CANCER

We were able to carry out an increasing number of major thoracic operations under non-intubated modality for lung cancer. Inclusion criteria for patient selection are technical feasibility, staging, age, and comorbidity.[30,31,63] These operations started in 2002 with anatomical segmentectomy using multiport access. At present we accrued a total of 36 segmentectomies, six of which were recently carried out using a uniportal approach (Table 1).[64] The ability acquired with VATS lobectomies under GA improved our confidence in performing these operations under non-intubated conditions. We accomplished non-intubated lobectomy in seven patients through three-port (n=2), uniport (n=3), and subxiphoid (n=2) approaches. In another two patients, conversion to an open approach was necessary for technical difficulties. The control of pain without opioids provides faster recovery with a prompt return to daily activity as well as lesser immuno-depression, with a potential impact on neoplastic recurrence.

THE BIOLOGICAL IMPLICATIONS

We focussed much attention on the numerous and intriguing biological implications of non-intubated VATS. Many of these positive effects originated from the avoidance of GA and above all from the rejection of one-lung ventilation.[13] We have shown that the operation performed in spontaneously ventilating patients can result in a remarkable reduction of perioperative stress response, as suggested by a lesser increase in several biomarkers of surgical trauma including cortisol, interleukin-6, and C-reactive protein.[65] We also experienced a stability of perioperative lymphocytes pool, thus suggesting a potential role for regional anaesthesia protocol in preventing perioperative immuno-depression and limiting postoperative morbidity.[66]

We are also investigating whether the employment of the non-intubated technique influences the biological behaviour of cancer cells. It is a common finding that surgical manipulation and GA favours the escape of tumour cells from their dormancy condition. This mechanism is generally explained as a kind of incompletely understood postoperative immuno-depression, affecting natural killers, T helper cells, and pro-inflammatory cytokines.[39] All these derangements are mainly due to response to surgical trauma, mechanical one-lung ventilation, and pharmacologic supports to sustain GA.

When compared with conventional surgery, both lymphocyte populations and cytokines were less altered and showed a faster recovery in the non-intubated VATS.[66] The impact on overall and disease-free survivals is expected but not yet proved in our series, most probably due to the limited sample size and the short time-span of follow-up.

RELEVANCE OF PSYCHOLOGICAL PROFILE

The clinical observation of patients undergoing non-intubated operations evidenced an emerging and underestimated problem: the different degree of patients' psychological tolerance to the procedure. Fully informed consent is one of the mainstays of ethical behaviour in modern surgery, but in the case of non-intubated modality it becomes essential for the positive outcome of the procedure itself. We expected that patients apparently more motivated to bear the non-intubated operation should be those who better tolerate it. However, we experienced that some of these patients did not tolerate the procedure very well. We have recently developed an investigational programme based on a series of self-administered psychological tests targeted to this purpose. Every patient scheduled for non-intubated surgery is now processed with newly developed questionnaires[67-70] that require 30 minutes to complete. Intraoperative evaluation of the tolerance and state of consciousness was conducted using the Richmond Agitation-Sedation scale.[71] Preliminary data from the study are now available and we found that a combination of Profile of Mood States and Mini Mental State Examination questionnaires provided a better prediction of the non-intubated procedure tolerance. No panic has been found in patients with low combined scores in these two questionnaires.

COMMENT

In 1987, Dr Rush and Dr Mountain described the first thoracoscopic procedures under regional anaesthesia,[72] and in 1997 Nezu et al.[73] presented the first lung resection in local anaesthesia; nobody could have foreseen what progress these new techniques would make. At present non-intubated uniportal lung resections represent the most advanced frontier in the evolution of conventional VATS. This technique meets all the requirements desired by the surgeons, asked by the patients, expected by the physicians, and wanted by the administrators.[10] Theoretically, indications for preferring a uniportal approach instead of a multiportal one do not exist. With adequate anaesthesiological knowledge and surgical practice, nearly all VATS operations can be accomplished under non-intubated modality through unique access. We only find useful the execution of a second access in the case of firm and dense adhesions. There is no doubt that our series show an unquestionable preponderance of minor operations. However, from these procedures we gained a remarkable amount of data that allowed us to approach the more major operations in a safer manner.

We are perfectly aware that operating with a breathing lung is a conceptual obstacle for many thoracic surgeons. To avoid serious complications and conversion, it is vital that these procedures are performed by experienced individuals. The Rivas group reduced conversion index from 6% to 3%.[18] However, we have found that the learning curve for surgeons well trained in non-intubated VATS is no longer than that required for any other new endoscopic procedure, and we perceived that young surgeons were increasingly attracted by this approach. Accordingly, it is not unreasonable to hypothesise that in high volume VATS centres, a new highly-specialised generation of thoracic surgeons as well as anaesthesiologists can be moulded.

In conclusion, uniportal non-intubated VATS is an effective technique that can be safely carried out in a variety of thoracic pathologies. This kind of thoracic surgery is projected towards the future and still represents an unexplored and potentially fruitful field. Can we consider non-intubated uniportal VATS the final stage in the evolution of minimally invasive surgery? If we answer yes, we would create an inappropriate hindrance to its technological development as surgery is a constantly evolving speciality.

Footnotes

More recently, data from the Official Awake Thoracic Surgery Research Group, Policlinico Tor Vergata have been manipulated and published by an unexisting group of awake thoracic surgery of University of Rome Tor Vergata that has neither beds nor operative sessions in theatre. We thank all colleagues that co-operate for the development of the group, and those who share with us their patients.

REFERENCES

1. Gonzalez-Rivas D et al. Uniportal video-assisted thoracoscopic lobectomy: two years of experience. Ann Thorac Surg. 2013;95(2):426-32.

2. Ng CS et al. Evolution in surgical approach and techniques for lung cancer. Thorax. 2013;68(7):681.

3. Ng CS et al. Uniportal VATS-a new era in lung cancer surgery. J Thorac Dis. 2015; 7(8):1489-91.

4. Rocco G et al. Ten-year experience on 644 patients undergoing single-port (uniportal) video-assisted thoracoscopic surgery. Ann Thorac Surg. 2013;96(2): 434-8.

5. Gonzalez-Rivas D et al. Advances in uniportal video-assisted thoracoscopic surgery: pushing the envelope. Thorac Surg Clin. 2016;26(2):187-201.

6. Migliore M et al. Video-assisted thoracic surgery through a single port. Thoracic surgery and interdisciplinary symposium on the threshold of the third millennium. An international continuing medical education programme. Available at: http://xoomer.virgilio.it/naples 2000/index.html. Last accessed: 5 October 2016.

7. Migliore M, Deodato G. A single-trocar technique for minimally-invasive surgery of the chest. Surg Endosc. 2001;15(8): 899-901.

8. Rocco G et al. Uniportal VATS wedge pulmonary resections. Ann Thorac Surg. 2004;77(2):726-8.

9. Rocco G. History and indications of uniportal pulmonary wedge resections. J Thorac Dis. 2013;5 Suppl 3:S212-3.

10. Yu PS et al. Single port VATS: recent developments in Asia. J Thorac Dis. 2016; 8(Suppl 3):S302-7.

11. Yang Y et al. Complex uniportal video-assisted thoracoscopic sleeve lobectomy during live surgery broadcasting. J Thorac Dis. 2016;8(6):1345-8.

12. Gonzalez-Rivas D et al. Non-intubated video-assisted thoracoscopic lung resections: the future of thoracic sugery? Eur J Cardiothorac Surg. 2016;49: 7(3)21-31.

13. Sugasawa Y et al. The effect of one-lung ventilation upon pulmonary inflammation responses during lung resections. J Anesth. 2011;25(2):170-7.

14. Mineo TC, Tacconi F. Nonintubated thoracic surgery: a lead role or just a walk on part? Chin J Cancer Res. 2014; 26(5):507-10.

15. Hung MH et al. Nonintubated uniportal thoracoscopic surgery: state of the art and future directions. J Thorac Dis. 2014; 6(1):2-9.

16. Zhao ZR et al. Non-intubated video-assisted thoracic surgery: the final frontier? Eur J Cardiothoracic Surg. 2016. [Epub ahead of print].

17. Deng HY et al. Non-intubated video-assisted thoracoscopic surgery under locoregional anaesthesia for thoracic surgery: a meta-analysis. Interact Cardiovasc Thorac Surg. 2016;23(1):31-40.

18. Rocco G. Non-intubated uniportal lung surgery. Eur J Cardiothorac Surg. 2016; 49 Suppl 1:i3-5.

19. Gonzalez-Rivas D. Uniportal thoracoscopic surgery: from medical thoracoscopy to non-intubated uniportal video-assisted major pulmonary resections. Ann Cardiothorac Surg. 2016; 5(2):85-91.

20. Mineo TC, Ambrogi V. Efficacy of awake thoracic surgery. J Thorac Cardiovasc Surg. 2012;143(1):249-50.

21. Mineo TC, Tacconi F. From "awake" to "monitored anesthesia care" thoracic surgery: A 15 year evolution. Thoracic Cancer. 2014;5(1):1-13.

22. Gonzalez-Rivas D et al. From open operations to nonintubated uniportal video-assisted thoracoscopic lobectomy: minimizing the trauma to the patients. Ann Thorac Surg. 2015;100(6):2003-5.

23. Irons JF, Martinez G. Anaesthetic considerations for non-intubated thoracic surgery. J Vis Surg. 2016;2.

24. Mineo TC. Epidural anesthesia in awake thoracic surgery. Eur J Cardiothorac Surg. 2007;32(1):13-9.

25. Al-Abdullatief M et al. Awake anaesthesia for major thoracic surgical procedures: an observational study. Eur J Cardiothorac Surg. 2007;32(2):346-50.

26. Liu YJ et al. Effects on respiration of nonintubated anesthesia in thoracoscopic surgery under spontaneous ventilation. Ann Transl Med. 2015;3(8):107.

27. Kiss G, Castillo M. Nonintubated anesthesia in thoracic surgery: general issues. Ann Transl Med. 2015;3:110.

28. Hung MH et al. Non-intubated thoracoscopic surgery using internal intercostal nerve block, vagal block and targeted sedation. Eur J Cardiothorac Surg. 2014;46(4):620-5.

29. Liu J et al. Nonintubated video-assisted thoracoscopic surgery under epidural anesthesia compared with conventional anesthetic option: a randomized control study. Surg Innov. 2015;22(2):123-30.

30. Katlic MR, Facktor MA. Video-assisted thoracic surgery utilizing local anesthesia and sedation: 384 consecutive cases. Ann Thorac Surg. 2010;90(1):240-5.

31. Katlic MR, Facktor MA. Non-intubated video-assisted thoracic surgery in patients aged 80 years and older. Ann Transl Med. 2015;3(8):101.

32. Chen JS et al. Nonintubated thoracoscopic lobectomy for lung cancer. Ann Surg. 2011;254(6):1038-43.

33. Gonzalez-Rivas D et al. Subxiphoid uniportal video-assisted thoracoscopic middle lobectomy and anterior anatomic segmentectomy (S3). J Thorac Dis. 2016; 8(3):540-3.

34. Song N et al. Subxiphoid uniportal VATS for lobectomy: a report of 105 cases. J Thorac Dis. 2016;8 (Suppl 3):S251-7.

35. Mineo TC et al. Video-assisted approach for transxiphoid bilateral lung metastasectomy. Ann Thorac Surg. 1999;67(6):1808-10.

36. Ambrogi V et al. Transxiphoid video-assisted pulmonary metastasectomy: relevance of helical computed tomography occult lesions. Ann Thorac Surg. 2000;70(6):1847-52.

37. Mineo TC et al. Transxiphoid bilateral palpation in video-assisted thoracoscopic lung metastasectomy. Arch Surg. 2001; 136(7):783-8.

38. Mineo TC et al. Transxiphoid hand-assisted videothoracoscopic surgery. Ann Thorac Surg. 2007;83(6):1978-84.

39. Mineo TC, Tacconi F. Nonintubated videothoracoscopic operations in thoracic oncology. J Surg. 2014;10:1.

40. Pompeo E et al. The role of awake video-assisted thoracoscopic surgery in spontaneous pneumothorax. J Thorac Cardiovasc Surg. 2007;133(3):786-90.

41. Mineo TC, Ambrogi V. Awake thoracic surgery for secondary spontaneous pneumothorax: another advancement. J Thorac Cardiovasc Surg. 2012;144(6): 1533-4.

42. Mineo TC et al. New simple classification for operated bullous emphysema. J Thorac Cardiovasc Surg. 2007;134(6):1491-7.

43. Pompeo E et al. Awake thoracoscopic bullaplasty. Eur J Cardiothorac Surg. 2011; 39(6):1012-7.

44. Tacconi F et al. Awake video-assisted pleural decortication for empyema thoracis. Eur J Cardiothorac Surg. 2010; 37(3):594-601.

45. Pompeo E et al. Awake thoracoscopic biopsy of interstitial lung disease. Ann Thorac Surg. 2013;95(2):445-52.

46. Ambrogi V, Mineo TC. VATS biopsy for undetermined interstitial lung disease under non-general anesthesia: comparison between uniportal approach under intercostal block vs. three-ports in epidural anesthesia. J Thorac Dis. 2014; 6(7):888-95.

47. Pompeo E et al. Reduction pneumoplasty versus respiratory rehabilitation in severe emphysema: a randomized study. Pulmonary Emphysema Research Group. Ann Thorac Surg. 2000;70(3):948-53.

48. Mineo TC et al. Impact of lung volume reduction surgery versus rehabilitation on quality of life. Eur Respir J. 2004; 23(2):275-80.

49. Mineo TC et al. Awake nonresectional lung volume reduction surgery. Ann Surg. 2006;243(1):131-6.

50. Pompeo E et al. Comparative results of non-resectional lung volume reduction performed by awake or non-awake anesthesia. Eur J Cardiothorac Surg. 2011; 39(4):e51-8.

51. Pompeo E et al.; Awake Thoracic Surgery Research Group. Randomized comparison of awake nonresectional versus nonawake resectional lung volume reduction surgery. J Thorac Cardiovasc Surg. 2012;143(1):47-54.

52. Mineo TC et al. Quality of life and outcomes after nonintubated versus intubated video-thoracoscopic pleurodesis for malignant pleural effusion: comparison by a case-matched study. J Palliat Med. 2014;17(7):761-8.

53. Hung MH et al. Nonintubated uniportal thoracoscopic surgery for peripheral lung nodules. Ann Thorac Surg. 2014;98(6):1998-2003.

54. Hung MH et al. Nonintubated video-assisted thoracoscopic surgery for management of indeterminate pulmonary nodules. Ann Transl Med. 2015;3:105.

55. Hung WT et al. Nonintubated uniportal thoracoscopic surgery for resection of lung lesions. J Thorac Dis. 2016;8 (Suppl 3):S242-50.

56. Rocco G et al. Awake single-access (uniportal) video-assisted thoracoscopic sugery for peripheral pulmonary nodules in a complete ambulatory setting. Ann Thorac Surg. 2010;89(5):1625-7.

57. Pompeo E et al. Feasibility and results of awake thoracoscopic resection of solitary pulmonary nodules. Ann Thorac Surg. 2004;78(5):1761-8.

58. Pompeo E, Mineo TC. Awake operative videothoracoscopic pulmonary resections. Thorac Surg Clin. 2008;18(3): 311-20.

59. Pompeo E, Mineo TC. Awake pulmonary metastasectomy. J Thorac Cardiovasc Surg. 2007;133(4):960-6.

60. Tacconi F et al. Substernal hand-assisted videothoracoscopic lung metastasectomy: Long term results in a selected patient cohort. Thoracic Cancer. 2011;2(2):45-53.

61. Mineo TC et al. Mediastinoscopy in superior vena cava obstruction: analysis of 80 consecutive patients. Ann Thorac Surg. 1999;68(1):223-6.

62. Pompeo E et al. Awake video-assisted thoracoscopic biopsy in complex anterior mediastinal masses. Thorac Surg Clin. 2010; 20(2):225-33.

63. Wu CY et al. Feasibility and safety of nonintubated thoracoscopic lobectomy for geriatric lung cancer patients. Ann Thorac Surg. 2013;95(2):405-11.

64. Mineo TC et al. Nonintubated VATS segmentectomy: when and for whom? Ann Thorac Surg. 2014;98(1):388.

65. Tacconi F et al. Surgical stress hormones response is reduced after awake videothoracoscopy. Interact Cardiovasc Thorac Surg. 2010;10(5): 666-71.

66. Vanni G et al. Impact of awake videothoracoscopic surgery on postoperative lymphocyte responses. Ann Thorac Surg. 2010;90(3):973-8.

67. Bartholomew K, Horowitz LM. Attachment styles among young adults: A test of a four-category model. J Person Soc Psych. 1991;61(2):226-44.

68. Bagby RM et al. The Twenty-Item Toronto Alexithymia Scale - I. Item selection and cross-validation of the factor structure. J Psych Res. 1994;38(1):23-32.

69. Gosling SD et al. A very brief measure of the Big-Five personality domains. J Res Person. 2003;37(6):504-28.

70. Folstein MF et al. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psych Res. 1975;12(3):189-98.

71. Perbet S et al. Evaluation of Richmond Agitation Sedation Scale According To Alveolar Concentration of Sevoflurane During a Sedation With Sevoflurane in Icu Patients. Intensive Care Med Exp. 2015; 3 (Suppl 1):A27.

72. Rusch VW, Mountain C. Thoracoscopy under regional anesthesia for the diagnosis and management of pleural disease. Am J Surg. 1987;154(3):274-8.

73. Nezu K et al. Thoracoscopic wedge resection of blebs under local anesthesia with sedation for treatment of a spontaneous pneumothorax. Chest. 1997;111(1):230-5.

Scaleo MEDICAL

Innovative Respiratory Solutions

RespiCare®, the first therapy chair to improve the lung function and breathing

Respicare® is a Medical Device enabling the practice of ventilatory exercises aiming to increase the depth of breathing and the lung capacity, thus allowing for a better gas exchange of the physiological breathing.

Most patients with respiratory issues such as asthma are treated with pharmaceutical products, research suggests that more than half of those patients could be treated with non pharmaceutical methods.

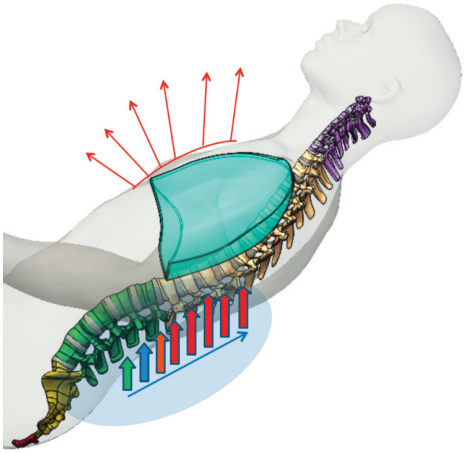
This observation paved the way for a new line of innovative solutions for **Spiropraxy®**, the respiratory orthopaedics, a field within SCALEO® medical pioneered by developing the **Respicare®**.

Respicare® is equipped with a patented technology that impulses precise and progressive thrusts at the spine level. The thrusts are combined with movements of a mechanical carriage within the chair, producing an effect that lowers the diaphragm, expands the floating ribs and stimulates the intercostal muscles.

Furthermore, the included software enables a voice to guide the user to sustain the desired breathing rate depending on the customized exercise chosen by the practitioner.

Breathing is strongly linked to the autonomic nervous system. Therefore, by improving the respiration, **Respicare®** aims to indirectly stimulate the sympathetic and the parasympathetic systems. As most health treatments reduce one system or encourage the other, the chair is a powerful tool to enhance the effects of such treatments.

This medical device is versatile as it can be used for prevention - primary, secondary and tertiary - rehabilitation and as a support to all respiratory treatments.



For patients under oxygen therapy, the **Respicare®** can also be used simultaneously with a pulse dose oxygen concentrator.

SCALEO® Medical, the developer of the **Respicare®**, is a French based company and is one of the main distributors of the Inogen oxygen concentrators, known worldwide for their breakthrough technology that combines the portability of the lightest with the performance of the most robust.

Innovation is in the core of SCALEO® Medical culture and is the result of many partnerships held with research centres and universities, but also with customers and patients, reinforcing this synergy.

ISO 13485 BUREAU VERITAS Certification

CE 0499

Scaleo® Medical - +33 467 72 94 86 - www.scaleomedical.com - info@scaleomedical.com

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ARTERIAL STIFFNESS

***Malay Sarkar**

Department of Pulmonary Medicine, Indira Gandhi Medical College, Shimla, India
**Correspondence to drsarkarmalay23@rediffmail.com*

Disclosure: The author has declared no conflicts of interest.
Received: 26.05.16 **Accepted:** 13.09.16
Citation: EMJ Respir. 2016;4[1]:114-121.

ABSTRACT

Comorbidities are common in chronic obstructive pulmonary disease (COPD). Cardiovascular comorbidity is a leading cause of morbidity and mortality in COPD patients. Low lung function is a risk factor for increased arterial stiffness, a condition that is common in COPD patients, independent of conventional cardiovascular risk factors. Arterial stiffness is an independent risk factor both for all-cause and for cardiovascular mortality, and carotid–femoral pulse wave velocity is the gold standard for the assessment of arterial stiffness. Various mechanisms proposed in the development of arterial stiffness include systemic inflammation, ageing, advanced glycation end products, renin–angiotensin–aldosterone system, increased elastolysis, and vitamin D deficiency. Early detection of arterial stiffness in COPD patients is warranted to detect cardiovascular comorbidity at the subclinical stage, which would help to prevent overt vascular events in the future. We need well-designed studies to see the impact of therapy that targets increased arterial stiffness on future cardiovascular events in COPD. This review discusses the epidemiology, diagnosis, and therapy of increased arterial stiffness in COPD patients.

Keywords: Chronic obstructive pulmonary disease (COPD), arterial stiffness, pulse wave velocity (PWV), augmentation index (AIx).

INTRODUCTION

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as "a common preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients."[1] COPD has a substantial impact in terms of morbidity, mortality, and economic loss.[2,3] Comorbidities may be present in the early stages of COPD[4] and are associated with a higher risk of exacerbations, hospitalisations, poor health status, and mortality.[5] Cardiovascular disease (CVD) is a major comorbidity and a significant contributor to morbidity and mortality in COPD patients. COPD patients have a 2 to 3-fold higher risk of developing CVD compared with the normal population[6,7] and the increased risk is independent of conventional cardiovascular risk factors such as smoking, ageing, and hypercholesterolaemia. In a large systematic review and meta-analysis, Chen et al.[8] showed that COPD is a risk factor for major CVD, and cardiovascular risk factors such as smoking, diabetes, and hypertension.

CVD is the leading cause of hospitalisation in patients with mild-to-moderate COPD.[9] About 12–50% of total deaths in COPD patients are attributed to this cardiovascular cause.[10] COPD patients have a 30% higher risk of sudden cardiac death, and the risk is higher in the frequent exacerbator phenotype.[11] Shared risk factors such as smoking, indoor air pollution, and ageing can explain the high prevalence of CVD in COPD patients. Other mechanisms include systemic inflammation, oxidative stress, physical inactivity, autonomic dysfunction, hypoxia, hypercapnia, and drug effects. Vascular dysfunction is an important mechanism that can explain the COPD–CVD link. COPD patients develop various vascular changes

such as carotid intima media thickness, endothelial dysfunction, and arterial stiffness. Arterial stiffness is a marker of early atherosclerosis[12] and is an independent predictor of CVD and cardiovascular events.[13] In a systematic review and meta-analysis of 17 longitudinal studies, Vlachopoulos et al.[14] reported that aortic stiffness is an independent risk factor both for all-cause and cardiovascular mortality. Every 1 metre (m)/second (s) increase in aortic pulse wave velocity (PWV) increases all-cause and cardiovascular mortality by 15%. Arterial stiffness is increased significantly in COPD patients compared to control subjects,[15] and early detection of arterial stiffness in COPD may help in adopting necessary preventive measures to avert future major overt vascular events.[16]

Disadvantages of Arterial Stiffness

The arterial pulse wave is generated by ventricular contraction. It has two main components: a forward-propagating wave and a reflected wave. Systolic ventricular contraction ejects the stroke volume into the vascular system, thereby generating the pulsatile forward-propagating wave. Resistance in the peripheral vascular system creates the reflected wave.[17] The reflected waves return during the diastolic phase in healthy persons and contribute to coronary perfusion. The pulsatile blood flow pattern may cause damage to high-flow and low-resistance cerebral and renal vascular systems.

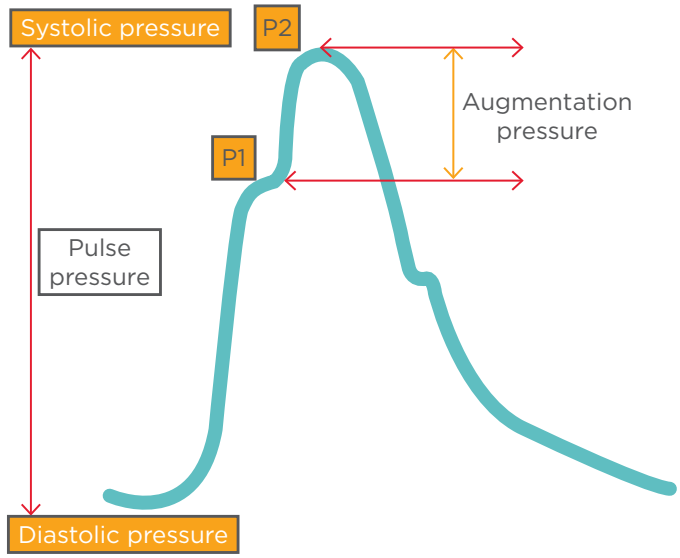


Figure 1: Augmentation pressure and pulse pressure.
Point P1 is the forward wave and point P2 is the reflecting wave. The difference between the reflected and forward wave is the augmentation pressure.

However, the elastin fibre-rich aorta dampens the pulsatile flow and prevents pressure-induced damage to cerebral and renal vascular systems. A stiffened aorta would fail to prevent the pulsatile flow-mediated target organ damage.[18] John et al.[19] have shown significantly increased microvascular renal damage in COPD patients related to increased arterial stiffness. Arterial stiffness also causes the earlier return of the reflected waves, during the systolic phase, rather than during diastole. It causes augmentation of systolic blood pressure (BP), development of left ventricular hypertrophy, and reduced coronary perfusion. This phenomenon of augmenting the systolic pressure by the reflected waves is measured by the augmentation index (AIx). Left ventricular hypertrophy manifested in electrocardiography is associated with a 3 to 15-fold increase in the risk of cardiovascular events.[20]

MEASUREMENT OF ARTERIAL STIFFNESS

There are several techniques to measure arterial stiffness, but in clinical practice PWV is the most commonly used non-invasive method.[13] PWV determines the speed at which the pulse wave travels over an arterial segment. It is measured as the ratio of the distance (m) to time (s) between two pressure waves recorded transcutaneously at two arterial sites. PWV can be measured in any arterial segment, but aortic stiffness measured as the carotid–femoral (cf)-PWV is considered the gold standard measurement of arterial stiffness,[13] as cf-PWV is a strong independent predictor of future adverse cardiovascular events.[14] cf-PWV is the ratio of the distance (m) and transit time (s) between the common carotid and femoral artery sites. The distance is measured by a tape from the sternal notch to the right carotid and the right femoral artery. The expert consensus document on the measurement of aortic stiffness recommends that 80% of the carotid–femoral distance should be used as the most accurate distance estimate of true aortic length.[21] The transit time measures the time delay between the proximal and distal pulse waves, and is most commonly measured by the foot-to-foot method. The foot of the pulse wave is defined as the point of minimal diastolic pressure or as the beginning of the steep rise in the systolic pressure. PWV depends on the elasticity of the arterial wall and its dimension.[22] Mean PWV in a healthy, normotensive person is 6.1±1.4 m/s.[23] Aortic PWV >10 m/s is considered a marker of target organ damage.[24]

AIx measures the augmentation of BP during the systolic phase by the reflected waves. Figure 1 shows the aortic pulse waveform derived from the radial artery. The AIx is the difference between the first and second systolic peaks as a percentage of pulse pressure. AIx is calculated by the following equation: AIx (%) = (ΔP/PP)×100. ΔP is the pressure difference between the peak systolic pressure (P2) and the first systolic peak that indicates the beginning upstroke of the reflected pressure wave (P1). In the equation, PP stands for pulse pressure. The gold standard and most commonly used technique to measure AIx is applanation tonometry.[25] It does not directly measure the central artery pressure waveform; instead, the aortic pressure waveform is derived from the radial artery pressure waveform.[26]

ARTERIAL STIFFNESS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD patients have consistently shown increased arterial stiffness across studies compared with ex-smokers without airway obstruction and with non-smoking healthy controls.[15]

In a cross-sectional study, Sabit et al.[27] measured arterial stiffness in 75 clinically stable COPD patients and 42 healthy current or ex-smoking participants. All participants were free of CVD. Arterial stiffness was measured by the SphygmoCor® CPV System (AtCor Medical, Sydney, Australia), and both the aortic PWV and the AIx were measured. Presence of osteoporosis was evaluated by measuring bone mineral density by a dual-energy X-ray absorptiometry scan. Both PWV and AIx were significantly higher in COPD patients than in age-matched controls. Increased aortic PWV was related to increased severity of airflow obstruction, systemic inflammation, and the presence of osteoporosis. Arterial stiffness was increased even with a mild degree of airway obstruction, indicating its early occurrence in the natural history of COPD.

In a prospective case-control study, Mills et al.[28] evaluated arterial stiffness in 102 patients with COPD and 103 healthy controls matched for age and smoking status. Using applanation tonometry (SphygmoCor CPV system), they measured the augmentation pressure and AIx of the radial artery at the wrist and derived the aortic pulse pressure waveform via a mathematical transfer function. COPD patients had elevated augmentation pressures (17±1 mmHg versus 14±1 mmHg, p=0.015) and reduced time-to-wave reflection (131±1 versus 137±2 m/s, p=0.005) compared with controls. Serum C-reactive protein concentrations were also significantly higher in COPD patients compared with controls and may explain the higher frequency of arterial stiffness in COPD patients.

Arterial stiffness is higher in severe COPD compared to mild-to-moderate COPD. A prospective cross-sectional study from Turkey by Cinarka et al.[29] assessed cf-PWV in 62 stable COPD patients and 22 healthy controls by using the SphygmoCor CPV system. The mean cf-PWV was significantly elevated in patients with COPD compared to the controls (10.95±3.74 m/s versus 7.32±1.88 m/s, p=0.003). Severe COPD patients had higher cf-PWV values compared to patients with the mild-to-moderate disease. They found airflow limitation measured by forced expiratory volume in 1 second (FEV_1) as the only independent predictor of cf-PWV.

Patel et al.[30] evaluated the aortic PWV and cardiac biomarkers in 98 COPD patients in a stable condition. Fifty-five of the patients were assessed in both stable state and exacerbation. Arterial stiffness was related to exacerbation frequency, and frequent exacerbators had greater mean aortic PWV than infrequent exacerbators (11.4±2.1 versus 10.3±2.0 m/s, p=0.025). Compared with the stable state, arterial stiffness increased acutely during episodes of exacerbation by 1.2 m/s, and the rise was higher in exacerbation caused by infection. Vlachopoulos et al.[14] performed a meta-analysis of 17 longitudinal studies involving 15,877 subjects that measured arterial stiffness by aortic PWV and showed that a 1 m/s increase in aortic PWV resulted in an age–sex and risk factor adjusted increase in total cardiovascular event, cardiovascular mortality, and all-cause mortality, of 14%, 15%, and 15%, respectively.

Bolton et al.[31] studied the relationship between aortic calcification and arterial stiffness in stable COPD patients and found a significant association between aortic PWV and calcification in the aorta. Age was the independent predictor of both processes. Bhatt et al.[32] evaluated arterial stiffness in 153 patients with moderate-to-severe COPD and found that age, higher systolic BP, and greater thoracic aortic calcification are independent predictors of elevated aortic PWV in multivariate analyses. Elastolysis in the aorta is the stimulus for calcium deposition. Qin et al.[33] demonstrated that inhibiting matrix metalloproteinases (MMPs), which are markers of elastolysis, reduced vascular calcium

deposition. Arterial stiffness is also increased in bronchiectasis, which is common in COPD.[34] In patients with acute exacerbation of COPD, Labonté et al.[35] found increased blood levels of club cell protein (CC16) and RelB levels, both of which have an inverse relation with arterial stiffness.

MECHANISM OF ELEVATED ARTERIAL STIFFNESS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The following factors have been incriminated in the development of arterial stiffness in COPD. They include some common risk factors, such smoking, physical inactivity, and ageing. Others include airway obstruction, systemic inflammation, oxidative stress, advanced glycation end products (AGEs), and renin–angiotensin–aldosterone system (RAAS).

Airway Obstruction and Emphysema

Airway obstruction is an independent risk factor for arterial stiffness. The Caerphilly population-based Prospective Study[36] found an inverse relationship between forced vital capacity (FVC) and FEV_1 with cf-PWV in men. They also observed that lung function assessments in mid-life rather than in later-life were stronger predictors of arterial stiffness and future CVD. This association was independent of smoking status, early life events, and inflammatory and metabolic factors. A 500 mL reduction in FEV_1 and FVC in mid-life resulted in PWV increases of 0.52 m/s and 0.42 m/s, respectively.

In a cross-sectional study involving 194 men, aged 30–70 years, who were free of coronary heart diseases, Zureik et al.[37] found a significant negative relationship between lung function parameters like FEV_1, FVC, and cf-PWV, suggesting that both obstructive and restrictive lung disorders are associated with increased arterial stiffness. This relationship is also independent of traditional cardiovascular risk factors such as smoking, hypercholesterolaemia, and hypertension. In an age and height-adjusted analysis, a decrease of 195.2±50.1 mL in FEV_1 and 190.4±55 mL in FVC increased the cf-PWV by 2.5 m/s.

McAllister et al.[16] demonstrated that arterial stiffness measured in 157 stable COPD patients (aortic PWV determined by the SphygmoCor CVD System) was related to emphysema severity (measured by quantitative thoracic computed tomography). This association was independent of smoking, age, sex, airflow limitation, systemic inflammation, dyslipidaemia, and hypoxaemia. One possible explanation for low lung function and arterial stiffness could be an alteration of elastolytic activity in both the alveoli and the vasculature. Elastolysis in COPD can occur in both the pulmonary and systemic levels. Maclay et al.[38] demonstrated increased skin elastin degradation in COPD patients compared to age and smoking-matched controls. The cutaneous level of MMP-9 messenger RNA was also increased in COPD patients. Upregulated skin elastolysis was related to the severity of emphysema and arterial stiffness. COPD patients probably develop increased elastin degradation in elastin-rich large conduit arteries such as the aorta that may explain increased arterial stiffness in COPD patients. The rise in elastolysis may be environmental or due to genetics. Studies have proven the common role of MMPs, an elastolytic enzyme, in both conditions. Serum levels of both MMP-9 and MMP-12 were found to be increased in both COPD and arteriosclerosis.[16] Furthermore, a polymorphism in MMP-9 increased the risk of both arterial stiffness and emphysema.[39,40]

Advanced Glycation End Products

AGEs are a heterogeneous group of substances formed irreversibly by non-enzymatic glycation and the oxidation of proteins, lipids, and nucleic acids.[41]

The classic Maillard reaction generates AGEs via several intermediate stages. Initially, Schiff base and Amadori products are formed via reversible reactions, and the final oxidation process leads to AGE formation.[42] An increased AGE level is seen in oxidative and inflammatory conditions like hyperglycaemia, renal failure, and COPD.[43,44] AGEs have been found to play a role in the pathogenesis of both COPD and arterial stiffness. AGEs, via the receptor for AGEs (RAGEs), may cause oxidative and inflammatory stress in tissues.[45,46] Wu et al.[44] have shown increased expression of both AGEs and RAGEs in COPD lung tissues compared to controls. The RAGE–AGEs axis can amplify and propagate cigarette smoking-induced airway inflammation in COPD patients.[47] AGEs can cause arterial stiffness by forming irreversible cross-links with proteins such as collagen and elastin. These proteins become structurally and functionally altered after glycation. AGEs may also affect endothelial cell synthesis of nitric oxide (NO). Rojas et al.[48] have shown significant reduction in endothelial NO synthase expression in bovine aortic endothelial cells after exposure to

albumin-derived AGEs. Kemeny et al.[49] similarly showed reduced NO release by cells of glycated collagen. NO reduces vascular oxidative stress and inflammation, the two key factors for atherosclerosis formation. Urban et al.[50] have demonstrated a link between reduced levels of soluble RAGE and endothelial dysfunction during acute COPD exacerbation. The soluble RAGE normally functions as a decoy receptor for AGEs, thereby limiting inflammation.

Renin–Angiotensin–Aldosterone System

The RAAS is activated in COPD and its role has been found in the causation of COPD and its extra-pulmonary manifestations.[51,52] Angiotensin II is a potent vasoconstrictor and vasoproliferator substance. Vasoproliferator action is mediated by the binding of angiotensin II to the angiotensin Type 1 (AT1) receptor present in vascular tissues.[53,54] Hypercholesterolaemia and diabetes are two important causes of increased expression of the AT1 receptor in vascular tissue,[55,56] and both the conditions are seen in COPD in high frequency.[57] Rats with fructose-induced hyperinsulinaemic conditions showed increased vascular AT1 receptor expression.[58] The increase in RAAS or AT1 may lead to structural changes of the vasculature, leading to altered vasoreactivity and arterial stiffness.

Vitamin D Deficiency

Vitamin D deficiency is common in COPD patients and is more prevalent in severe COPD. Janssens et al.[59] found vitamin D deficiency in 60% and 77% of patients with GOLD Stage 3 and 4 COPD, respectively, compared with 31% of smokers with normal lung function. Vitamin D deficiency has also been incriminated in causing increased arterial stiffness and endothelial dysfunction independent of traditional risk factors. In a community-based asymptomatic population study, Al Mheid et al.[60] observed that low vitamin D levels are independently associated with increased PWV, AIx, and impaired flow-mediated dilatation after adjustments of confounders such as age, sex, race, BMI, total cholesterol, low-density lipoprotein, triglycerides, C-reactive protein, and medication use. There are various mechanisms by which vitamin D deficiency can cause endothelial dysfunction. Vitamin D normally inhibits the deleterious effects of AGEs on endothelial cells.[61] Vitamin D deficiency by activating RAAS may produce vasoproliferative actions.[60]

Ageing

Both COPD and its systemic manifestations are related to an accelerated ageing process. Oxidative stress has a role in this ageing process. Boyer et al.[62] studied the telomere shortening and systemic manifestations in 100 COPD patients, and smoking and non-smoking controls without COPD. COPD patients showed higher PWV, reduced bone mineral density and appendicular skeletal muscle mass index, and increased telomere length shortening; features not seen in control smokers. Therefore, systemic manifestations in COPD are mainly due to COPD itself.

Systemic Inflammation and Oxidative Stress

Systemic inflammation is common in COPD patients and has been identified as one of the mechanisms associated with a higher risk of CVD in COPD patients. In a systematic review and a meta-analysis, Gan et al.[63] reported the presence of systemic inflammation in COPD patients, which may explain the high prevalence of comorbidities in COPD. Sin and Mann[64] have shown that in patients with moderate-to-severe airflow obstruction, low-grade systemic inflammation explained the increased risk of cardiac injury in COPD. However, the association between systemic inflammation and arterial stiffness varies in literature. Several studies have shown a positive association between systemic inflammation and arterial stiffness.[16,27] A study conducted with healthy volunteers using *Salmonella* typhi vaccination as a model of acute systemic inflammation showed endothelial dysfunction and an increase in arterial stiffness.[65,66] Further studies have shown no link between the two.[67-69] It can be explained by the varying methodologies in these studies. Mills et al.[28] found no significant differences in C-reactive protein levels in COPD patients with and without cardiovascular comorbidities.

Moreover, not all COPD patients show systemic inflammation.[70] Systemic inflammation causes arterial stiffness by altering the extracellular matrix of the vasculature.[71] It causes the degradation of elastic fibres by elastolysis and their replacement by collagen.[72] An important biomarker of elastin degradation is the plasma desmosine (pDES) level. Rabinovich et al.[73] have shown that pDES levels were significantly higher in COPD patients with CVD and correlated with arterial stiffness ($p<0.05$). However, no correlation was seen with emphysema or emphysema progression indicating that pDES is

primarily a marker of vascular elastin degradation. Systemic inflammation by altering NO production may also lead to functional arterial stiffness development.[74] Hypoxaemia is another mechanism in COPD that has been linked to arterial stiffness.[29] It may be mediated by a hypoxaemia-induced rise in systemic inflammation.[75]

Altered Redox Balance in Chronic Obstructive Pulmonary Disease

Ives et al.[76] showed that compared to age and sex-matched controls, COPD patients developed altered redox balance characterised by lower antioxidant effects and higher oxidative stress. Altered redox balance has been linked with increased PWV in COPD as an antioxidant cocktail (vitamin C, vitamin E, α-lipoic acid), and was associated with significant improvements in PWV in patients with COPD. Oxidative stress alters arterial stiffness by impacting on the endothelial NO pathway.[77]

TREATMENT OF AORTIC STIFFNESS

Comprehensive management of COPD should also include assessment and management of comorbidities. However, current COPD guidelines are not focussed on this issue. Arterial stiffness can be modifiable. Endurance exercise has been shown to improve arterial stiffness in the healthy person.[78,79] It does so in COPD patients also. A case-controlled study by Vivodtzev et al.[67] evaluated the impact of exercise in 17 stable COPD patients. Endurance exercise lasting 4 weeks resulted in a significant reduction in carotid-radial PWV in COPD patients. The improvement in arterial stiffness occurred proportionally to changes in exercise capacity. The mechanisms of improvement include a reduction in BP and blood glucose. Exercise training lowers BP by reducing basal sympathetic activity and restoring baroreflex sensitivity.[80] Another mechanism may be an exercise-induced reduction in oxidative stress and subsequent arterial stiffness.[23] Gale et al.[68] conducted a prospective cohort study which further supported the role of exercise as a modifier of arterial stiffness. A multidisciplinary pulmonary rehabilitation programme resulted in improvement in several cardiovascular risk factors in COPD patients: aortic PWV, BP, and cholesterol.

Dransfield et al.[81] conducted a multicentre, randomised, double-blind, placebo-controlled study, which evaluated the effects of fluticasone propionate/salmeterol (FSC; 250/50 µg) twice daily on aortic PWV in COPD patients. Reduction in PWV is maximum in patients with highest baseline arterial stiffness and is only seen in those patients who continued the therapy throughout the study period. Sabit et al.[82] similarly evaluated the effects of FSC (500/50 µg) in patients with moderate-to-severe COPD and found significant improvement in arterial stiffness after 8 weeks of treatment. The exact mechanism by which inhaled corticosteroid improves arterial stiffness is not known. It may be mediated by its impact on systemic inflammation,[83] or neurohumoral activation.[84] Statins having an anti-inflammatory effect would be an attractive option in COPD with CVD. In a double-blind, randomised trial, John et al.[85] evaluated the effects of simvastatin 20 mg once daily for 6 weeks on aortic stiffness, and systemic and airway inflammation in patients with COPD. Simvastatin improved aortic PWV only in the subgroup with a higher baseline PWV (>10 m/s). Beta blockers with vasodilatory effect, for example nebivolol, have the potential to reduce arterial stiffness by increasing NO activity.[86] Nebivolol also demonstrates anti-inflammatory effects which are also responsible for an improvement in vascular function.[87] Although beta blockers appear to be safe in COPD, their role in terms of reduction in arterial stiffness and the subsequent impact on cardiovascular comorbidity needs to be studied in prospective randomised, controlled trials.[88]

CONCLUSION

CVD occurs frequently and is a major cause of morbidity and mortality in COPD patients. Arterial stiffness is an independent predictor of adverse cardiovascular events and all-cause mortality. Arterial stiffness is increased in patients with COPD and there are several potential mechanisms by which COPD can influence the development of arterial stiffness. Early detection of arterial stiffness is important for future prevention of overt CVD.

REFERENCES

1. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. Available at: http://www.goldcopd.org/. Last accessed: 15 May 2016.

2. Lozano R et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a

systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380(9859):2095-128.

3. Ford ES et al. Total and state-specific medical and absenteeism costs of chronic obstructive pulmonary disease among adults aged $18 years in the United States for 2010 and projections through 2020. Chest. 2015;147(1):31-45.

4. Decramer M et al. COPD as a lung disease with systemic consequences-clinical impact, mechanisms, and potential for early intervention. COPD. 2008;5(4): 235-56.

5. Patel AR, Hurst JR. Extra-pulmonary comorbidities in chronic obstructive pulmonary disease: State of the art. Expert Rev Respir Med. 2011;5(5):647-62.

6. Huiart L et al. Cardiovascular morbidity and mortality in COPD. Chest. 2005; 128(4):2640-6.

7. Sidney S et al. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. Chest. 2005;128:2068-75.

8. Chen W et al. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Lancet Respir Med. 2015;3(8):631-9.

9. Anthonisen NR et al.; Lung Health Study Research Group. Hospitalizations and mortality in the Lung health study. Am J Respir Crit Care Med. 2002;166(3):333-9.

10. Stone IS et al. Chronic obstructive pulmonary disease: a modifiable risk factor for cardiovascular disease? Heart. 2012;98(14):1055-62.

11. Lahousse L et al. Chronic obstructive pulmonary disease and sudden cardiac death: the Rotterdam study. Eur Heart J. 2015;36(27):1754-61.

12. Duprez DA, Cohn JN. Arterial stiffness as a risk factor for coronary atherosclerosis. Curr Atheroscler Rep. 2007;9(2):139-44.

13. Laurent S et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27(21): 2588-605.

14. Vlachopoulos C et al. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55(3):1318-27.

15. Vivodtzev I et al. Arterial stiffness in COPD. Chest. 2014;145(4):861-75.

16. McAllister DA et al. Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;176(12): 1208-14.

17. Mackenzie IS et al. Assessment of arterial stiffness in clinical practice. QJM. 2002;95(2):67-74.

18. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension. 2005;46(1):200-4.

19. John M et al. Target renal damage: the microvascular associations of increased aortic stiffness in patients with COPD. Respir Res. 2013;14:31.

20. Kannel WB. Left ventricular hypertrophy as a risk factor: the Framingham experience. J Hypertens Suppl. 1991;9(2):S3-9.

21. Van Bortel LM et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens. 2012;30(3):445-8.

22. Rhee MY et al. Measurements of Arterial Stiffness: Methodological Aspects. Korean Circ J. 2008;38(7):343-50.

23. Lessiani G et al. Arterial stiffness and sedentary lifestyle: Role of oxidative stress. Vascul Pharmacol. 2016;79:1-5.

24. Mancia G et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34: 2159-219.

25. O'Rourke MF, Jiang APXJ. Pulse wave analysis. Br J Clin Pharmacol. 2001; 51(6):507-22.

26. Wilkinson IB et al. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens. 1998;16(12 pt 2):2079-84.

27. Sabit R et al. Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;175(12):1259-65.

28. Mills NL et al. Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. Thorax. 2008;63(4):306-11.

29. Cinarka H et al. Arterial stiffness measured by carotid femoral pulse wave velocity is associated with disease severity in chronic obstructive pulmonary disease. Respir Care. 2014;59(2):274-80.

30. Patel AR et al. Cardiovascular risk, myocardial injury, and exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;188(9): 1091-9.

31. Bolton CE et al. Aortic calcification, arterial stiffness and bone mineral density in patients with COPD. Artery Res. 2011;5(1):30-6.

32. Bhatt SP et al. Determinants of arterial stiffness in COPD. BMC Pulm Med. 2014;14:1.

33. Qin X et al. Matrix metalloproteinase inhibition attenuates aortic calcification. Arterioscler Thromb Vasc Biol. 2006; 26(7):1510-6.

34. Gale NS et al. Systemic comorbidities in bronchiectasis. Chron Respir Dis. 2012; 9(4):231-8.

35. Labonté LE et al. Club Cell-16 and RelB as Novel Determinants of Arterial Stiffness in Exacerbating COPD Patients. PLoS One. 2016;11(2):e0149974.

36. Bolton CE et al. Lung function in mid-life compared with later life is a stronger predictor of arterial stiffness in men: the Caerphilly Prospective Study. Int J Epidemiol. 2009;38(3):867-76.

37. Zureik M et al. Reduced pulmonary function is associated with central arterial stiffness in men. Am J Respir Crit Care Med. 2001;164:2181-5.

38. Maclay JD et al. Systemic elastin degradation in chronic obstructive pulmonary disease. Thorax. 2012;67(7): 606-12.

39. Zhou S et al. Matrix metalloproteinase-9 polymorphism contributes to blood pressure and arterial stiffness in essential hypertension. J Hum Hypertens. 2007; 21(11):861-7.

40. Ito I et al. Matrix metalloproteinase-9 promoter polymorphism associated with upper lung dominant emphysema. Am J Respir Crit Care Med. 2005;172(11): 1378-82.

41. Ahmed N. Advanced glycation end products - role in pathology of diabetic complications. Diabetes Res Clin Pract. 2005;67(1):3-21.

42. Gkogkolou P, Böhm M. Advanced glycation end products: Key players in skin aging? Dermatoendocrinol. 2012; 4(3):259-70.

43. Smit AJ, Lutgers HL. The clinical relevance of advanced glycation endproducts (AGE) and recent developments in pharmaceutics to reduce AGE accumulation. Curr Med Chem. 2004;11(20):2767-84.

44. Wu L et al. Advanced glycation end products and its receptor (RAGE) are increased in patients with COPD. Respir Med. 2011;105(3):329-36.

45. Goh SY, Cooper ME. Clinical review: The role of advanced glycation end products in progression and complications of diabetes. J Clin Endocrinol Metab. 2008; 93(4):1143-52.

46. Bierhaus A et al. Understanding RAGE, the receptor for advanced glycation end products. J Mol Med. 2005;83(11):876-86.

47. Li M et al. RAGE-ligands axis: A new 'driving force' for cigarette smoke-induced airway inflammation in COPD? Respirology. 2015;20(6):998-9.

48. Rojas A et al. Regulation of endothelial nitric oxide synthase expression by

albumin-derived advanced glycosylation end products. Circ Res. 2000;86(3): E50-4.

49. Kemeny SF et al. Glycated collagen alters endothelial cell actin alignment and nitric oxide release in response to fluid shear stress. J Biomech. 2011;44(10): 1927-35.

50. Urban MH et al. Soluble receptor of advanced glycation end-products and endothelial dysfunction in COPD. Respir Med. 2014;108(6):891-7.

51. Vlahakos DV et al. Association between activation of the renin-angiotensin system and secondary erythrocytosis in patients with chronic obstructive pulmonary disease. Am J Med. 1999;106(2):158-64.

52. Shrikrishna D et al. Renin–angiotensin system blockade: a novel therapeutic approach in chronic obstructive pulmonary disease. Clin Sci (Lond). 2012; 123(8):487-98.

53. Geisterfer AAT et al. Angiotensin II induces hypertrophy, not hyperplasia, of cultured rat aortic smooth muscle cells. Circ Res. 1988;62(4):749-56.

54. Pratt RE et al. Role of angiotensin in the control of vascular smooth muscle cell growth. J Vasc Med Biol. 1991;3(1): 25-9.

55. Yang BC et al. Increased Angiotensin II Type 1 Receptor Expression in hypercholesterolemic atherosclerosis in rabbits. Arterioscler Thromb Vasc Biol. 1998;18(9):1433-39.

56. Wagner J et al. Angiotensin II receptor type 1 gene expression in human glomerulonephritis and diabetes mellitus. J Am Soc Nephrol. 1999;10(3):545-51.

57. Naik D et al. Chronic obstructive pulmonary disease and the metabolic syndrome: Consequences of a dual threat. Indian J Endocrinol Metab. 2014;18(5): 608-16.

58. Nyby MD et al. Vascular Angiotensin type 1 receptor expression is associated with vascular dysfunction, oxidative stress and inflammation in fructose-fed rats. Hypertens Res. 2007;30(5):451-7.

59. Janssens W et al. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. Thorax. 2010;65(3):215-20.

60. Al Mheid I et al. Vitamin D status is associated with arterial stiffness and vascular dysfunction in healthy humans. J Am Coll Cardiol. 2011;58(2):186-92.

61. Talmor Y et al. Calcitriol blunts the deleterious impact of advanced glycation end products on endothelial cells. Am J Physiol Renal Physiol. 2008;294(5): F1059-64.

62. Boyer L et al. Aging-related systemic manifestations in COPD patients and cigarette smokers. PLoS One. 2015; 10(3):e0121539.

63. Gan W et al. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004; 59(7):574-80.

64. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation. 2003;107(11):1514-19.

65. Vlachopoulos C et al. Acute systemic inflammation increases arterial stiffness and decreases wave reflections in healthy individuals. Circulation. 2005;112(14): 2193-200.

66. Hingorani AD et al. Acute systemic inflammation impairs endothelium-dependent dilatation in humans. Circulation. 2000;102(9):994-9.

67. Vivodtzev I et al. Significant Improvement in arterial stiffness after endurance training in patients with COPD. Chest. 2010;137(3):585-92.

68. Gale NS et al. Does pulmonary rehabilitation address cardiovascular risk factors in patients with COPD? BMC Pulm Med. 2011;11:20.

69. Van Fleteren LE et al. Arterial stiffness in patients with COPD: the role of systemic inflammation and the effects of pulmonary rehabilitation. Eur Respir J. 2014;43(5):1306-15.

70. Agusti A et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PloS One. 2012;7(5):e37483.

71. Zieman SJ et al. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol. 2005;25(5):932-43.

72. Ben David D et al. Exposure to pro-inflammatory cytokines upregulates MMP-9 synthesis by mesenchymal stem cells-derived osteoprogenitors. Histochem Cell Biol. 2008;129(5):589-97.

73. Rabinovich RA et al. Circulating desmosine levels do not predict emphysema progression but are associated with cardiovascular risk and mortality in COPD. Eur Respir J. 2016;47(5):1365-73.

74. Wilkinson IB et al. Nitric oxide and the regulation of large artery stiffness: from physiology to pharmacology. Hypertension. 2004;44(2):112-6.

75. Takabatake N et al. The relationship between chronic hypoxemia and activation of the tumor necrosis factor-alfa system in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;161(4 Pt 1): 1179-84.

76. Ives SJ et al. Vascular dysfunction and chronic obstructive pulmonary disease: the role of redox balance. Hypertension. 2014;63(3):459-67.

77. Kuzkaya N et al. Interactions of peroxynitrite, tetrahydrobiopterin, ascorbic acid, and thiols: implications for uncoupling endothelial nitric-oxide synthase. J Biol Chem. 2003;278(25): 22546-54.

78. Kingwell BA et al. Four weeks of cycle training increases basal production of nitric oxide from the forearm. Am J Physiol. 1997;272(3 Pt 2):H1070-7.

79. Tanaka H et al. Aging, habitual exercise, and dynamic arterial compliance. Circulation. 2000;102(11):1270-5.

80. Costes F et al. Influence of exercise training on cardiac baroreflex sensitivity in patients with COPD. Eur Respir J. 2004; 23(3):396-401.

81. Dransfield MT et al. Effect of fluticasone propionate/salmeterol on arterial stiffness in patients with COPD. Respir Med. 2011;105(9):1322-30.

82. Sabit R et al. Arterial stiffness is reduced by combination inhaled corticosteroid/long acting beta-2 agonist therapy in patients with COPD. A142. British Thoracic Society Winter Meeting 2007.

83. Sin DD et al. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004;170(7): 760-5.

84. Andreas S et al. Neurohumoral activation as a link to systemic manifestations of chronic lung disease. Chest. 2005;128(5):3618-24.

85. John ME et al. Cardiovascular and inflammatory effects of simvastatin therapy in patients with COPD: a randomized controlled trial. Int J Chron Obstruct Pulmon Dis. 2015;10(1):211-21.

86. Mason RP, Cockcroft JR. Targeting nitric oxide with drug therapy. J Clin Hypertens. 2006;8(suppl 12):40-52.

87. McEniery CM et al. Nebivolol increases arterial distensibility in vivo. Hypertension. 2004;44(3):305-10.

88. Cockcroft JR, Pedersen ME. B-Blockade: Benefits beyond Blood Pressure Reduction? J Clin Hypertens (Greenwich). 2012;14(2):112-20.

UPCOMING EVENTS

24th Annual Meeting of the German Society of Sleep Research and Sleep Medicine (DGSM)

1st–3rd December 2016

Dresden, Germany

This year's meeting will be hosted by one of the most modern congress centres in Europe, the International Congress Center, Dresden, which offers remarkable architecture and a beautiful setting, situated by the River Elbe. At this year's event, there will be a particular focus on new technologies such as driver assistance systems, health apps, and infrastructure for home care, as well as an array of presentations on other topics related to this area of medicine.

The International Association for the Study of Lung Cancer (IASLC) 17th World Conference on Lung Cancer 2016

4th–7th December 2016

Vienna, Austria

This conference aims to cover the management of lung cancers, mesothelioma, and thymic and other thoracic malignancies. Lectures will focus on accurate diagnoses, state-of-the-art treatments, and recent advances in the field. Workshops will also be held to help guests learn about palliative care and patient support, as well as about clinical trial designs and how to become successful members of research groups in this field.

British Thoracic Society (BTS) Winter Meeting 2016

7th–9th December 2016

London, UK

This scientific programme boasts a whole host of esteemed respiratory experts. The meeting offers numerous symposia covering aspects of respiratory medicine, including emphysema, sarcoidosis, respiratory medicines, treatments for obstructive sleep apnoea, chronic obstructive pulmonary disease, and malignant pleural disease. Poster discussion sessions are also offered, concentrating on lung cancer investigations and imaging in lung disease, among other current research topics within the field.

4th International Workshop on Lung Health, Asthma and COPD: New Paradigms in Preventing Exacerbations in Respiratory Diseases 2017

19th–21st January 2017

Budapest, Hungary

This scientific event focusses on the prevention of exacerbations as a result of various respiratory diseases. The workshop offers insights into bronchiectasis, idiopathic pulmonary fibrosis, cystic fibrosis, pulmonary rehabilitation, and lung transplantation, among many other key areas. This occasion also provides the opportunity for young medical professionals to meet esteemed experts in the field of respiratory medicine to discuss current research interests and approaches.

Asthma: From Pathway Biology to Precision Therapeutics 2017

12th–16th February 2017

Keystone, Colorado, USA

At this Keystone Symposia event, numerous esteemed experts from the field of respiratory medicine will present investigations and viewpoints on various topics, including phenotyping methods, cluster analysis, regulation and treatment of Type 2 inflammation in the airway, biomarkers for personalised treatments, and many more. It will include poster sessions, talks on chosen abstracts, and social events, providing guests with the opportunity to meet the experts.

Turkish National Lung Health Congress (NLHC/UASK) 2017

15th–19th March 2017

Antalya, Turkey

This congress focusses on various aspects of respiratory medicine, including pulmonology, thoracic oncology, intensive care, and a whole host of prevalent issues touched upon in the field's latest research. There will be poster sessions, industry stands, and social events for guests to meet the professionals, with talks covering the diagnosis and treatment of patients, as well as the most recent innovations in respiratory medicine.

Multidisciplinary Update in Pulmonary and Critical Care Medicine 2017

6th–9th April 2017

Phoenix, Arizona, USA

This year's course covers a host of topics, including a review of current pulmonary literature, a review of present critical care literature, and interactive case-based presentations. There will also be opportunities for guests to gain further insight in question and answer sessions. The format of the course, complete with lectures and case presentations, aims to meet the educational needs of the guests through its specially designed learning formats.

The European Respiratory Society (ERS) International Congress 2017

9th–13th September 2017

Milan, Italy

This scientific programme, offered in conjunction with the European Sleep and Research Society (ESRS), presents case-based sessions aimed at explaining the history, pathology, analysis, and treatment of various clinical cases in many areas, as well as 'meet the expert' sessions, skills workshops, and symposia, hosting four field-renowned experts who will present reviews on all features of respiratory medicine. The congress will focus on countless respiratory areas, including respiratory intensive care, cell and molecular biology, and airway diseases, and provide ample networking opportunities for all those who attend.

Buyer's Guide

- 3D SYSTEMS HEALTHCARE
- ACTELION PHARMACEUTICALS LTD.
- ADELPHI REAL WORLD
- ADHERIUM
- AEROCRINE AB
- AEROGEN
- AIR LIQUIDE SANTÉ INTERNATIONAL
- ARMSTRONG MEDICAL LTD.
- ASTRAZENECA
- BAYER AG
- BAYWATER HEALTHCARE
- BD
- BEAUTYGATE LTD.
- BEDFONT SCIENTIFIC
- BEIJING RONGURI-CENTURY SCIE. & TECH. CO., LTD.
- BESMED HEALTH BUSINESS CORP.
- BIOMEDICAL SYSTEMS
- BIOXYDYN LTD.
- BLUESOM
- BMC MEDICAL CO., LTD.
- BOEHRINGER-INGELHEIM
- BOSCH HEALTHCARE SOLUTIONS GMBH
- BOSTON SCIENTIFIC INTERNATIONAL
- BPR MEDICAL LTD.
- BREAS MEDICAL AB
- BRESO TEC, INC.
- BRONCUS MEDICAL, INC.
- CAREFUSION GERMANY 234 GMBH
- CHART BIOMEDICAL LTD.
- CHIESI FARMACEUTICI SPA
- CIDELEC
- CIRCADIANCE
- CLEMENT CLARKE INTERNATIONAL
- COOK MEDICAL
- COSMED
- COVIDIEN AG
- CSL BEHRING GMBH
- CYCLOMEDICA EUROPE LTD.
- DEHAS MEDIZINTECHNIK & PROJEKTIERUNG GMBH
- DRIVE DEVILBISS HEALTHCARE GMBH
- ECO MEDICS AG
- EMKA TECHNOLOGIES
- EOVE
- ERBE ELEKTROMEDIZIN GMBH
- ERT
- E-TOP UNION, INC.
- F. HOFFMANN - LA ROCHE
- FISHER & PAYKEL HEALTHCARE
- FLAEM NUOVA SPA
- FLEXICARE MEDICAL LTD.
- FLUIDDA NV
- FOSHAN MIC MEDICAL TECHNOLOGY CO., LTD.
- FRESENIUS MEDICAL CARE
- FUJIFILM SONOSITE EUROPE
- GALILEO NOVOTEC MEDICAL
- GANSHORN MEDIZIN ELECTRONIC GMBH
- GCE GROUP
- GE HEALTHCARE GMBH
- GERATHERM RESPIRATORY GMBH
- GLAXOSMITHKLINE
- GRIFOLS
- HANS RUDOLPH, INC.
- HCMED INNOVATION CO., LTD.
- HEINEN + LÖWENSTEIN GMBH & CO., KG
- HILL ROM
- HSINER CO., LTD.
- IBSA INSTITUT BIOCHEMIQUE SA
- ICARDIAC TECHNLOGOIES, INC.
- INSMED INCORPORATED
- INSPIRE MEDICAL SYSTEMS, INC.
- INTERSURGICAL LTD.
- JIANGSU YUYUE MEDICAL EQUIPMENT & SUPPLY CO., LTD.
- KAPITEX HEALTHCARE LTD.
- KARL STORZ GMBH & CO., KG
- KOO EUROPE SRL
- KORUST KOREA ULTRA SOUND TECHNOLOGY CO., LTD.
- LEUFEN MEDICAL GMBH
- LINDE AG, LINDE HEALTHCARE
- LITTMANN/3M HEALTH CARE
- LÖWENSTEIN MEDICAL TECHNOLOGY GMBH & CO., KG
- M3 (EU) LTD.
- MADA SPIROMETRY FILTERS SRL
- MCROBERTS
- MD DIAGNOSTICS LTD.

Respiratory

- MEDCHIP SOLUTIONS
- MEDICAL DEVELOPMENTS INTERNATIONAL
- MEDICAL EQUIPMENT EUROPE GMBH
- MEDICINES EVALUATION UNIT
- MEDI-GLOBE GMBH
- MEDISOFT
- MEK-ICS CO., LTD.
- MERCURY MEDICAL
- METHAPHARM SPECIALITY PHARMACEUTICALS
- MGC DIAGNOSTICS
- MICOMME MEDICAL TECHNOLOGY DEVELOPMENT CO., LTD.
- MICROBASE TECHNOLOGY CORP
- MIR - MEDICAL INTERNATIONAL RESEARCH
- MERCK SHARP AND DOHME LTD.
- MUNDIPHARMA INTERNATIONAL LTD.
- NATUS NEUROLOGY, INC.
- NDD MEDIZINTECHNIK AG
- NIGHTBALANCE
- NONIN MEDICAL
- NOVARTIS PHARMA AG
- NOVATECH SA
- NOX MEDICAL
- NSPIRE HEALTH LTD.
- NUTRICIA LTD.
- OLYMPUS EUROPA SE & CO., KG
- ONIRIS
- ORACLEBIO LTD.
- ORION PHARMA
- OXFORD IMMUNOTEC LTD.
- OXYNOV, INC.
- PARI GMBH
- PENTAX EUROPE GMBH
- PFIZER INTERNATIONAL OPERATIONS
- PHILIPS
- PNEUMACARE LTD.
- PNEUMRX LTD.
- POWERBREATHE INTERNATIONAL LTD.
- PRECISION MEDICAL, INC.
- PULMONE ADVANCED MEDICAL DEVICES LTD.
- PULMONX INTERNATIONAL SÀRL
- QIAGEN
- RADIOMETER MEDICAL APS
- RAPTOR PHARMACEUTICALS
- REGENERON
- RESMED
- RESPIRATORY CLINICAL TRIALS LTD.
- REVENT MEDICAL TECHNOLOGY CO., LTD.
- RICHARD WOLF GMBH
- ROCKET MEDICAL PLC
- SALTER LABS
- SANOFI GENERICS
- SANOFI GENZYME
- SCALEO MEDICAL
- SEFAM
- SENTEC AG
- SEOIL PACIFIC CORP
- SEVEN DREAMERS LABORATORIES, INC.
- SGS
- SHENYANG RMS MEDICAL TECH LTD.
- SIMEX MEDIZINTECHNIK GMBH
- SHENZHEN DYMIND BIOTECHNOLOGY CO., LTD.
- SHENZHEN HOMED MEDICAL DEVICE CO., LTD.
- SMTEC SPORT & MEDICAL TECHNOLOGIES SA
- SOCLEAN, INC.
- SOMNICS, INC.
- SOMNOMEDICS GMBH
- SRETT MEDICAL
- SYSMED CO., LTD.
- TEVA PHARMACEUTICALS EUROPE BV
- THE MENARINI GROUP
- THORASYS EUROPE UG
- TNI MEDICAL AG
- TRACOE MEDICAL GMBH
- TRUDELL MEDICAL INTERNATIONAL
- UNITED HAYEK
- UNITED THERAPEUTICS EUROPE LTD.
- VIDA DIAGNOSTICS, INC.
- VITALOGRAPH LTD.
- VITO NV
- VIVISOL SRL
- VRV SPA
- YURIA-PHARM LLC
- ZAMBON SPA