TREATMENT STRATEGIES
RESPIRATORY

Volume 3 Issue 2

- Asthma
- COPD
- Cystic Fibrosis
- Lung Cancer
- Pulmonary Hypertension
- Sleep Apnoea
- Ventilation

Articles include:

Dual Virus-bacteria Infections in COPD Exacerbations

Improvements in Lung Cancer

Pulmonary Hypertension in Cystic Fibrosis

Patient Ventilator Asyncronies in Neuromuscular Disease During Nocturnal Non Invasive Ventilation

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TREATMENT STRATEGIES RESPIRATORY

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Welcome...

I am pleased to welcome you to the latest edition of *Treatment Strategies - Respiratory. Treatment Strategies - Respiratory* enables time-pressured professors and doctors to stay abreast of key advances and opinions. It will provide healthcare practitioners with the opportunity to network with colleagues and discuss the latest thinking and research breakthroughs.

We have included balanced and comprehensive articles written by the leading specialists and professors that address the most important issues and developments in the field of respiratory. Key topical areas include asthma, COPD, cystic fibrosis, lung cancer, pulmonary hypertension and sleep apnoea.

In addition, there will also be a review of the European Respiratory Society (ERS) 2012 Annual Congress, which this year took place in Vienna. This review includes the latest updates from the industry featuring all the highlights and exhibitors from the conference. The congress featured a plethora of sessions, with highlights including hot topic and grand round sessions, which offer the opporunity to debate and discuss a range of important issues. The European Respiratory Society is the leading professional respiratory organisation in Europe, which has over 10,000 members from 100 different countries. The congress offers an ideal forum to discuss the latest breakthroughs, research, treatment options and products within the field of respiratory.

We hope that this information will be useful for the readers and will act as a forum in which to present the constantly evolving and developing findings from the respiratory field. We hope to provide the highest standards for the series. It would be most helpful if you would provide us with your feedback. By working with your opinions, we will ensure that the *Treatment Strategies Series* will become one of the most useful publications in healthcare.

We are looking forward to meeting you next year in Barcelona for the 2013 ERS Annual Congress.

Nigel Lloyd, Editorial Director

The Cambridge Research Centre wishes to thank the following societies for their assistance and involvement in this publication.

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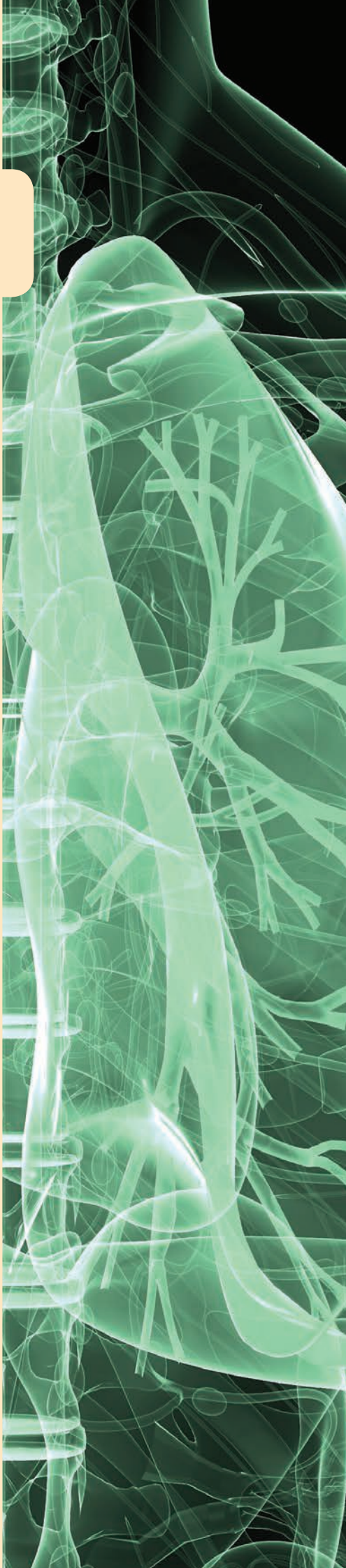

EDITORIAL ADVISORY PANEL

Foreword

Marion Delcroix
Department of Respiratory Diseases, University Hospitals of Leuven, Leuvens

Welcome to the latest issue of T*reatment Strategies – Respiratory*. We hope that this edition continues the resounding success of the last, and fulfils its aim of bringing healthcare professionals the latest updates and developments within the field of respiratory.

Pulmonary arterial hypertension (PAH) is a rare and severe disease characterised by progressive narrowing and occlusion of precapillary pulmonary arteries. Increased pulmonary vascular resistance ultimately leads to right heart failure and death. PAH is either idiopathic, heritable or associated to other conditions such as congenital heart or connective tissue diseases. Although it qualifies as an orphan disease by its low prevalence of 30-50 cases per million inhabitants, incredible resources have been put in the development of PAH therapies. Over the last 15 years, 7 drugs have shown efficacy, improving symptoms and exercise capacity over a period of 3 to 4 months. Meta-analysis and registries also suggest improved long-term outcome. However, mortality is still unacceptably high with an average rate of 8-10% per year. Moreover, health related quality of life (HRQoL) in PAH is impaired for several reasons, such as functional limitation, adverse effects from medication and parenteral drug delivery systems, uncertainty about the future, limited knowledge of the disease and therapy in local medical and emergency settings, and severe functional abnormalities for those with connective tissue diseases. Measured with the SF-36 questionnaire, the impairment in PAH is similar to spinal cord injury and metastatic cancer[1] and drug therapy only improves the physical domains of HRQoL.

PAH expert guidelines provide recommendations about drug use and surgical treatment but do not consider global patient care. Patient HRQoL nor care organisation are taken into account. An attempt to define expert centres for PAH has been made in the ESC/ERS guidelines, requiring multidisciplinary/multiprofessional care, access to surgery and lung transplantation, a minimal number of patients followed and participation to collaborative clinical research.[2] However, we miss recommendations on how to handle medical/surgical potentially life-threatening urgencies, as well as highly prevalent pain and psychological symptoms, such as depression, stress and anxiety, related to the disease or its treatment. On the other hand, the European Medical Agency "guideline on the clinical investigations of medicinal products for the treatment of PAH", strongly emphasises the importance of including a measurement of patient perception of the impact of his disease and its treatment on his daily life, physical, psychological and social functioning and wellbeing in current clinical trials.[3] Palliative care, as defined by the World Health Organisation, is an approach aiming to improve QoL of patients and families facing the problems associated with a life-threatening illness, without intention to hasten death. When started early, it has been shown to improve QoL, but also survival length in patients with metastatic small cell lung cancer,[4] and should be evaluated in PAH in order to improve the other than physical domains of HRQoL.

We hope that you enjoy the latest edition of *Treatment Strategies – Respiratory* and the papers that have been included. Respiratory is one of the most dynamic areas of medicine, in which new discoveries and developments are constantly being made. We hope that the publication gives an in-depth overview of some of the most important and interesting topics within the field today.

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ERS 2012 Annual Congress Review

01 - 05 September 2012 - Vienna

European Respiratory Society (ERS) Annual Congress Review

INSIDE...

The Meeting

The Exhibition

Hannah Corby, *Treatment Strategies*, takes a look over a number of key sessions, as well as spotlighting several stands and products being demonstrated at the exhibition. We then follow with papers and reviews which give a brief insight from a number of sessions, highlighting findings that will have direct repercussions on clinical practise that are still very much being discussed.

The European Respiratory Society is the leading professional respiratory organisation in Europe, which has a wide scope covering both basic science and clinical medicine. It has over 10,000 members from 100 different countries, with members being made up of individuals working within a number of areas within respiratory health. These include medical practitioners, respiratory specialists, scientists and allied health professionals. The society seeks to alleviate suffering from respiratory disease, and promote lung health through research, the sharing of knowledge and medical and public education. The ERS Annual Congress offers the opportunity to put these aims into practise and to discuss the latest breakthroughs, research, treatment options and products within the field of respiratory.

The outstanding reputation of the ERS is largely derived from the exceptional programme offered at its annual congress.

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The conference was held at the Reed Messe Wein conference centre

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This programme is made up of a range of different sessions, including symposiums on topics such as Infection Control of Respiratory Pathogens and Contributing Factors to Pulmonary Hypertension, as well as seminars, poster and oral presentations. HERMES examinations in both adult and paediatric respiratory diseases are available, as are a wide range of postgraduate courses on areas such as Pulmonary Fibrosis and Progress in the Treatment of COPD.

Within the programme there are also Hot Topic sessions, which focus on a particularly interesting or up and coming areas within the respiratory field. Topics covered include The Bacterial Microbiota: Implication for Health and Disease, a joint session with the World Allergy Organisation and Respiratory Support in Children and Young Adults. In addition, Grand Round sessions also form an important part of the programme, as it offers the opportunity for attendees and experts to interact and debate specific issues and research. This year, these Grand Round sessions focus upon Paediatrics, Respiratory Infectious Diseases and How to Diagnose and Manage NSCLC with New Drugs.

The congress also gives the opportunity to honour those who have made an important contribution in the field, and several award ceremonies are held here. These include the ERS Award for Rare Pulmonary Diseases, the ERS COPD Research Award and the award for Achievement in the Field of NSCLC.

This year the ERS Annual Congress is held in Vienna. Vienna is both the largest city and the capital of Austria, as well as one of the country's nine states. It is located in northeastern Austria, at the easternmost extension of the Alps in the Vienna Basin. It has a population of 1.731 million and it is the 9th largest city in the EU. The city is rich in history, and has its roots in early Celtic and Roman settlements. It was both a medieval and baroque city, and was the capital of the Austro-Hungarian Empire. In 2001, the city centre was designated a UNESCO World Heritage Site.

Vienna is also Austria's cultural, economic and political centre, as well as being the main centre of education. It is home to a large number of universities and professional colleges, including many international establishments. In 2012 it was ranked 2nd in a study of the world's most livable cities.

As home to the world's first psychoanalyst Sigmund Freud, the city is often described as the 'city of dreams', as well as the 'city of music' due to its long musical tradition. Vienna was the leading European music centre from the great age of Viennese classicism to the early part of 20th Century. It has been host to a range of influential composers such as Brahms, Bruckner, Mahler and Richard Strauss.

In addition, Vienna has a long tradition of art and culture, including theatre, opera, classical music and fine arts. Indeed, the Burgtheater is considered one of the best theatres in the German-speaking world. The city was ranked 1st globally for culture and innovation in both 2007 and 2008, and attracts around 5 million visitors annually. Major tourist attractions in Vienna include the imperial palaces of the Hofburg and Schönbrunn, which is also home to the world's oldest zoo, Tiergarten Schönbrunn, as well as the Riesenrad in the Prater. The historic centre of Vienna is rich in architectural ensembles including Baroque castles and gardens, as well as 19th Century

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Ringstrasse, which is lined with grand buildings, monument and parks.

Furthermore, Vienna is famous for its culinary creations, in particular the production of the finest cakes and desserts. These include hot apple strudel, sweet pancakes and Sachertorte. It is also one of the few remaining world cities which has its own vineyards, and the dry white wine Grüner Veltliner is the most widely cultivated wine in Austria. Beer is also of importance in Vienna. The city has a single large brewery, Ottakringer, and more than ten microbreweries. Viennese cafés also have a long and distinguished history in Vienna, which dates back centuries. In the 19th Century, many famous writers, artists, politicians and scientists were constant coffee house patrons.

The conference was held in the Reed Messe Wein conference centre, a 'chameleon-like' exhibition centre which is uniquely transformable to meet event organiser's every need, a process aided by Reed Messe Wein's enthusiastic and knowledgable team. In 2011, almost 950,000 visitors and participants attended a total of 143 trade fairs and exterior events organised, staged or hosted by the Reed Exhibitions Messe Salzberg and the Reed Exhibitions Messe Wien. This level of expertise and experience, alongside the attractive and innovative venue, proved to be an ideal location for the ERS Congress.

Following on from the last successful edition, we have once again commissioned a number of authors to discuss the various sessions that took place across the five-days, spotlighted findings and research that were presented, as well as bringing you a round-up of the stands found within the lively exhibition hall.

Ex-Smokers Are Unstoppable

Austrian Woman Represents European Ex-smokers by Competing in the Lung Run at ERS Congress

At the start of the Lung Run – part of the 2012 ERS Congress, the European Commission's Dr Martin Seychell, alongside Sonja Wehsely, Executive City Councillor for Public Health and Social Affairs in Vienna will present the "Ex-Smokers are Unstoppable" campaign and its important role in keeping Europeans' lungs smoke-free. The European Respiratory Society (ERS) and the Austrian Society of Pneumology (ÖGP), organisers of the event, will hold the run under the slogan "Move Your Lungs". The "Ex-Smokers are Unstoppable" campaign supports the initiative and agrees that cardiovascular exercise plays an important role in preventing respiratory diseases.

The official face of the Ex-Smokers campaign in Austria, Elisabeth Liu, will take part in the Lung Run.
An example for the 28 million smokers across Europe, Ms Liu stopped smoking thanks to iCoach and does not regret it at all. Furthermore, her two daughters are proud of their "smoke-free and athletic mother!"

"Every year nearly 700,000 Europeans die from the smoking-related diseases, representing an unacceptable human cost and the largest avoidable health risk. We are acting now to change things and since the beginning of our campaign, almost a quarter of a million smokers across Europe, equivalent to 1 in every 500 smokers, have registered for iCoach and begun their journey to smoke free lives."

Martin Seychell

The "Ex-Smokers" campaign, launched by the European Commission in 2011, aims to support smokers across Europe quit and go on to lead 'Unstoppable' lives. Smokers are helped with tools such as the dedicated website (www.exsmokers.eu) and social media pages. They are further supported by the free online tool iCoach which provides professional tips and advice to help people kick the habit. Users receive regular emails to encourage them each step of the way towards a smoke-free life. An online forum enables smokers to support each other with inspirational stories.

A recent pan-European survey revealed that 33% of Austrians smoke, putting Austria above the European average of 28%. 61% of smokers throughout Europe want to kick the habit, but 39% have not tried yet. Here, Austria is below average: only 37% of the Austrian smokers have tried to quit. Via the Ex-Smokers campaign, the EC provides tailored assistance, to help Austrians improve their health record in Europe. One in every 1,000 Austrian smokers has currently signed up to iCoach.

For more information please visit www.exsmokers.eu

MucilAir™: A Premium 3D Human Airway Epithelia Reconstituted *in vitro* with Long Shelf-Life

Epithelix Sàrl, the Swiss biotech company specialising in tissue engineering has developed, provides and sells a unique 3D model of the Human Airway Epithelium, which is made of primary human cells isolated from the nasal cavity, the trachea and the bronchis. Cultured at Air-liquid Interface, it mimics the in vivo tissue of the human respiratory epithlium, including:

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Cilia Beating
Tight junctions
Active ion transport
Metabolic activity / detoxification (CYP450)
Cytokine / chemokine / metalloproteinase release

It is ready and easy to use, and has a very high batch to batch reproducibility. It is also fully differentiated and functional for more than one year.

MucilAir™ is available with several pathologies including normal, smoker, allergic rhiniis, asthma and COPD.

ERS Research Award on Idiopathic Pulmonary Fibrosis 2012

Through the support of the InterMune, the ERS offers a €7,500 award, which is given to a young investigator in recognition of achievement for advances and successful research in the area of respiratory medicine with focus on Idiopathic Pulmonary Fibrosis (IPF). The Award is to be used to further investigate in the area of IPF and will be partially given to the institution.

The 2012 Award was won by Dr Katerina Antoniou at the IPF Research Award ceremony on Tuesday 4 September 2012. Dr Katerina Antoniou, a former ERS Research Fellow, is Lecturer in Thoracic Medicine at the Medical School University of Crete.

Dr Antoniou has made important contributions to IPF research in the field of understanding the mechanisms and effects of interferon-gamma1b treatment, and into angiogenesis in the disease, as well as in sarcoidosis. The award was presented to Dr. Antoniou during a special session at the Annual Congress of the ERS being held in Vienna, Austria.

Giacomo Di Nepi, Senior Vice President and Managing Director of Europe for InterMune, said, "We are especially pleased to join with ERS to recognise the talent and dedication of a young researcher who is making meaningful advancements in our understanding of idiopathic pulmonary fibrosis (IPF), a relentless and devastating disease of the lungs. We congratulate Dr. Antoniou as the initial recipient of this grant, which will be awarded annually to a young researcher in recognition of their work to advance the field of respiratory medicine with a focus on IPF."

Dr. Antoniou said, "I would like to thank both ERS and InterMune for this award. I am honoured to be the first young investigator to receive this recognition and support for research in IPF. This award will enhance my research efforts in this puzzling and devastating disease. ERS twice made it possible for me to be an ERS fellow in the past. Now, InterMune is the first pharmaceutical company to support people that are working in IPF. I will try to do my best with this grant!"

The grant is to be used to conducted additional research, and a portion of the grant awarded to the researcher's institution.

Her current research work has two major aspects. Firstly, to investigate the possible role of bone marrow mesenchymal stem cells as therapeutic agents in IPF and rheumatoid lung. Building on her work to assess the molecular and expression characteristics and survival of such cells in rheumatoid arthritis and in IPF – and their role in pathogenesis – her group's current study aims to assess the characteristics of the stem cells in patients with rheumatoid arthritis-associated pulmonary fibrosis, to try to understand why IPF is restricted to the lung, while rheumatoid arthritis-associated fibrosis is a systemic disease.

Secondly, Dr Antoniou is investigating the role of the NALP3 inflammasome pathway in the pathogenesis of lung fibrosis, in IPF, UIP and NSIP to discover whether distinct inflammatory profiles between the diseases can explain the differences in pathogenesis, prognosis and treatment response. Early results suggest that IPF patients may have an impaired ability to activate the NALP3 pathway in response to infection.

With future projects planned to investigate the citrullination pathway in the pathogenesis of fibrotic lung disorder, and the regulation of microRNAs in HSV infection in IPF, Dr Antoniou's contribution to our understanding of IPF is only set to grow.

Other Award Highlights from the ERS 2012 Congress

COPD Research Award 2012 - Supported by Boehringer Ingelheim

Dr John Hurst's research into COPD exacerbations focuses on high-risk patients and high-risk time periods. He was lead author on the first study that demonstrated that the timing of COPD exacerbations is not random, a discovery that has major implications for clinical follow-up and may lead to new approaches to reducing risk of exacerbation. Dr Hurst was also lead author of a 2010 study that confirmed the presence of a 'frequent exacerbator' phenotype in COPD.

ERS Romain Pauwels Research Award 2012 - Supported by GlaxoSmithKline

The 2012 ERS Romain Pauwels Research Fund is awarded to Dr Carlos Miguel Farinha for his research into the different aspects of CFTR biology, study of the mechanisms of rescue of F508del-CFTR and elucidation of the role of novel CFTR interactors. Dr Farinha is Assistant Professor of Molecular Genetics and Biochemistry at the University of Lisbon's Department of Chemistry and Biochemistry.

Maurizio Vignola Award for Innovation in Pneumology 2012 - Supported by the Chiesi Foundation

The 2012 winner of the Maurizio Vignola Award is Dr Tom Wilkinson of the University of Southampton, UK, for "Preexisting influenza-specific CD4+ T cells correlate with disease protection against influenza challenge in humans", published in *Nature Medicine* in January (vol. 18, pp. 274–280).

ERS Award for Rare Pulmonary Disease 2012 - Financially Supported by GlaxoSmithKline

The 2012 Awardee, Dr Claire Shovlin, runs the Pulmonary Endothelial research group, is the co-ordinator for the respiratory module of the Imperial College MBBS Graduate Entry Programme, and as part of her clinical portfolio, runs a national clinic for people with hereditary haemorrhagic telangiectasia (HHT) and pulmonary arteriovenous malformations.

ERS 2012 Award for Achievement in the Field of Non Small Cell Lung Carcinoma - Financially Supported by AstraZeneca

2012 Award for Achievement in the field on NSCLC was given to Professor Jens Benn Sørensen, head of research activities for thoracic oncology at the Finsen Centre, Copenhagen, for his trials focusing on predictive biomarkers for customised treatment in NSCLC, mostly for patients with advanced (metastatic) disease.

Lifetime Achievement Award in Pulmonary Arterial Hypertension 2012 - Supported by Actelion Pharmaceuticals Ltd

Dr Ralph Schermuly is associate professor in experimental pneumonology and pathophysiology at the Justus-Liebig University, Giessen, Germany. He is currently project leader in clinical research groups on respiratory insufficiency and pulmonary fibrosis, as well as in a collaborative research centre on cardiopulmonary vasculature.

Sir John Vane Award for Innovation in Pulmonary Vascular Research 2012 - Supported by United Therapeutics Europe Ltd

The 2012 Sir John Vane Award is given to Professor David Montani, for "C-kit positive cells accumulate in remodeled vessels of idiopathic pulmonary hypertension", published in the *American Journal of Respiratory and Critical Care Medicine* in July 2011 (vol. 184, pp. 116–123).

ERS 2012 Assembly Lifetime Achievement Awards:

The ERS Scientific Committee has chosen to honour Professors Jean-François Cordier, Rik Gosselink and Robert Naeije with the 2012 Lifetime Achievement Awards.

The ERS Assembly Lifetime Achievement Awards 2012. were presented during the related Assembly Members' Meetings.

Best Poster Competition

For the first time in 2012, a Best Poster Competition was organised. In each assembly, the best abstracts have been identified based on the outcome and results of the peer-review. The results were announced during the Young Scientists' Networking evening.

Dahai Zheng for his abstract "Clara cells serve as the progenitors to regenerate alveolar epithelium in response to severe lung injury"

Christian Gerges for his abstract "Pulmonary vascular gradient: A predictor of prognosis in pulmonary hypertension due to left heart disease"

Thierry Berghmans for his abstract "A mRNA signature predicts outcome of patients (pts) with advanced non small cell lung cancer (NSCLC) treated with cisplatin (C) and vinorelbine (V): A ELCWP prospective study."

OMRON Healthcare Introduces the Powerful CompAIR™ Pro Nebuliser

Minimised operating time allows medical staff more quality time with their patients

OMRON Healthcare Europe introduces their newest innovation in clinical respiratory therapy, the high-output CompAIR™ Pro (NE-C900) nebuliser with minimised operating time, giving medical staff more quality time with their patients. The CompAIR™ Pro is OMRON's first compressor-based nebuliser to produce 7 liters/min at a pressure of 100 kPa, yielding a medication output of up to 0.4 ml/min. The CompAIR™ Pro is simple to operate, and thanks to its high-output performance, medical staff can maximise the quality and level of patient care.

"OMRON Healthcare is dedicated to providing complete healthcare management to every patient by offering reliable treatment and building healthier lives for all," says Josip Stojic of OMRON Healthcare Europe's Respiratory Therapy Division. "The CompAIR™ Pro nebuliser is a valuable addition to OMRON Healthcare's extensive line of professional-grade nebulisers. It requires less operating time, is user-friendly and allows medical professionals to dedicate more time to their patients."

The CompAIR™ Pro uses OMRON's two-part Smart Structure™ kit, resulting in a simplified design with fewer parts to clean and maintain, making the device more hygienic and allowing medical staff to spend more time on direct patient care.

The high-performance CompAIR™ Pro nebuliser is ideally suited for use in both hospitals and clinics. With its integrated grip handle, the CompAIR™ Pro can be transported quickly and easily and requires little storage space. The CompAIR™ Pro also comes equipped with masks for both adults and children, and all parts that contact the patient can be disinfected for use in multiple patients.

The CompAIR™ Pro Nebuliser will be launched in various European markets between July and September 2012. Please see the website for more details.

Olympic Rowing Star Scoops Lung Health Award

Norwegian Olympic rowing star, Olaf Tufte, has been awarded the annual European Lung Foundation award in recognition of his sporting success on the international stage, despite living with a lung condition.

Olaf received the award on 1st September 2012 at the annual European Respiratory Society Congress in Vienna. The award is bestowed upon people who have made a significant contribution to championing lung health.

Olaf developed asthma during years of hard work in bad environments on the family farm and hard training in all kinds of weather, but has just competed in his fifth Olympic Games in London – a feat achieved by few rowers. Olaf has also recently headed up the World Spirometry Day (WSD) campaign as a Lung Champion.

Organised by the Forum of International Respiratory Societies (FIRS), the WSD campaign aimed to raise awareness of the benefits of exercise for lung health and celebrate the achievements of individuals who have succeeded in a sporting activity, despite living with a lung condition.

A survey, conducted by the FIRS, revealed a lack of understanding about how to manage lung disease, with 70% of respondents believing that people with lung disease were unable to undertake even moderate exercise like swimming or going to the gym. However, in reality, physical activity can help to manage and improve the symptoms of lung disease such as breathlessness, even in the most severe cases.

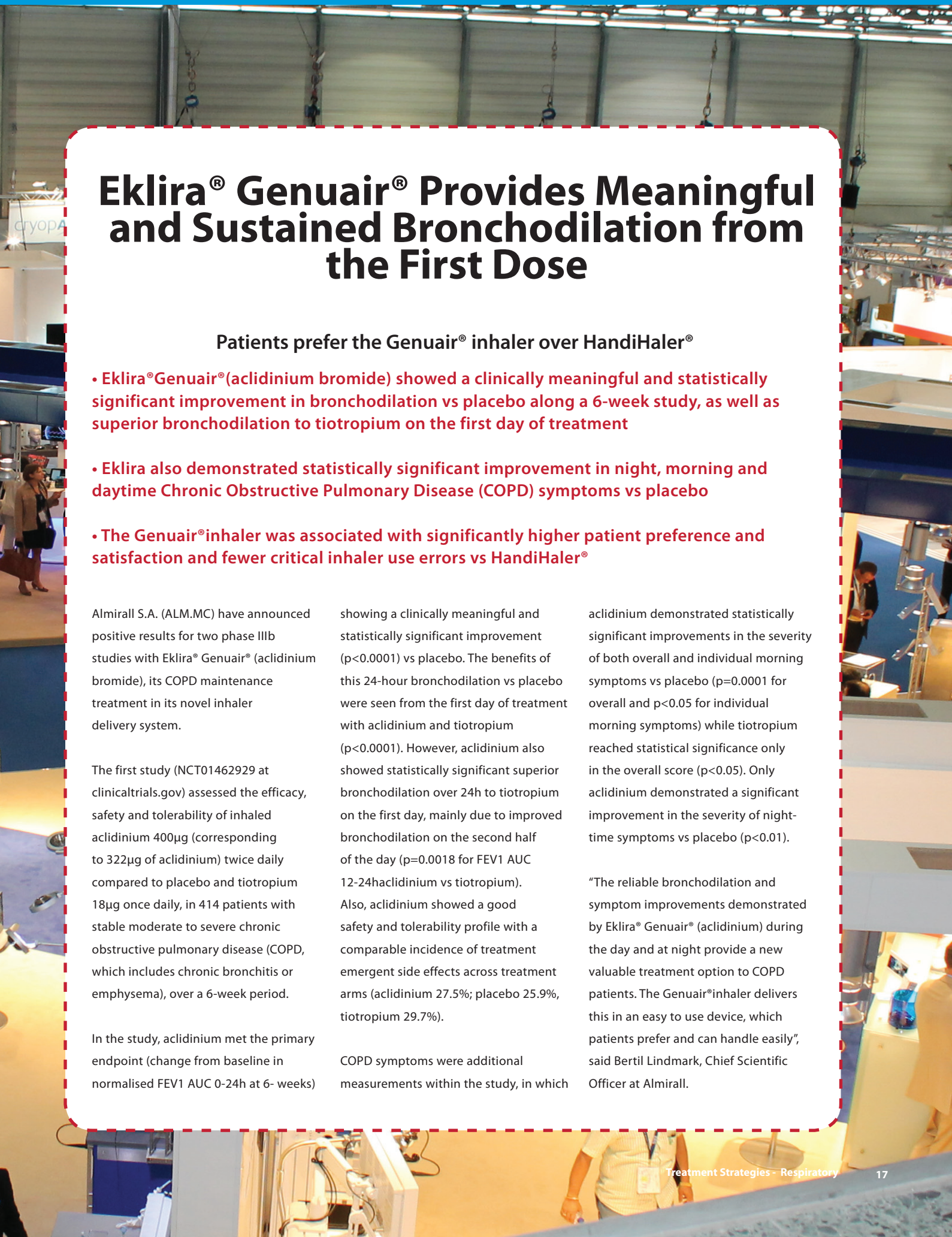
> "I'm delighted to have received the ELF award and I hope it can inspire others in my position to get involved in exercise or sport, at any level.
>
> "I am determined not to let my asthma limit me or restrict my ambitions. Instead, I see it as one challenge among many that I need to master in order to come top in my sport. People with lung conditions can lead healthy, active lives – if they take steps to ensure their condition is identified early enough and treated well."
>
> Olaf Tufte

Olaf accepted the award on behalf of the 30 Lung Champions whose achievements were showcased during the campaign.

When Olaf is not competing on the world stage, he works on his family's grain and forestry farm, which involves daily, strenuous work out in the weather, crops, dirt and dust. These conditions could cause problems for a person with asthma, but Olaf is disciplined with managing his condition to enable him to carry out the work.

His achievements include two gold medals in the Beijing and Athens Olympics in the single sculls and one silver medal at the Sydney Olympics in the double sculls. He finished 9th in the Men's Single Sculls race at London 2012, out of 33 initial competitors.

Chair of the European Lung Foundation, Monica Fletcher, said: "Olaf is a true champion and does not let his asthma limit or impact on his dedication to his goals. As the face of the World Spirometry Day campaign, we wanted to recognise Olaf's hard work at achieving his ambitions and inspiring the next generation of athletes. Exercise is such an important part of managing asthma and we hope others with the condition will be motivated by Olaf's attitude to reaching the peak of his sport."



Eklira® Genuair® Provides Meaningful and Sustained Bronchodilation from the First Dose

Patients prefer the Genuair® inhaler over HandiHaler®

• Eklira®Genuair®(aclidinium bromide) showed a clinically meaningful and statistically significant improvement in bronchodilation vs placebo along a 6-week study, as well as superior bronchodilation to tiotropium on the first day of treatment

• Eklira also demonstrated statistically significant improvement in night, morning and daytime Chronic Obstructive Pulmonary Disease (COPD) symptoms vs placebo

• The Genuair®inhaler was associated with significantly higher patient preference and satisfaction and fewer critical inhaler use errors vs HandiHaler®

Almirall S.A. (ALM.MC) have announced positive results for two phase IIIb studies with Eklira® Genuair® (aclidinium bromide), its COPD maintenance treatment in its novel inhaler delivery system.

The first study (NCT01462929 at clinicaltrials.gov) assessed the efficacy, safety and tolerability of inhaled aclidinium 400µg (corresponding to 322µg of aclidinium) twice daily compared to placebo and tiotropium 18µg once daily, in 414 patients with stable moderate to severe chronic obstructive pulmonary disease (COPD, which includes chronic bronchitis or emphysema), over a 6-week period.

In the study, aclidinium met the primary endpoint (change from baseline in normalised FEV1 AUC 0-24h at 6- weeks) showing a clinically meaningful and statistically significant improvement ($p<0.0001$) vs placebo. The benefits of this 24-hour bronchodilation vs placebo were seen from the first day of treatment with aclidinium and tiotropium ($p<0.0001$). However, aclidinium also showed statistically significant superior bronchodilation over 24h to tiotropium on the first day, mainly due to improved bronchodilation on the second half of the day ($p=0.0018$ for FEV1 AUC 12-24haclidinium vs tiotropium). Also, aclidinium showed a good safety and tolerability profile with a comparable incidence of treatment emergent side effects across treatment arms (aclidinium 27.5%; placebo 25.9%, tiotropium 29.7%).

COPD symptoms were additional measurements within the study, in which aclidinium demonstrated statistically significant improvements in the severity of both overall and individual morning symptoms vs placebo ($p=0.0001$ for overall and $p<0.05$ for individual morning symptoms) while tiotropium reached statistical significance only in the overall score ($p<0.05$). Only aclidinium demonstrated a significant improvement in the severity of night-time symptoms vs placebo ($p<0.01$).

"The reliable bronchodilation and symptom improvements demonstrated by Eklira® Genuair® (aclidinium) during the day and at night provide a new valuable treatment option to COPD patients. The Genuair®inhaler delivers this in an easy to use device, which patients prefer and can handle easily", said Bertil Lindmark, Chief Scientific Officer at Almirall.

Continued from page 17

A second study (NCT01385696at clinicaltrials.org), which is being presented at ERS as a poster (P2177) on 3rd September, was conducted in 130 randomised COPD patients, evaluating device preference, satisfaction and critical errors showed that a significantly higher proportion of patients expressed a preference for the Almirall's Genuair® inhaler vs HandiHaler® (*) (79.1% vs 20.9% respectively; p<0.0001) which was consistent with findings observed in the first study reported above. Patients were also more satisfied using the Genuair® than HandiHaler® (p<0.0001). Importantly, critical errors were significantly less frequent with Genuair® (p<0.0001),with only 10.5% of patients making one or more critical errors versus 26.7% for HandiHaler®.

Aclidinium was approved in the USA and in Europe in July 2012 for the maintenance treatment of COPD. In Europe, it will be marketed by Almirall under the trade name Eklira®Genuair®and by Menarini under the name Bretaris®Genuair®.

Additionally, a Phase III clinical development programme of a fixed dose combination of aclidinium plus formoterol twice daily is currently underway, also using the Genuair® device.

Air Liquid Medical Systems Launch Monnal ® T60 fan

Air Liquide Medical Systems, developer and manufacturer of medical equipment for respiratory assistance launches its new transport ventilator Monnal ® T60, the latest range Monnal ®

The Monnal ® T60 fan has been designed to meet the greatest needs and challenges facing medical teams. In emergency situations, these teams need medical equipment which has high levels of autonomy and performance to ensure both the continuity and quality of care offered to children and adults under respiratory assistance.

Extensive testing has showed that Monnal ® T60 resists the harshest conditions in air and ground transportation. The Monnal® T60 also offers a range of accessories with which to attach the fan at different locations inside and outside the hospital.

Both lightweight and compact, the Monnal ® T60 is the transport ventilator lightest in its class, weighing less than 3.7 kg. Monnal ® T60 has a battery life of 5 hours by interchangeable batteries, and a patented micro-blower.

Monnal ® T60 is recognised for its high level of ergonomics and user interface reference for a common Monnal ®. Performance in invasive and noninvasive ventilation, as well as complete monitoring, were at the heart of its development.

For more information visit www.airliquide.com

Study Finds Increase in Number of Non-smokers Being Diagnosed with Lung Cancer

There has been an increase in the number of non-smokers being diagnosed with non-small cell lung cancer, according to new findings.

The report, which were presented on 4th September 2012 at the European Respiratory Society's Annual Congress in Vienna, also found an increase in the number of women being diagnosed with the condition.

Little is known about risk factors that can cause lung cancer in non-smokers, although recently the World Health Organisation (WHO) confirmed earlier this year that exhaust fumes from diesel engines were a cause of lung cancer.

Over the last decade, the management of lung cancer has changed considerably with new drugs and new diagnostic techniques being used. Researchers from the French College of General Hospital Respiratory Physicians aimed to examine the effect of these changes and understand the incidence and effects of lung cancer amongst the population.

They studied 7,610 people with lung cancer and 7,610 new cases of lung cancer in France in 2010; 6,083 had non-small cell lung cancer. The study follows on from a similar investigation in 2000, which also examined the characteristics of new cases of lung cancer.

Researchers collected background information on each patient, including age, smoking history, the histology of their cancer, which involves analysing tissue to understand variations in the disease, and the stage of their lung cancer upon diagnosis.

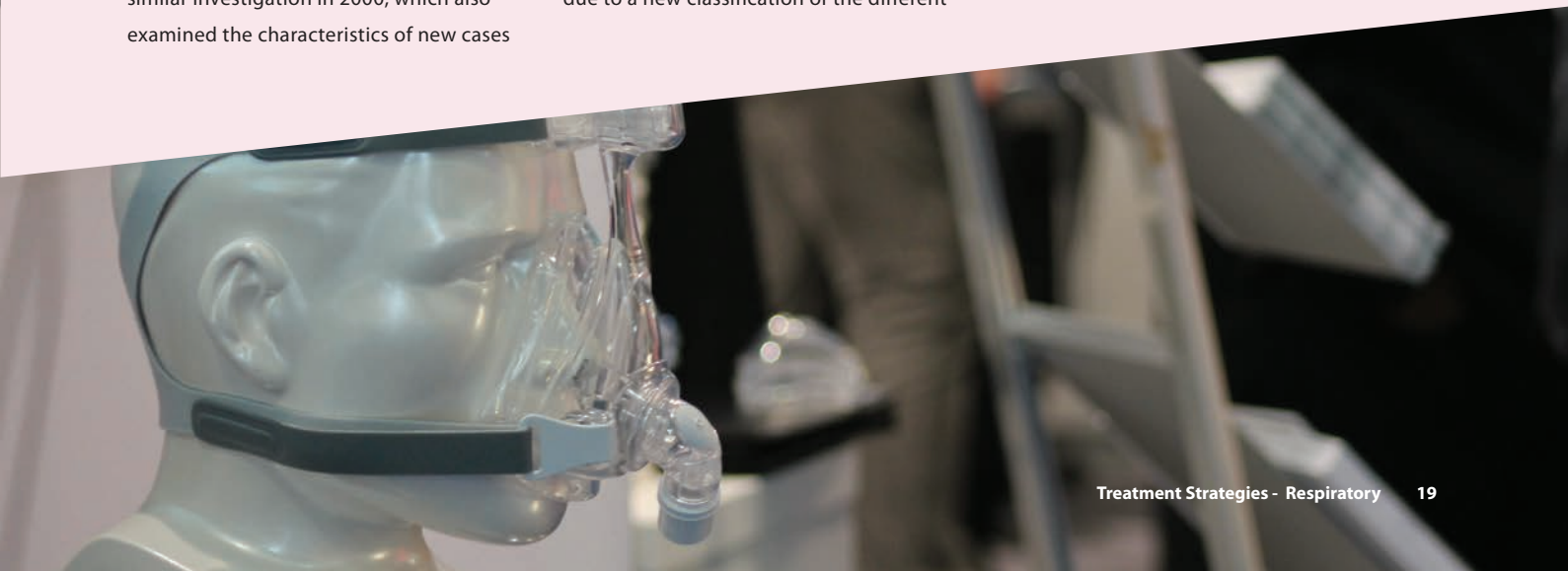
The results found an increase in the number of women and non-smokers developing lung cancer. 11.9% of the lung cancer cases in the study were non-smokers, which had also increased from 7.9% from 10 years previously. 24.4% of lung cancer patients in the 2010 study were female; an increase from 16% in 2000. When looking at the female smokers or former-smokers in the study, lung cancer rates had barely changed from 64% in 2000 to 66% in 2010. This figure had decreased in men, in addition to the rate of male never-smokers also increasing.

Additionally, the study also found that 58% of people with lung cancer were diagnosed at stage 4 of the disease. This is the most advanced stage of the disease, when the cancer has spread to both lungs, or another part of the body. This marks an increase of 15 percentage points from 43% in 2000, although authors believe this could be due to a new classification of the different stages of the disease. The study also found a change in the type of lung cancer with an increase in the number of people developing adenocarcinoma from 35.8% to 53.5%.

Lead author, Dr Chrystèle Locher, said: "We have seen from these results the change in lung cancer over the last 10 years. Not only has there been an increase in the number of women and non-smokers contracting the disease, but there has also been an increase in the number of cases diagnosed in stage 4 of the illness.

"We recently saw that the WHO have classified diesel fumes as carcinogenic, but more research is needed to understand other factors that could contribute to lung cancer in non-smokers. Anti-smoking campaigns must also target women more specifically, as we can see little change in lung cancer rates caused by smoking in women.

"It is also important to note changes in the type of lung cancer. The prevalence of cases of adenocarcinoma lung cancer is growing and further research is needed to understand the characteristics of this form of the disease."



Hoffrichter Respiration and Ventilation Therapies

Hoffichter offers a wide range of respiration and ventilation therapies which aim to offer an individualised treatment programme

Respiration Therapy

The Hoffrichter respiration therapy devices, to be used in sleep, aim to contribute to the decomposition of debilitating breath resistance in short sleep apnea, and to improve the general lung performance. Due to the many setting possibilities and different therapy modes, an individualised treatment programme can be achieved.

The VECTOR et is a respiration device with powerful therapy properties and extraordinary design. This device series is very silent despite its powerful turbine, and it is easy-to-operate thanks to its clearly arranged user interface. Respiratory therapy meets design in this perfect combination of comfort and functionality.

The TREND II is the newest device generation of Hoffrichter GmbH. This series features a combination of both modern technology and high quality material which is most commonly used for housing. The series adds a new glamour to respiration therapy.

The new design of Point 2 gives the smallest Hoffrichter respiration therapy device a fresh look. Its stable therapy pressure and extreme low noise level ensure a safe and comfortable use.

Ventilation

TRENDvent and CARAT are the specialist devices for pressure- and volume controlled home care ventilation. Various ventilation modes are available for an individual therapy adaptation to the requirements of the patient in the field of invasive and non-invasive ventilation.

TRENDvent was developed for the pressure-controlled home ventilation and respiration therapy of both adults and children, who are not yet completely dependent on mechanical ventilation. Various ventilation modes enable individual adjustment of the therapy to the requirements of the patient from a respiratory volume of 50 ml, in invasive and non-invasive ventilation.

CARAT I has to be used with a single line patient circuit, whereas CARAT II is suitable to be used with a double line patient circuit. The application of a single line patient circuit is also possible and is recognised by the device automatically.

We offer different accessories for our ventilator CARAT for a effective using. AKKUPACK uni (External battery) Functional bag Alarmbox (Remote alarm box) APM (Airflow-Pressure-Meter - service device) CaratControl (Powerful Software).

For more information visit www.hoffrichter.de

AirPROM: Improving the Treatment of Airway Diseases

Airway diseases affect the lives of over 500 million people around the world. Diseases such as asthma and chronic obstructive pulmonary disease (COPD) can cause symptoms including wheezing, coughing and breathlessness. Current methods to treat these diseases are inadequate due to the incomplete understanding of the pathophysiology, and the lack of recognition of the significant disease heterogeneity in other words, one size does not fit all. In addition clinicians are frequently being introduced to new treatments, which makes it even harder for doctors to select the best treatment to meet an individual's need.

The AirPROM project brings together existing clinical consortia (EvA FP7, U-BIOPRED IMI and BTS Severe Asthma), with expertise in physiology, radiology, image analysis, bioengineering, data harmonisation, security and ethics, computational modelling and systems biology. By developing digital models of the lungs, the project will help scientists look at how air flows through the airways in people with COPD and asthma. They will be able to use these models to test new treatments to see how the air ways of different people respond to each treatment.

The overall aim of the project is to develop more personalised treatments to help improve quality of life for people with COPD and asthma.

Analysis from results gathered from patients indicates that by using diagnostic tests it is possible to identify where treatments can be tailored on an individual basis. The benefit of using tailored treatments is twofold in that patients receive a more specialised level of care and clinicians save time in diagnosing and treating the airways disease.

The Airprom Project Methodology

Researchers will carry out a range of investigations including:

- Blood tests to look at DNA
- Taking samples from cells in the airways
- Lung function tests
- CT and MRI scans

How is AirPROM Unique?

The topic of personalised, or tailored, medicine is increasingly becoming a key area for research. The AirPROM project is part of this field of research, but it is also unique in both its approach to collecting data and the large amount of data that will be used. It is common of research studies to categorise participants by simply looking at the positive and negative results of particular tests they have taken such as blood tests and lung function tests. The AirPROM project is using a new mathematical process to group participants by linking together results from a number of different tests.

What will this Mean for People with Airway Conditions?

John Green, who has severe asthma and has taken part in the AirPROM trials, says: "The AirPROM project has the potential to make a tremendous difference to people with airway diseases. By gaining a full understanding of how asthma affects each individual, the findings have the potential to give people a better quality of life by providing the best treatment for that individual. When the results of the AirPROM study are put into practice, individuals will be able to understand their asthma better and therefore be in a better position to decide which treatments will be most beneficial for them. They will also find it easier to work out coping strategies, for example through exercise. When people are provided with the best treatment and are able to combine that with a positive attitude, they can more easily achieve their goals, despite their condition."

How Can you Get Involved in this Project?

You can attend an AirPROM living lab workshop. The living lab workshops aim to:

- Describe and explain in depth the concept of patient specific modelling
- Demonstrate the use of patient-specific models using attendees submitted example problems
- Teach the concepts of systems medicine

For more information visit www.airprom.eu

Philips Respironics Showcases Solutions for Better Sleep and Breathing at the ERS Congress 2012

Royal Philips Electronics will showcase respiratory innovations to help manage long term health conditions such as sleep disordered breathing and obstructive and restrictive lung diseases at the 2012 European Respiratory Society (ERS) Annual Congress, the largest scientific meeting for respiratory professionals, 1-5 September in Vienna.

For more than three decades, healthcare professionals have looked to Philips Respironics for a complete range of therapy solutions, including drug delivery, oxygen therapy and ventilation, to optimise the management of these patients. Philips Respironics is a pioneer in helping improve patient comfort and quality of life through improved therapies using unique clinically proven technologies. During ERS, Philips Respironics will showcase several existing and soon-to-be-released respiratory innovations.

New Respiratory Range of Products Unveiled at ERS 2012:

The BiPAP A40, a soon to be released bi-level ventilator capable of non-invasive and invasive pressure ventilation for patients suffering from obesity hypoventilation syndrome, COPD or neuromuscular diseases. This ventilator helps paediatric patients and patients with low inspiratory drive, by combining technological and comfort innovations with ease-of-use while increasing patients' support and mobility.

"The ERS 2012 Congress draws global attention to respiratory issues with broad societal and economic implications such as increased morbidity and high health costs. As part of our Allies in Better Sleep and Breathing initiative, we are committed to aligning with clinicians to provide integrated programs and science-based solutions that address rising incidences of obstructive sleep apnea and chronic obstructive pulmonary disease in adults, and asthma and neuromuscular diseases in adults and children, leading to better sleep, easier breathing and healthier lives for people of all ages."

Mats Dahlquist, Philips Home Healthcare Solutions International

The CoughAssist E70, a soon to be released mechanical in-exsufflation device, simulates a real cough and helps mobilise patients' secretions. Just like other Philips Respiratory devices, this portable system will also include full access to patient therapy information that allows the clinician to assess therapy efficacy and make the necessary adjustments.

Sami the Seal, Philips Respironics' first nebuliser compressor system for children, supports aerosol therapy compliance and encourages children with asthma to take their medication. Sami is paired with the SideStream nebuliser and Tucker the Turtle mask to help parents and caregivers achieve fast and efficient treatments. The device has been developed to withstand frequent use in hospital and is also a robust and reliable option for the home.

The SimplyGo is the first portable oxygen concentrator able to provide pulse-dose and continuous flow oxygen therapy up to 2 liters per minute. It can adapt to most oxygen patients' needs and weighs only 4.5 kg. SimplyGo enables patients to have the independance too enjoy time away from home.

NEW VacuAide Suction Unit from DeVilbiss Healthcare

DeVilbiss Healthcare is pleased to announce the introduction of the NEW VacuAide QSU portable suction device, which is planned for International and European launch at the end of September.

The NEW VacuAide QSU is quiet, easy to use and incorporates the following features and benefits:

- Low noise level without compromising suction performance
- High performance with a pressure range of between 50 - 550 mmHg and 27 l/ min air flow
- Simple to operate with a single on/off switch and easy-grip pressure adjustment gauge

New collection bottle design with flexible lid for ease of removal and integrated bacterial filter

Personal carry bag which allows the device to be operated without removing it from the bag

If you are interested in receiving further information regarding the new suction unit or wish to be contacted by a member of the sales team please email us at enquiries@devilbisshc.com

For more information visit www.devilbisshc.com

COPD & Malnutrition Explained in ERS Video

The European Respiratory Society (ERS) published a series of videos on the importance of nutrition assessment in the prevention and management of COPD.

The video "Dealing with Malnutrition in COPD" shows also a body composition test on a COPD patient using COSMED air displacement plethysmography system Bod Pod.

See the online video at:

www.ersvision.org/index.php/videos/dealing-with-malnutrition-in-copd

CASTAR "R" for Treatment of Respiratory Failure

Starmed Spa specialises in the design, manufacturing and sale of non-invasive ventilation devices to treat acue patients in ICU or other departments, such as pneumology, post-operative or emergency.

CASTAR "R" Adult-Ped is a single-patient device for treatment of respiratory failure:

- Cardiogenic pulmonary edema
- Non-cardiogenic pulmonary edema (A.L.I. - ARDS)
- Thoracic trauma
- Atelectasis
- Post-operative hypoaxemia
- Asthma
- COPD exacerbation
- Pre- and post-extubation respiratory support

Technical features:
- Made of biocompatible plastic material
- Single-patient
- Non-sterile
- 22M connectors compliant to ISO standard
- Weight about 380 gr
- Armpit fastening straps. Alternatively, straps can be fastened to an abdominal belt available among the accessories
- HYGIENIC antibacterial fabric protections lined with DUPONT COOLMAX
- Two sealed accesses for probes or catheters of 4-6.5 mm
- Latex-free
- Two-ways safety valve with automatic opening
- Airtight patient access port with cap
- Integrated cuffs which, if inflated, allow further reduction of the internal volume of the hood (about 3 litres)
- Airtight sealing of the system is ensured by an elastic membrane which does not adhere to the neck but to the upper part of patient's torso.

The device allows non-invasive pressure support ventilation, and can be well tolerated for extended periods. It is lightweight and comfortable, with a practical transparent mask. The Castar "R" also prevents decubitus ulcers which can be caused by face masks, and the endotracheal intubation overcomes the risks of infection. The device can be used in both the standing or supine positions, and is suitable for both adults and children.

ERS Annual Congress 2013

07 — 11 September 2013

Barcelona, Spain

The European Respiration Society is the leading respiratory organisation in Europe, which has a wide scope covering both basic and clinical medicine. The congress brings together a wide range of professionals with an interest in the field. The congress offers a varied programme, which includes symposiums, plenary lectures, morning seminars, meet the professor sessions, workshops and more.

Next year, the congress is held in Barcelona, the second largest city in Spain, which has become an important cultural centre and a major tourist destination. With some of the world's best beaches and a reputation for hosting world-class conferences and expositions, Barcelona is set to be an excellent location for the ERS Annual Congress in 2013.

For more information please visit

www.ersnet.org

Prevention of Exacerbations in COPD: Expanding Scope and Strategies

Introduction

Sanjay Sethi
(Buffalo, US)

Our understanding of exacerbations in chronic obstructive pulmonary disease (COPD) has changed dramatically in recent years. They were initially believed to be of little consequence but are now realised to be a major contributor to disease evolution and cost of healthcare provision to COPD patients, the major driver of which is hospitalisation.[1] In fact, exacerbations are believed to be responsible for around half of the total cost of COPD management, have a significant impact on patient quality of life[2, 3] and have been shown to lead to the loss of lung function over time.[4, 5] Exacerbations are also a major cause of mortality in advanced disease.[6]

In the recent large ECLIPSE study, patients experienced frequent exacerbations despite active treatment in tertiary care centres.[7]

Although progress has been made in the prevention of exacerbations in COPD, more still needs to be done and there is a recognised unmet clinical need in this aspect of COPD management.

Infection and Inflammation in AECOPD: Understanding Patient Phenotypes

Sanjay Sethi
(Buffalo, US)

The best way to define the role of infection in COPD is to classify it as a comorbidity, i.e., a co-existing condition that is influenced by, and also influences, a primary condition. COPD patients are at increased risk of infection, and infection has significant consequences in terms of clinical outcome for these patients because of the underlying lung disease.

Infection and Inflammation in Exacerbations

There is still a debate about how exacerbations should be defined and graded, and their mechanisms are poorly understood. In general, exacerbations represent an increase in the inflammation that is present in the stable state, with increased numbers of inflammatory cells (particularly neutrophils), cytokines, chemokines and proteases in the airways, and increased concentrations of certain cytokines and C-reactive protein in the blood.[8]

Studies have shown that the exacerbation profile can be divided into four main groups: bacterial predominant, eosinophil dominant, viral predominant and a small group where no change in inflammation from baseline is observed.[9] The aetiology of exacerbations in COPD can be due to any one of these single entities or a combination of two or more.[9, 10]

A number of bacteria have been identified as important in the development of acute COPD exacerbation (AECOPD), including nontypeable *Haemophilus influenzae* (NTHi: 20-30%), *Streptococcus pneumoniae* (10-15%), *Moraxella catarrhalis* (10-15%) and *Pseudomonas aeruginosa* (5-10% in advanced cases), among others.[11] In contrast, *Haemophilus haemolyticus* and *Haemophilus parainfluenzae*, although isolated frequently, are unlikely causes of exacerbations.[11]

The influence of bacteria on COPD exacerbations is not driven through bacterial load but by the acquisition of new bacterial strains and their virulence.[11] The subsequent immune response is often strain specific and this strain specificity most likely allows recurrent exacerbations by antigenically diverse strains.[11]

Although sputum interleukin-8 (IL-8) levels are similar across different causes in an exacerbation, changes in sputum tumour necrosis factor α (TNFα), active neutrophil elastase (NE) and

Prevention of Exacerbations in COPD: Expanding Scope and Strategies
Satellite Symposium at the European Respiratory Society (ERS) Congress, Vienna, Austria, 2nd September, 2012

Chair: Sanjay Sethi, Professor , Professor and Chief, Pulmonary, Critical Care and Sleep Medicine; Vice Chair for Research, University of Buffalo, United States

Lecture 1 - Infection and Inflammation in AECOPD: Understanding Patient Phenotypes
Sanjay Sethi, University of Buffalo, United States

Lecture 2 - Usefulness and Limit of Current AECOPD Prevention Practices
Hartmut M. Lode, Charité - Universitätsmedizin Berlin, Germany

Lecture 3 - OM85: From Mode of Action to Clinical Possibilities
Dario Olivieri, University Hospital of Parma, Italy

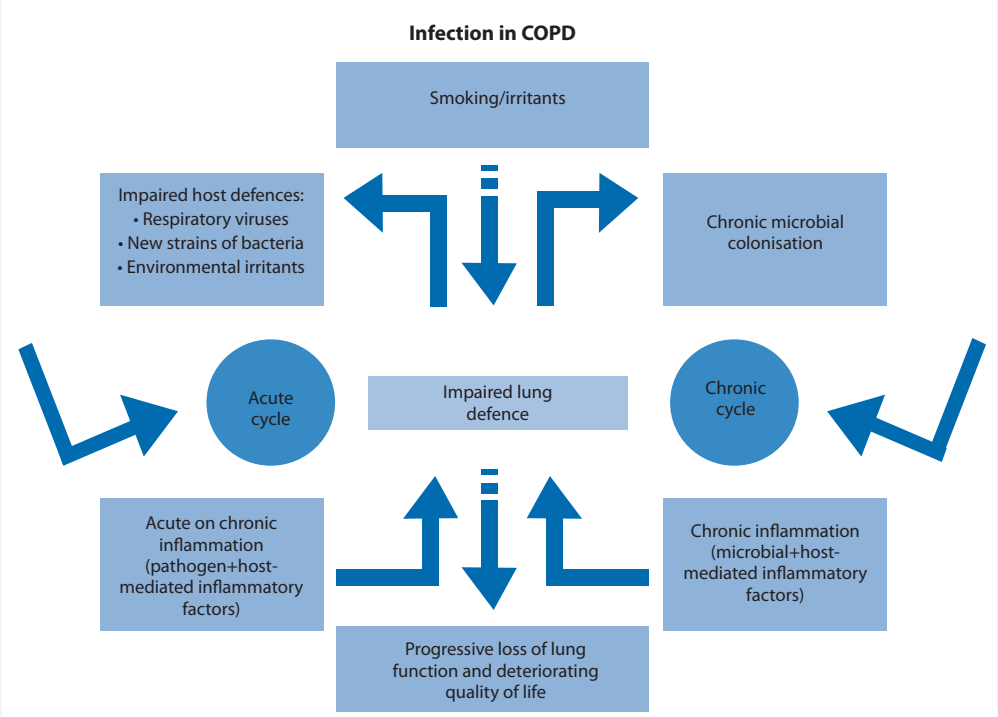


Figure 1. Infection and inflammation in exacerbations. COPD patients are at an increased risk of infection, which can have significant consequences in terms of patient's clinical outcome due to the underlying lung disease.

C-reactive protein (CRP) levels are greater in exacerbations associated with new bacterial strains.[12] These results show that new bacterial strains exacerbations tend to be the most inflammatory at the cellular level.

Patients with COPD are at risk for cardiovascular events, and interestingly, the risk of stroke or myocardial infarction is increased after a COPD exacerbation requiring antibiotics and/or inhaled corticosteroids (ICS).[13] This is attributed to increased systemic inflammation.

Infection and Inflammation in Chronic Disease

A number of pathogens have been found to be significant in chronic infection in COPD, such as the bacteria *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Chlamydia pneumoniae*; the viruses adenovirus and respiratory syncytial virus; and fungal infection with *Pneumocystis jirvocei*.

The chronic presence of bacteria in COPD can be damaging and, hence, according to currently recognised definitions, is not bacterial colonisation (Figure 1). This has been confirmed in a study demonstrating the relationship between chronic infection and airway inflammation.[14] In this study, patients with so called bacterial 'colonisation' in stable COPD were found to have increased titres of neutrophils, interleukin 8 (IL-8) and matrix metalloproteinase 9 (MMP-9).[14]

As patients progress to severe COPD, they develop lymphoid follicles in the small airways, which have germinal centres full of B cells.[15] The number of lymphoid follicles increases in direct relation to the severity of disease. One explanation for this is the mucosal inflammatory response trying to deal with infection. This has been demonstrated in a mouse model.[16]

Emerging data on bronchiectasis suggests that it develops in moderate to severe COPD patients.[17] Factors that have been found to influence the development of bronchiectasis are the severity of COPD, the presence of pathogenic bacteria in sputum cultures and hospitalisation at least once in the previous year.[18]

A change in the protease/antiprotease balance contributes to the progression of airway disease in COPD.[19] Acquisition of *Moraxella catarrhalis* in COPD has been shown to cause increased airway inflammation and worsening protease/antiprotease imbalance during exacerbations and also in colonisation, even in the absence of increased symptoms.[19]

Identifying the Infected Patient Phenotype of COPD

It is important to be able to identify patients at risk for exacerbation. A number of patient phenotypes appear to be associated with an increased risk of exacerbations. These include patients with moderate to severe COPD, frequent exacerbations (two or more/year), a history of one severe exacerbation, home oxygen use and bronchiectasis on computed tomography (CT) scanning.[18, 20, 21]

A number of clinical indicators can be used to identify chronically infected patients, including chronic sputum production, particularly if it is mucopurulent/purulent and the presence of a potentially pathogenic microorganism, in particular *Pseudomonas*.[18, 20, 21]

The use of quantitative polymerase chain reaction (PCR) increases the sensitivity of detection of bacterial infection in COPD vs. the use of cultures,[22] and may be a useful tool in identifying patients at risk of exacerbation.

Usefulness and Limit of Current AECOPD Prevention Practices

Hartmut M. Lode
(Berlin, Germany)

As we have seen, patients with AECOPD have a faster decline in lung function, poorer quality of life, greater airway inflammation and higher mortality.[23]

Preventative Measures for AECOPD
→ Long active bronchodilators
→ Inhaled corticosteriods
→ Combination of LABA/ICS*
→ Phosphodiesterase inhibitors
→ Mucolytic agents
→ Long-term antibiotics
→ Vaccines
→ Immunostimulants

Table 1. Measures available to prevent the faster decline in lung function, poorer quality of life, greater airway inflammation and higher mortality prevalent in AECOPD patients. * LABA = Long Acting Bronchodilators; ICS = Inhaled Corticosteroids

There are a number of preventative measures for AECOPD, including long acting bronchodilators (LABA), ICS and their combination; phosphodiesterase (PPD) inhibitors; mucolytic agents; long term antibiotics; vaccines and immunostimulants (Table 1).[23, 24, 25]

In the case of LABA, a study of 1,207 COPD patients administered tiotropium (18 µg once daily), salmeterol (50 µg twice daily) or matching placebos over 6 months, demonstrated fewer COPD exacerbations/patient/year in the tiotropium group vs. placebo (1.07 vs. 1.49 events/year, p<0.05).[26] No significant difference was seen for the salmeterol group vs. placebo (1.23 events/year). This positive effect of tiotropium was confirmed in the UPLIFT and POET studies.[27, 28]

Another LABA, indacaterol, which provides 24 hour bronchodilation on once daily dosing with a fast onset of action, has also been shown to improve symptoms and health status and confer clinical improvements vs. the twice daily LABA formoterol over 1 year.[29]

A meta-analysis to evaluate the effect of LABA treatment found that it was associated with a reduction in the frequency of COPD exacerbations.[30] Salmeterol, formoterol and indacaterol significantly reduced COPD exacerbations vs. placebo. However, only salmeterol, but not formoterol, decreased exacerbations significantly in the absence of ICS.

The impact of LABA/ICS combination therapy on survival has been investigated in the TORCH trial.[31] This randomised, double blind trial compared salmeterol (50 µg) plus fluticasone propionate (500 µg) twice daily (combination regimen) to placebo, salmeterol alone or fluticasone propionate alone for a period of 3 years. In addition, the combination regimen reduced the annual rate of exacerbations from 1.13 to 0.85 and improved health status and spirometric values vs. placebo (p<0.001).

The PPD-4 inhibitor roflumilast can improve lung function and prevent exacerbations in certain patients with COPD, and has also been shown to reduce the frequency of moderate/severe exacerbations requiring ICS.[32] The effect of roflumilast on exacerbations has been shown to be greatest in patients with chronic cough and sputum production.[33] Overall, patients with chronic bronchitis experienced a 26.2% reduction in exacerbations vs. 1.1% reduction in patients with emphysema only and no chronic bronchitis.[33]

The mucolytic agent, carbocisteine, has been investigated in the PEACE study for its effects on AECOPD.[34] Carbocisteine has anti-inflammatory and antioxidative effects, and has been shown to decrease the risk for AECOPD, with a decline in the number of exacerbations/ patient/year vs. placebo (p=0.004). Similar results have been seen with the macrolide antibiotics erythromycin[35] and azithromycin.[20] However, in a recent study, during 5 days of azithromycin therapy a small absolute increase in cardiovascular deaths was observed.[36] This was most pronounced among patients with a high baseline risk of cardiovascular disease. Patients who took amoxicillin in this study had no increase in the risk of death during the same period. The risk of cardiovascular death was significantly greater with azithromycin vs. ciprofloxacin but did not differ significantly from that with levofloxacin. As a result, a number of criteria for selecting patients with COPD for long term azithromycin prophylaxis have recently been proposed. These include a COPD history >2 acute exacerbations in the previous year, patients who are compliant with therapy, a QT interval <450 msec, alanine aminotransferase (ALT) <3 times the upper limit of normal, no high baseline risk for cardiovascular disease, patients not on medication that can cause QT prolongation, no decrement in hearing and sputum cultures negative for mycobacteria.[37]

The PULSE study, which evaluated whether intermittent pulsed moxifloxacin (fluoroquinolone antibacterial agent) treatment could reduce the frequency of COPD exacerbations, found that there was a reduction in the odds of exacerbation by 20% in the intent-to-treat (ITT) population, by 25% among the per-protocol (PP) population and by 45% in PP patients with purulent/mucopurulent sputum at baseline.[21] However, there were no significant differences between moxifloxacin and placebo in any pre-specified efficacy subgroup analyses or in hospitalisation rates, mortality rates, lung function or changes in St. George's Respiratory Questionnaire (SGRQ) total scores. There was, however, a significant difference in favour of moxifloxacin in the SGRQ symptom domain (ITT: -8.2 vs -3.8, p=0.009; PP: -8.8 vs -4.4, p=0.006).

The benefits of pneumococcal vaccination in COPD are less well established.[38] Data from a meta-analysis of a limited number of trials has shown no benefit in reducing COPD exacerbations; one large cohort study showed a significant association between vaccination and a reduction in hospitalisations for pneumonia and in risk of death in persons with chronic lung disease, but another study did not.

Current recommendations are that all patients with COPD, except

those who are hypersensitive to any component of pneumococcal vaccine, should be vaccinated. For patients <65 years of age, this should be once or twice in a lifetime; for patients ≥65 years of age, a one-time revaccination is recommended if they have been vaccinated ≥5 years earlier and in patients <65 years of age vaccination should occur at the time of primary vaccination. With regard to the type of pneumococcal vaccine, PCV7 has been shown to induce a superior immune response at 1 month post vaccination vs. PPSV23 in COPD.[39]

By contrast, all patients with COPD, except those who are hypersensitive to any component of vaccine, are recommended to receive annual inactivated influenza vaccine, preferably before influenza season or at any time throughout the season.[38] Data from a meta-analysis of a limited number of trials has shown a substantial reduction in influenza-related respiratory illnesses; a large cohort study showed significant association between vaccination and reductions in hospitalisations for pneumonia and influenza and in the risk of death during the influenza season in persons with chronic lung disease.

As we have seen, a wide variety of pharmacotherapeutic agents targeting different parts of the pathways leading to AECOPD have been investigated. LABA/ICS combination therapy is the most widely recommended strategy for exacerbation prevention. New therapies are needed to provide additional benefit to current treatment options. It will be important to determine in which patient subgroups these therapies are most effective, and why, so that therapeutic regimens can be appropriately developed.

OM-85: From Mode of Action to Clinical Possibilities

Dario Olivieri
(Parma, Italy)

As we have seen, the immune response to infection in COPD is dynamic, involving many inflammatory cells and multiple cytokines that play a role in the orchestration of the resultant inflammation. The impact of drug therapy will, therefore, be affected by the extent and severity of the infection and its impact on the various stages of the inflammatory response.

In the first stages of infection there is an innate immune response, which is then followed by adaptation of the immune system with secondary infection.[40] In COPD this immune remodelling occurs alongside the lung remodelling seen.[41] Chronic infection amplifies and perpetuates inflammation in stable COPD via pathogen associated molecular patterns involving both the innate and adaptive immune response, including B and T cell responses, which lead in turn to the development of lymphoid follicles.

NTHi commonly colonises the lower airways of patients with COPD, and may contribute to the pathogenesis of the small airways disease seen in COPD.[16] With repetitive exposure, infiltration of macrophages, CD8+ T cells, and B cells around airways and blood vessels, and collagen deposition in airway and alveolar walls, without the involvement of TNFα, has been observed in mice models.
An association between small airway pathology and GOLD categories of disease severity in COPD has been observed, with adaptive immune responses appearing in GOLD stage 3 and 4.[15]

The severity and course of AECOPD reflects the success of the adaptive immune response in appropriately modulating the innate response to pathogen-related molecular patterns. In some cases, the innate and adaptive immune responses successfully eliminate the infection, and the response is mild and transient ("just right"). Pulmonary immune response is inappropriate in either of two ways: adaptive immunity could fail when needed to control certain infections ("too little") or it could excessively amplify or prolong lung inflammation through its regulatory effects on innate immunity ("too much"). This is called the Goldilocks hypothesis.

OM-85 is a lyophilised extract manufactured from eight bacteria species (four gram+ and four gram-, from 21 different strains) commonly involved in respiratory tract infections.

OM-85 has been shown to modulate impaired local and systemic immune function through an increase in the level of cytokines and secretory immunoglobulin A (IgA) and activation of the airway macrophages by stimulating mucosa associated lymphoid tissue.[43, 44, 45, 46, 47] The role of transforming growth factor β (TGFβ) and natural killer T cells has also been demonstrated.[48]

Pattern recognition receptors (PRRs) of the innate immune system play a key role in infection associated exacerbations of COPD. They are expressed in alveolar macrophages, lung epithelial cells and in intraepithelial dendritic cells (DCs), which come in contact with invading pathogens and subsequently recruited immune cells.[49]
PRRs sense microbial infection by recognising conserved microbial molecules classically defined as pathogen associated molecular patterns (PAMPs). In addition, many PRRs are activated by endogenous, normally intracellular molecules that are released after cell injury. The released endogenous molecules are then called danger associated molecular patterns (DAMPs).

OM-85 stimulates natural killer cell activity through toll-like receptor (TLR) activation.[48] While TLRs are activated by many factors, including infections, bacteria have counter receptors and can in turn be stimulated by TLRs.[50]

The adaptive immune response is enhanced by OM-85 where levels of serum and secretory Igs are increased.[47, 51-56] These responses are important for fighting infections; in particular, secretory IgA can resist the proteolytic action of many bacteria. In the lower airways and alveolar surface, Igs are critical for lysing bacteria and facilitating their

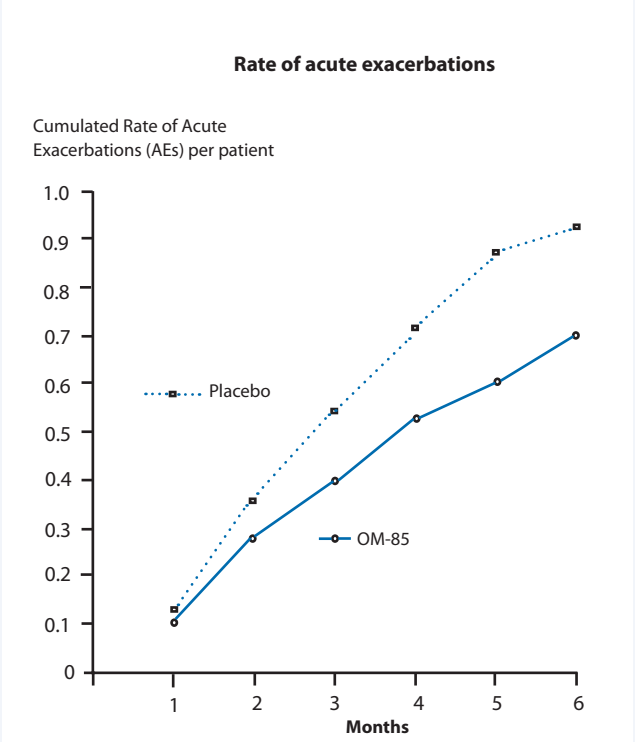


Figure 2. OM-85 significantly reduces the rate of acute exacerbations at the end of treatment at month 5 (-29%, p=0.03). Adapted from Soler *et al.* 2007.

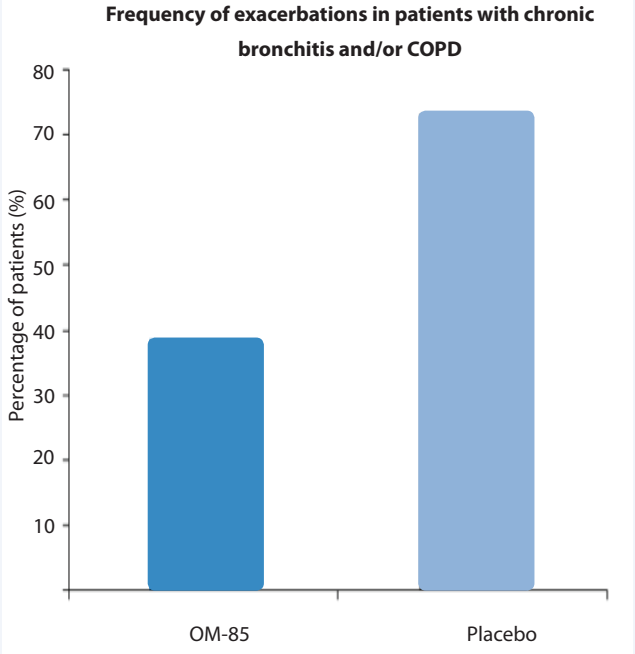


Figure 3. Efficiency of OM-85 in reducing frequent (>2) exacerbations (in subjects with at least one exacerbation) vs. placebo in patients with chronic bronchitis and/or COPD.

phagocytosis by macrophages.

Novel insights suggest that OM-85 can influence immune responses, in particular DC, activation through immune receptors in the intestine, raising, in a modulated way, the overall body defences against infections.[57]

A number of randomised, double blind, placebo controlled studies of OM-85 have been conducted in adults with COPD.[58-61] In these studies, a significant reduction in exacerbations, hospital stays, as well as antibiotic and concomitant treatment use have been observed.

In the Solèr study, the mean number of acute exacerbations in the OM-85 group was 0.61/patient vs. 0.86/patient for placebo (-29%; p=0.03) (Figure 2).[58]

The difference between treatments was most notable in patients with a history of current or past smoking (-40%; p<0.01).[58] In the The PARI-IS study, the risk of having at least one episode of acute exacerbation (primary outcome) was similar for both OM-85 and placebo (p=0.872). However, the total number of days of hospitalisation for a respiratory problem was 55% less for OM-85 (287 days) vs. placebo (642 days). Patients treated with OM-85 spent an average of 1.5 days in hospital vs. 3.4 days for placebo (p=0.037).

A number of other studies have reported significant results with OM-85. Li *et al*. showed a significant decrease in the incidence, duration and severity of acute exacerbation, as well as a reduction in the course of antibiotics administered and in the dosage of bronchodilator and mucolytic agent with OM-85 vs. placebo in 90 patients with moderate COPD (p<0.05).[62] Xinogalos *et al.* reported significant decreases over 6 months in the number of acute exacerbations (50%) and improvement in clinical signs, as well a 42% decrease in antibiotic, antitussive and bronchodilator use in 62 patients with chronic bronchitis.[63] Finally, Collet *et al*. demonstrated significant cost savings in 381 patients with severe COPD treated over 6 months.[64]

OM-85 has over 30 years of post-marketing experience and has been associated with a very low incidence of adverse events (3 cases per 100,000 patients treated), which are mainly nonserious and transitory.

This year, the PLATINO study showed that chronic bronchitis in COPD is possibly associated with worse outcomes.[65] Interestingly, a recently completed study from China has demonstrated the efficacy of OM-85 in reducing frequent (≥2) exacerbations vs. placebo in patients with chronic bronchitis and/or COPD (Figure 3).[66]

Therefore OM-85 may offer a potentially effective approach in preventing AECOPD.

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Bronchial Thermoplasty: A Life Changing Therapy for Severe Asthma Patients

Introduction

The practical workshop titled, "Bronchial Thermoplasty: A Life Changing Therapy for Severe Asthma Patients" was held during the European Respiratory Society (ERS) Annual Congress on Tuesday 4th September 2012 at the Reed Messe Wein conference centre, Vienna, Austria. The meeting was chaired by Doctor Felix Herth, Thoraxklinik Heidelberg, Heidelberg, Germany.

Background

Bronchial thermoplasty (BT) is a bronchoscopic procedure to reduce the mass of airway smooth muscle and attenuate bronchoconstriction.[1] Randomised trials of BT have produced consistant positve results. In the AIR trial, the mean rate of mild exacerbations, compared with baseline, was reduced in the BT group, and there was also a higher percentage of symptom-free days and symptom scores in the BT group.[1] In the RISA trial, BT subjects had significant improvements versus control subjects in rescue medication use.[2] In the AIR2 trial, results showed that the proportion of patients achieving a clinically significant improvement in the integrated Asthma Quality of Life Questionnaire (AQLQ) was 79%.[3]

The clinical effectiveness and long-term safety of BT are supported by more than 10 years of extensive clinical research, and individual case reviews show that BT results in improved quality of life (QoL) for patients. Furthermore, the majority of AIR2 study patients reported that they would have BT again and recommend it to a family or friend.

Evidence from the randomised trials and individual case studies suggests that BT is a promising treatment option for patients with severe asthma.

Bronchial Thermoplasty: A New Option for Patients with Asthma
Boston Scientific Sponsored Practical Workshop at the European Respiratory Society (ERS) Annual Congress, Vienna, Amsterdam, 4th September 2012

Chair: Felix Herth, Thoraxklinik Heidelberg, Heidelberg, Germany

BT Clinical Outcomes: Beyond the Symptoms
Ian Pavord, University Hospitals of Leicester NHS Trust, Glenfield Hospital, Leicester, United Kingdom

BT Long Term Benefit: Real Life Cases
Gerard Cox, Director, Division of Respirology, Professor of Medicine, McMaster University, Hamilton, Canada

Patient Management: Build a BT Program & Hands-on
Hans Christian Siersted, Odense University Hospital, Odense, Denmark

Questions & Hands-on
Felix Herth, Thoraxklinik Heidelberg, Heidelberg, Germany

Close
Felix Herth, Thoraxklinik Heidelberg, Heidelberg, Germany

Bronchial Thermoplasty Clinical Outcomes: Beyond the Symptoms

Ian Pavord
(Leicester, UK)

Findings of the AIR Trial

There have so far been three randomised trials of BT: the AIR, RISA and AIR2 trials. The earliest, the AIR trial, included 55 BT (BT plus inhaled corticosteroids [ICS] plus long-acting beta agonists [LABA]) and 54 control patients (ICS plus LABA).[1] The primary outcome was the frequency of mild exacerbations. Airflow, airway responsiveness, asthma symptoms, the number of symptom-free days, use of rescue medication, and scores on the AQLQ and the Asthma Control Questionnaire (ACQ) were also assessed.[1] The results showed that the mean rate of mild exacerbations, compared with baseline, was reduced in the BT group, but there was no change in the control group (change in frequency per subject per week, -0.16+/-0.37 versus 0.04+/-0.029; p=0.005). There was also significant improvement in morning peak expiratory flow (PEF) in the BT group (39.3+/-48.7 versus 8.5+/-44.2l/min).[1] AQLQ scores were also higher in the BT group (1.3+/-1.0 versus 0.6+/-1.1) as were ACQ results (reduction, 1.2+/-1.0 versus 0.5+/-1.0). There was also a higher percentage of symptom-free days (40.6+/-39.7 versus 17.0+/-37.9), and symptom scores (reduction,1.9+/-2.1 vs. 0.7+/-2.5) in the BT group, while fewer puffs of rescue medication were required. Values for airway responsiveness and forced expiratory volume in one second (FEV1) did not differ significantly between the two groups. These results led the investigators to conclude that BT in subjects with moderate or severe asthma results in an improvement in asthma control.[1]

Findings of the RISA Trial

The RISA trial randomised 32 subjects to a control group (ICS plus LABA; n=17) or a BT group (BT plus ICS plus LABA; n=15).[2] After treatment, subjects entered a 16-week steroid stable phase, a 14-week steroid wean phase and a 16-week reduced steroid phase. The results showed that BT resulted in a transient worsening of asthma symptoms. Seven hospitalisations for respiratory symptoms occurred in four of 15 BT subjects during the treatment period. There were no hospitalisations during this period in the 17 control subjects. The rate of hospitalisations was similar in both groups in the post-treatment period. At 22 weeks, BT subjects had significant improvements versus control subjects in rescue medication use (-26.6 +/- 40.1 versus -1.5 +/- 11.7 puffs/7 d, p<0.05), prebronchodilator FEV1% predicted (14.9 +/- 17.4 versus -0.94 +/- 22.3%, p=0.04), and ACQ scores (-1.04+/- 1.03 versus -0.13+/-1.00, p=0.02). Improvements in rescue medication use and ACQ scores remained significantly different from those of controls at 52 weeks. The results led the investigators to conclude that BT is associated with a short-term increase in asthma-related morbidity, but that there is preliminary evidence of long-lasting improvement in asthma control.[2]

Findings of the AIR2 Trial

The AIR2 trial evaluated the safety and effectiveness of BT versus a sham procedure in subjects with severe asthma.[3] A total of 288 adult subjects were randomised to BT or sham control and underwent three bronchoscopy procedures. The primary outcome was the difference in AQLQ scores from baseline to an average of six, nine and 12 months.[3] Adverse events and healthcare use were collected to assess safety. The results showed that improvement from baseline in the integrated AQLQ score was superior in the BT group compared with sham (BT, 1.35+/-1.10; sham, 1.16+/-1.23 [posterior probability of superiority, 96.0% intention to treat and 97.9% per protocol]). 79% of BT and 64% of sham subjects achieved changes in AQLQ of 0.5 or greater (posterior probability of superiority, 99.6%).[3] 6% more BT subjects were hospitalised in the treatment period, however, in the post-treatment period, the BT group experienced fewer severe exacerbations, emergency department visits, and days missed from work/school compared with the sham group (posterior probability of superiority, 95.5%, 99.9%, and 99.3%, respectively).[3] From these results, the trial investigators concluded that BT in subjects with severe asthma improves asthma-specific QoL with a reduction in severe exacerbations and healthcare use in the post-treatment period.[3]

Results

The effectiveness of BT has been found to persist for at least two years.[4] In a 2011 study, subjects from the AIR2 trial were evaluated by comparing the proportion of subjects who experienced exacerbations, adverse events, or healthcare utilisation during the first year after BT treatment with the proportion of subjects who experienced the same during the subsequent 12 months.[4] It was found that severe exacerbations, respiratory adverse events, emergency department visits for respiratory symptoms, hospitalisations for respiratory symptoms (proportion of subjects experiencing and rates of events) and stability of pre- and post-bronchodilator FEV1, were comparable between years 1 and 2.[4] The proportion of subjects experiencing severe exacerbations in year 2 after BT was 23.0%, compared with 30.9% in year 1.[4] These results showed that reduction in the proportion of subjects experiencing severe exacerbations after BT is maintained for at least two years, and that BT provides beneficial long-term effects on asthma outcomes in patients with severe asthma.[4]

Procedure Safety

Regarding procedure safety, of the 850 bronchoscopies performed in the AIR2 trial, in patients with severe asthma (558 BT and 292 sham procedures), there were no device-related deaths or major adverse events such as pneumothorax, mechanical ventilation, airway stenosis or focal narrowing.[3] More respiratory adverse events were reported in the BT group in the short term after the procedure, typically occurring within one day and resolving within one week with standard care. There were also fewer respiratory adverse events, hospitalisations and emergency department visits in the BT group during the post-treatment period.[3]

Five-year Safety Profile from AIR

The five-year safety data from the AIR trial show that the rate of respiratory adverse events per subject was stable in years 2 to 5 following BT (1.2, 1.3, 1.2, and 1.1, respectively).[5] There was also no increase in hospitalisations or emergency department visits for respiratory symptoms in years 2, 3, 4, and 5 compared to year 1. The forced vital capacity (FVC) and FEV1 values showed no deterioration over the five-year period in the BT group. Similar results were obtained for the control group.[5] Therefore, these results support the long-term safety of the procedure out to five years.[5]

High Patient Satisfaction

The safety and efficacy data from the trials are supported by the results of a patient questionnaire, in which the majority of AIR2 study patients reported that they would have BT again and recommend it to a family or friend.

Patient Case Review

In a case study, a 43-year-old agricultural worker with a 30-year history of episodic wheeze and breathlessness, which had become worse over the last two years was using salmeterol 50mcg bd, fluticasone 500mcg bd and up to one canister of salbutamol per week. The PEF was marked within day variability (250 to 500l/min). FEV1 2.6 improved to 3.4 L after salbutamol. Methacholine PC20 was 0.03mg/ml; and sputum was non-eosinophilic. There was no response to prednisolone. Post-BT outcomes were reduced symptoms, methacholine PC20 >16mg/ml, PEF 400-500l/min and no use of rescue salbutamol.

BT Long-Term Benefit: Real Life Cases

Gerard Cox

(Hamilton, Canada)

First Clinical Study Published in 2006

The first clinical study of BT was published in 2006, in which the safety of

BT was studied in 16 subjects with mild to moderate asthma. All subjects demonstrated improvement in airway responsiveness. The mean PC(20) increased by 2.37+/-1.72 ($p<0.001$), 2.77+/-1.53 ($p=0.007$), and 2.64+/-1.52 doubling ($p<0.001$), at 12 weeks, one year, and two years post-procedure, respectively. Data from daily diaries collected for 12 weeks indicated significant improvements over baseline in symptom-free days ($p=0.015$), morning peak flow ($p=0.01$), and evening peak flow ($p\leq0.007$). These results showed that BT was well tolerated in these patients with asthma and resulted in decreased airway hyper-responsiveness that persisted for at least two years.[6]

Evolution of Bronchial Thermoplasty: A Rigorous Clinical Approach

The clinical effectiveness and long-term safety of BT are supported by more than 10 years of extensive clinical research. The procedure has been developed with the input of thought leaders in the field of asthma and, of the four clinical trials on the treatment of asthma, the AIR2 trial was specifically designed to provide pivotal evidence to the US Food and Drug Administration (FDA) for approval of the procedure for treatment of severe asthma.

Clinical Study History

Prior to conducting the AIR2 trial, Boston Scientific conducted three clinical studies of the Alair® System in patient populations ranging from mild to severe refractory asthma. These studies were submitted to the FDA as proof-of-principle and evidence of safety prior to beginning the pivotal AIR2 trial. Long-term follow-up results from these prior clinical studies were reviewed by the FDA during the Premarket Approval (PMA) process for the Alair® System. The Alair® System is indicated for the treatment of severe persistent asthma in patients 18 years and older, whose asthma is not well controlled with inhaled corticosteroids and LABAs.

Long-term Safety Profile

Table 1 summarises five years of follow-up data from the BT clinical trials. Results from the AIR and RISA studies showed no deaths in the BT group.[5,7] There was also an absence of long-term clinical complications based on adverse event reporting. Furthermore, stable pulmonary function (no deterioration of FVC and FEV1) and in annual computed tomography scans for five years (feasibility study) and for one year (AIR2 study) no clinically significant findings or structural changes were found.[3,6]

Patient Case Review: Feasibility Study Patient

The following patient case review, a patient from the feasibility study, demonstrates the good results that can be achieved with BT. The patient was female, aged 52 years, and had had severe asthma since the age of 25. She had significant reliance on asthma medications, and reported that she "always carried [her] rescue inhaler". She also reported that cold weather and cat allergens exacerbated her asthma, and that her daily activities and QoL were hindered by asthma.

Following the procedure, the patient reported no pain associated with the BT procedure, however, she experienced increased coughing and wheezing immediately after each procedure, which resolved within one to two days. The patient was followed up after 10 years and it was found that she had had no asthma exacerbations requiring steroids and no emergent visits for asthma-related symptoms. Furthermore, cold air and cat allergens no longer affected her asthma, she had an increased activity level without shortness of breath and had experienced weight loss as a result of increased exercise.

Patient Management: Build a BT programme

Hans Christian Siersted

(Odense, Denmark)

Which Patients?

A BT programme was constructed at Odense University Hospital, in accordance with other trials and with the FDA guidelines for recruiting patients who were adult severe, persistent asthmatics (≥ 18 years old). Criteria for inclusion were that the asthma should be inadequately controlled despite combination of ICS and a LABA, and that the patient must be able to safely undergo bronchoscopy per hospital guidelines. Also important is that the patient is compliant with medication.

Patients who should not be included in a BT programme include those with a pacemaker, internal defibrillator or other implantable electronic device or those with known sensitivity to medications required to perform bronchoscopy, including lidocaine, atropine and benzodiazepines. Finally, patients who have previously been treated

Study	Asthma Severity	Bronchial Thermoplasty (n)	Sham (n)	Total (n)	Study Follow Up
AIR2 Pivotal IDE Trial (RCT)	Severe	190	98	288	5 years
		BT (n)	**Control (n)**	**Total (n)**	
Feasibility	Mild-moderate-severe	16	0	16	5 years
AIR (RCT)	Moderate-severe	55	54	109	5 years
RISA (RCT)	Severe	15	17	32	5 years

Table 1. Clinical Studies Evaluating Safety and Effectiveness in Asthma

with the Alair® System should not be included.

Consider Individually

Some individual considerations may apply, for example, pulmonary function if FEV1 is less than 65%. Also, if inflammation dominates the clinical picture, the exacerbation may be more severe than usual and this should be considered. Comorbidities should also be considered individually, as should cardiac issues, recurrent infections, differential diagnosis to asthma, vocal cord dysfunction and chronic obstructive pulmonary disease.

The procedure should be postponed in the case of active respiratory infection, if there is asthma exacerbation or a change in dose of systemic corticosteroids (up or down) in the past 14 days.

Procedure

The Alair® System, which is approved by the FDA in the US and the CE mark in the EU, is a means to deliver thermal energy to the airway via a bronchoscope to reduce airway smooth muscle. The Alair® Catheter is a flexible tube with an expandable wire array at the tip. The Alair® Radiofrequency Controller supplies energy via the catheter to heat the airway wall.

The Alair® System is designed to treat airways distal to the main stem bronchus with a diameter range of 3mm to 10mm. The treatment is divided into three sessions of 45 to 60 minutes, with an interval of three weeks or more. In the first procedure, the right lower lobe is treated, in the second the left lower lobe is treated and in the third both upper lobes are treated (the right median lobe is not currently treated with BT).

Patient Flow

In the Odense programme, initially the patient was referred to a BT-certified respirologist. The patient was then evaluated for indication and contraindication. Patient information was then given and acceptance gained from the patient. The procedure was then undertaken via bronchoscopy either through the nose or orally. Analgesia and/or sedation were given. The procedure is undertaken with one bronchoscopist and two assistants. The patient must fast for two hours and is then discharged when they are deemed stable and post-brochodilator FEV1 is more that 80% of the pre-procedure value.

Follow-up is performed by telephone on day 1, 2 and 7 for status (exacerbation expected) and an outpatient check is done two to three weeks after BT.

Getting Started

As a guide for pioneering a BT programme in a specific area/country, in the first instance, approval must be obtained from National Board of Health, regional and local authorities. The potential for the programme must also be assessed and funding secured through development projects. A procedure coding and reimbursement structure must also be put in place and consultation with Boston Scientific is recommended.

Programme success depends on in-house organisation and programme training of doctors and nurses. There must also be effective internal patient evaluation, competition for space and resources. Referral incitements can be achieved through "spreading the word" via media, meetings and guidelines. Clear official instructions to referring specialists/hospitals (paper and internet) and clear rules for follow-up (including return to referring physician).

The Odense Experience

The Odense investigators reported that their experience and the procedure was well tolerated, and outpatient procedures were also found to be feasible. The procedure was not difficult, but requires concentration. Individual differences in severity of post-procedure exacerbation (probably associated with pre-procedure inflammation).

BT is a new treatment option for patients with asthma. Results from randomised trials have been good, and feedback from patient questionnaires has revealed that patients have experienced improved QoL as a result of BT. The long-term safety profile for BT is also good to five years. Individual centres wishing to implement a BT programme should follow relevant country-specific guidelines, obtain funding and consult with Boston Scientific.

Disclaimers

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Asthma and Long-Term Work Disability

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Introduction

Asthma is one of the leading non-musculoskeletal causes of work limitations and has major economic and quality-of-life impacts through occupational disability. Associations of asthma with allergic rhinitis and gastroesophageal reflux disease are well known. A weak association of asthma has also been reported with hyperlipidemia, depression, diabetes mellitus, and osteoporosis. However, the role of comorbidity in asthma has rarely been taken into consideration in sickness absence studies. Previous studies suggest that both asthma and allergic rhinitis may reduce work productivity.[1-4]

Results of the Finnish Public Sector Study

The study cohort comprised 68,686 public sector employees in 10 towns and 21 public hospitals in Finland[5-6] (the Finnish Public Sector Study). Surveys were conducted in 1997-98, 2000-2002, and/or 2004 (74% of the eligible population responded at least once). We linked the survey data to records from national health and pension registers (the Drug Reimbursement and Prescription Registers and Sickness Absence Registers maintained by the Social Insurance Institution of Finland (SII)).

We defined those respondents who were entitled to special reimbursement for asthma medication as asthmatic employees (persistent asthma). Depression (that is, those on antidepressant medication during the survey year), ischemic heart disease, diabetes, rheumatic disease, cancer and hypertension were analysed as comorbidities.[3] The primary end-point was very long sickness absence (>90 days) or disability pension.

There were 2332 (3.4%) asthmatic employees. Compared to other employees, they were older (there were more those in age group 55-63 years), more often women, and obese (BMI >30). In addition, employees with asthma were more often ex-smokers, lower-grade non-manual workers and they had psychological distress.

Those with asthma had an almost 2-fold increased risk of long-term all-cause work disability when the results were adjusted for age, gender, socio-economic status (SES), smoking, and obesity. Comorbidities further increased the risk of work disability in asthmatic employees. Thus, asthmatic employees with at least two other chronic conditions had a 4.5 fold risk for long-term work disability as compared with non-asthmatic employees with no co-morbidities.[3] Depression, which was related to a 3.6-fold increased risk of long-term work disability, was a particularly important co-morbid condition (Figure 1).[3] Persistent asthma and depression, in combination, increased the risk for disability pension by 6.8 fold (Figure 1).[3]

Conclusions and Recommendations

Data from Finnish employees showed that employees with asthma have an increased risk of work disability, in particularly when combined with co-morbid conditions, such as depression.[3, 4] Our finding is in agreement with previous work suggesting that asthmatic employees receive more often compensation for work disability (both

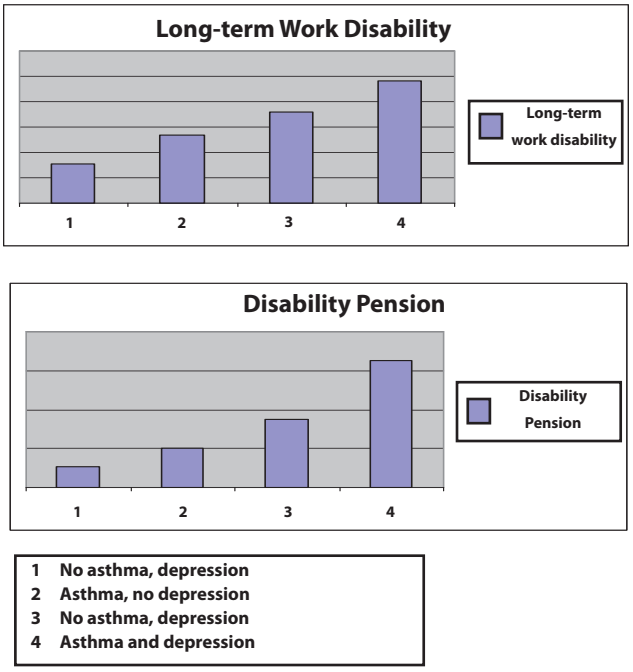

Figure 1. Illustration of risk of very long-term work disability and disability pension associated with asthma and depression according to the Finnish Public Sector Study (consisting of public sector employees in 10 towns and 21 public hospitals in Finland).[3]

sick leave and disability) than non-asthmatic employees.[2] Blue collar workers are especially in risk of work disability because of asthma, since occupational exposures are often more detrimental than in office work (reference). Medication adherence (defined as 80% or more of days with mediation) has been shown to decrease work absenteeism and also short-term work disability in asthma as well as other chronic diseases.[1]

Current evidence emphasises the need to expand our concept of asthma patients and their treatment when estimating work disability, and to take co-morbidities into consideration both in the treatment options and work disability estimations.

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Real-life Asthma Strategies: The Missing Piece in the Jigsaw

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Introduction

Asthma treatment strategies are well addressed by evidence-based guidelines, but the guidelines are mostly based on data derived from classical randomised controlled trials (RCT).

RCTs aim to demonstrate direct cause-and-effect between a trial drug and an outcome, and represent the standard in evaluating safety and efficacy over relatively short trial periods.[1–3] Yet most RCTs include highly-selected patient populations, which limits the ability to which their results can be generalised to the wider patient population. Indeed, strict patient selection can result in an inherent form of bias within RCT results. Data from other types of study designs can provide valuable supplementary data around the comparative effectiveness of interventions, as used in real patients managed in routine care, as well as data on the long-term safety and effectiveness of therapies used in diverse patient populations and the influence of lifestyle factors, comorbidities and polypharmacy on real-life, therapeutic outcomes.

Study Designs – Their Relative Pros and Cons

Classical Randomised Controlled Trials

The classical RCT evaluates the safety and efficacy profiles of emerging therapies. Their high internal validity currently places them atop the medical evidence hierarchy for examining management and therapeutic interventions.[1–3] Indeed, their design aims to maximise internal validity to establish an unequivocal cause-and-effect relationship between an intervention and (typically a limited number of) outcomes by limiting extraneous variables that may confound the ability to isolate treatment-related effects. To achieve this, RCTs are designed to include only well-characterised patient populations who are managed under optimised and tightly-controlled conditions. Asthma RCTs, for example, tend to recruit non-smokers, those with no (or negligible) comorbid illnesses or concurrent medications, good inhaler technique and high adherence to study therapies. Patients are frequently required to have a clear-cut asthma diagnosis, some lung function impairment, substantial reversibility to short-acting beta-agonists and frequent rescue medication usage. In addition, patient participation in clinical trials is often associated with a better knowledge of their disease and more efficient health behaviours than the "average" asthma patient.

Exclusion of patients who fail to meet the tight inclusion criteria used in RCTs benefits internal validity, but the result is a highly-characterised subgroup of the true asthma population. Thus the external validity of RCTs—the ability to extrapolate their results to the diverse asthma patient population managed in routine care—is limited.[4–10] Indeed, by including only highly-characterised patients, RCTs arguably "over-select" patients and introduce bias to their findings. The high level of treatment adherence required by RCTs may, for example, result in an over-estimation of the true treatment outcomes possible at more standard levels of adherence. Moreover, excluding smokers and patients with allergic rhinitis from asthma RCTs designed to evaluate the efficacy of inhaled corticosteroids (ICS) results in a biased, "responder" population, one that disregards the issue of steroid resistance among smokers (see Figure 1) and the need to address upper (as well as the lower) airways inflammation in patients with comorbid rhinitis (see Figure 2).[11–13] The licensing requirement that new therapies must be compared with (and demonstrate non-inferiority to) existing gold standard treatment results in replication of pre-existing study designs and patient inclusion criteria. As a result, biases can be echoed through successive generations of trials and, when pooled in meta-analyses to inform asthma guidelines, can result in an over-grading of the available evidence. Indeed, when systematic selection biases are present, their effect on results is likely to be amplified by mathematical processes such as those used in meta-analyses.

In terms of study design, RCTs may be short in duration in order to: limit organisational constraints; limit intercurrent external influences; control costs, and minimise patient dropouts. Thus, they provide limited insight into the longer-term effectiveness and safety of new

Mean (95% CI) peak expiratory flow (l/min) in non-smoking and smoking asthmatic patients following treatment with inhaled placebo or fluticasone propionate 1000 µg per day. *p=0.016, greater than non-smokers after placebo; **p=0.001, greater than smokers after fluticasone.

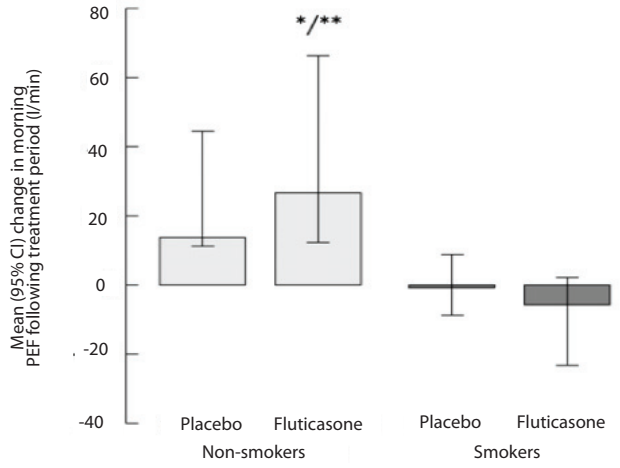

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Figure 1. The impact of smoking on inhaled corticosteroid response is clearly show here by the change from baseline in morning PEF in smokers vs non-smokers treated with fluticasone and placebo. By excluding smokers from ICS RCTs in asthma, the treatment-related outcomes are positively biased and unrepresentative of outcomes across all smoking-subgroups.[11]

agents, which might be modulated by incident medical events or environmental changes occurring in the patient's life.[14–16] The tightly-controlled protocols (e.g. mandatory high adherence, frequency of patient monitoring) and procedures (e.g. patient blinding) used in RCTs, and their highly interventional nature, undoubtedly affects "ecology" of care – making it diverge from real-life, routine care.[17]

The asthma management guidelines published by the Global Initiative for Asthma (GINA) draw heavily on RCT evidence.[3] Yet when the generalisability of the criteria used to inform GINA's recommendations were evaluated in a cohort of 179 patients with current asthma managed in routine care, only 29% met the GINA-recommended diagnostic criterion of ≥12% bronchodilator reversibility, and 34% the peak expiratory flow (PEF) variability criterion.[8] Similarly, a study conducted in Norway to evaluate the extent to which a real-life obstructive lung disease population met criteria frequently used in RCTs found that a minority of patients met the various eligibility requirements, and the eligible proportion decreased dramatically with stepwise introduction of each additional criterion: 37.1% had forced expiratory volume in one second (FEV1) 50–85% of predicted; 14.9% also had ≥12% reversibility within the past year; 9.6% were still eligible when the lack of comorbid disease criterion was added and only 5.4% fulfilled all these criteria and were non-smokers (or ex-smokers with a nicotine burden <10 pack-years).[9] If patients were also required to be symptomatic and to have regular ICS usage, the percentage of eligible patients fell further to 3.3%.[9]

It is also of note that the majority of RCTs are funded by the pharmaceutical industry and typically performed by the company responsible for manufacturing and/or promoting the particular drug under investigation. Through very strict inclusion criteria and outcome selection, funders can often design trials to optimise the characteristics and benefits of their own compound compared to the active comparator.[18] Moreover, pharmaceutical companies' funding of RCTs results in few head-to-head comparisons of competitor products (trials designed to demonstrate superiority are particularly limited) and difficulties in performing studies combining two drugs in the same active arm. Propose that Company A owns the drug AX. The drug, by itself, has limited effect on desirable outcome parameters, but is likely to act synergistically with Company B's drug, drug BX. The legal and

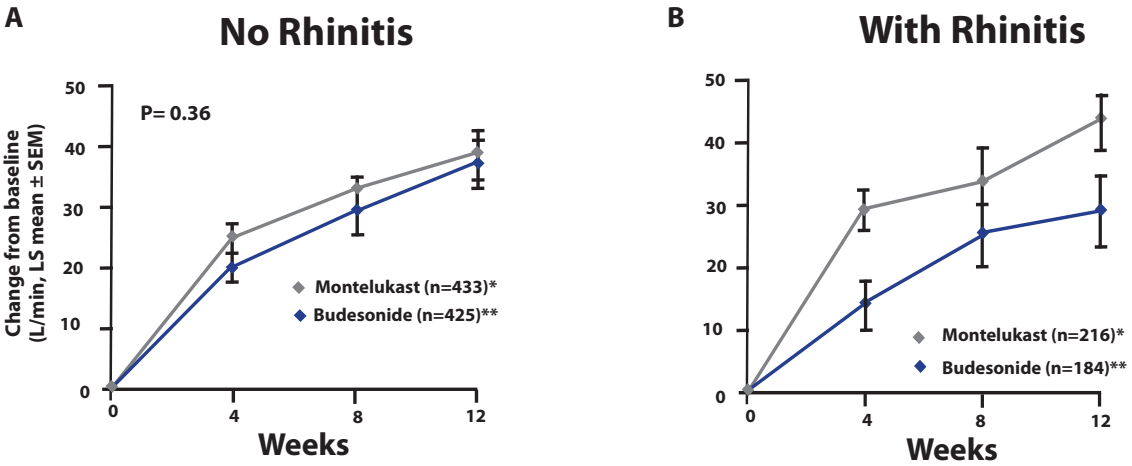

Figure 2. The COMPACT study demonstrated the difference in outcomes associated with management of only lower airways inflammation (budesonide) compared with systemic (upper and lower airways) inflammation management (montelukast) in patients without (A) and with (B) rhinitis. The increase in morning PEF for patients without rhinitis was similar for both therapies (p=0.36), but significantly different (p<0.03 in favour of montelukast) for patients with comorbid rhinitis.[12,13]

(A) Adapted from Allergy, Price DB, *et al*; Vol 6:737-42, 2006 with permission from John Wiley and Sons (B) Reproduced from Thorax, Price DB, *et al*; Vol 58:211-6, 2005 with permission from BMJ Publishing Group Ltd.

regulatory processes required to conduct an evaluation of the synergistic effects of combining AX plus BX are complicated and hamper the ability to perform such clinically-relevant investigations. Where trials of drug synergies do occur, it is likely that one company owns both component drugs.

Moreover, asthma and COPD trials involve inhaler devices and access to placebo inhalers is often challenging. Pharmaceutical companies are often reluctant to provide placebo devices for trials other than their own, which not only limits the ability to make fair comparisons of active agents compared with placebo, but also compromises the performance of independent research. One method of obstructing procurement of placebo is to raise the price such that it becomes prohibitive for independent researchers. In a recent letter to the *Lancet*, Christensen and Knop wrote of a trial in diabetes where a company took six months to review (and make critical amends) to a proposed trial protocol before they agreed to provide the independent researchers with placebo.[19] Christensen and Knop rightly pose the question: "is it acceptable that drug companies with an established placebo-manufacturing process (for their own marketing authorisation trials) can choose whether they wish to sell placebo to independent researchers?"

Thus, while RCTs necessarily underpin the evidence hierarchy and the drug licensing process, there is growing recognition of the need to look beyond RCTs and towards complementary data on the long-term, real-life safety and effectiveness of therapies in populations more reflective of those treated in routine care and in studies performed by independent researchers.

Within its key points, the 2008 Brussels Declaration on Asthma stated a need to include evidence from real world studies in treatment guidelines.[20] This sentiment was echoed in 2009 in the European Respiratory Society/American Thoracic Society Taskforce paper on asthma control and exacerbations,[2] which proposed the use of composite measures when evaluating asthma control. The Taskforce also called for the measurement properties to be validated in clinical trials and in: "large, prospective studies in 'real-world' settings (e.g., trials designed pragmatically to reflect everyday clinical practice) to ensure they provide content validity as well as reflect clinically meaningful outcomes".[2]

Pragmatic Trials

Pragmatic trials are designed to have greater external validity and to better model and reflect everyday clinical practice than classical RCTs. They can offer greater external validity than classical RCTS but do so at the expense of internal validity. Thus pragmatic trials complement RCTs, by testing a hypothesis in a more naturalistic, real-life setting, but cannot replace them.

While consenting patients are still randomly assigned to predefined study arms, pragmatic trials have broader inclusion criteria than classical RCTs and tend to be longer in duration and to maintain ecology of care (especially if comparing technologies whose impact might be changed by blinding, such as oral versus inhaled therapy).[22–24] Well-designed pragmatic trials (such as ELEVATE[24] and others discussed in later sections of this paper) often include both objective outcome measures (e.g., survival, test results) and subjective measures (e.g., quality of life [QoL] questionnaires), which, when broadly consistent, add rigour to the analysis. Further weight is added through adherence to consistent, quality standards, such as the CONSORT extension for pragmatic trials, which includes recommendations and a check-list for reporting pragmatic trials (http://www.consort-statement.org/extensions/designs/pragmatic-trials/).[25]

Yet however naturalistic pragmatic trials are designed to be, they still require: patient consent; collaboration of 'trial-minded' physicians; adherence to a strict trial protocol and treatment plan, and higher than usual monitoring and patient–clinician interaction.[6, 26–28] Additional challenges arise from the fact that the very characteristics of real-life practice that pragmatic trials are designed to capture (e.g. variable adherence, use of concomitant therapies, concomitant illness and symptom variability over time) tend to reduce measureable differences between therapies. Some of these shortcomings can be addressed by observational studies.

Observational Studies

An observational study is a type of non-randomised study in which the investigators seek to observe and measure the course of events rather than to instigate an intervention.[29] By definition, therefore, observational studies allow evaluation of naturalistic outcomes achieved by real-life patient populations treated in routine care.

Clinical databases are typically used to perform retrospective analyses to evaluate the real-life safety, effectiveness, or comparative effectiveness of licensed agents. The Clinical Practice Research Datalink (CPRD, formerly the General Practice Research Database [GPRD]), the Doctors Independent Network (DIN-Link) Database and the Optimum Patient Care Research Database (OPCRD) are primary care clinical databases widely used for respiratory research in the United Kingdom (UK).[30–34] Observational studies using clinical datasets can be longitudinal or cross-sectional in design, and can be used to characterise prescribing patterns and to evaluate the comparative safety and effectiveness of therapies in broad patient populations (and subgroups of interest) over longer outcome periods than typically used in RCTs.[6] They can also inform meaningful cost-effectiveness models and test and challenge clinical research hypotheses un-evaluable in the RCT setting.

The use of long-term, real-life clinical data (and the non-interventional nature of observational studies) means they have high external validity. However, they are limited by the lack of

• Expert clinical working group to advise on appropriate interpretation of disease-related coding within research databases
• A priori planning: → Patient eligibility criteria → Study Design → Outcomes definitions → Statistical analysis plan (with relevant statistical modelling/ matching informed by baseline data)
• Use of meaningful (sensitive and responsive) outcome measures
• Evaluation of outcomes across appropriate subgroups (and in both matched and unmatched cohorts) to ensure consistency and robustness of analyses
• Validation of outcomes and results, e.g. using patient reported outcomes (PROS) and alternative databases
• Steering Committee for indepenent review of study protocol, a priori outcomes, baseline data, statistical analysis plan and outcomes
• Registration of studies with relevant clinical trial repositories (e.g. ClinicalTrials.gov)
• Commitment to publish all results at relevant congresses and/or peer reviewed journals
• Adherence ro relevant publication guidelines, e. g. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)

Figure 3. Checklist for ensuring high-quality observational and real-life research (devised by Research in Real Life: www.rirl.org)

treatment randomisation, by potential bias through subjectivity of treatment choice, and the inclusion of patients with many and varied, potentially confounding, characteristics. Well-designed database studies overcome some of these challenges by defining a priori patient cohorts and outcomes based on a pre-specified index event (e.g. a recorded treatment change), which can result in useful hypothesis testing (see Figure 3 and later study examples).

Concerns around potential differences between treatment cohorts in comparative observational studies can be addressed by a number of statistical techniques. Statistical modelling (e.g. regression modelling) can be used to adjust outcomes for statistically and/or clinically significant differences noted between treatment arms over a baseline evaluation period occurring prior to the index event of interest. To further minimise potential confounding by indication, patients in comparator treatment arms can be matched on a number of key predictive variables identified through baseline characterisation (e.g. demographic characteristics—age and sex—and clinical characteristics—exacerbations, asthma treatment and respiratory resource utilisation). Alternatively, matching can be performed based on propensity scores, where patients are matched on their probability of being assigned to a particular treatment arm given a set of known covariates. Statistical modelling (conditional logistic regression modelling) can then be used to account for any residual differences remaining between treatment arms following matching. Another approach used to mitigate concerns around the robustness of observational study findings is the performance of pre-defined subgroup analyses to demonstrate consistency of results across all relevant patient groups.

The possibility remains that some differences between treatment cohorts may be indiscernible through evaluation of routine practice data, which are usually less detailed than in RCTs. These concerns are mitigated by use of datasets comprising the minimal set of variables (defined a priori) required to adequately characterise patients to test a given hypothesis, and by validating results across a variety of relevant subgroups, and across different datasets. Furthermore, outcomes should be selected a priori, tested (as to their relevance regarding the database content) and kept consistent across studies to avoid biases in the analysis itself, which could lead to over- or under-estimations of treatment effects. The goal is that use of rigorous methodologies (as described above) should result in only the minimum of residual bias in observational studies; bias too subtle to have a clinically relevant impact on results.

The move towards registration of funded clinical trials in online study databases and centralised repositories (e.g., http://www.clinicaltrials.gov), and greater adherence to standardised, high-quality publication standards (e.g. those published by STrengthening the Reporting of OBservational studies in Epidemiology [STROBE, http://www.strobe-statement.org]) should also help increase the transparency and improve wider communication of quality methodologies in observational research.

Combining Study Data

Concerns surrounding the limitations in extrapolating RCT findings to wider patient populations are particularly pertinent when considering outcomes in patient subgroups. In asthma, subgroups of particular interest include those with poor inhaler technique and/or low adherence, current smokers, patients with comorbid conditions (e.g., rhinitis) and overweight/obese patients.[35–46] When considering inhaler handling, for example, RCTs require patients to have good technique, yet there are data to suggest that correct use of inhalers is variable and that improper use of pressurised metered-dose inhalers (pMDIs) for the delivery of inhaled corticosteroids (ICS) is associated with decreased asthma control.[39]

Smoking and severity of rhinitis are also important determinants of asthma control; patients with severe rhinitis and/or higher average cigarette consumption exhibit poorer control.[35] While cigarette smoking is known to reduce the effect of ICS therapy,[44–46] a subgroup analysis of the recent ELEVATE study suggests therapeutic benefit of leukotriene receptor antagonists (LTRA) is maintained among asthma patients, irrespective of their smoking status.[24] Other factors that have been shown to affect asthma patients' response to therapy are obesity, likely through inflammatory mechanisms and alterations in lung mechanics,[40] and presence of comorbidities such as chronic obstructive pulmonary disease and heart failure.[47] Indeed, such real-life factors may explain the

wide gap between the level of asthma control that can be achieved in RCTs and the frequently disappointing results observed in observational studies carried out among less selected populations.[16, 48]

By excluding from RCTs all patients except those meeting an "idealised" set of patient eligibility criteria, the perceived efficacy and safety of therapies may be biased, over-stated and/or unrepresentative of their true, real-life safety and effectiveness.

Extending the Evidence Base

Step-up Options

What the RCT-based Guidelines Say

GINA guidelines recommend the initiation of low-dose ICS or use of an LTRA for patients who remain symptomatic despite use of as-needed short-acting bronchodilator therapy (i.e. recommend stepping up from Step 1 to Step 2 therapy). For patients who fail to achieve optimal control despite Step 2 management, further step-up options include medium- or high-dose ICS or the addition of a long-acting bronchodilator (LABA) or LTRA to low-dose ICS (Step 3 management).[3]

UK guidelines assign the highest evidence grade to the statement: *Inhaled steroids are the most effective preventer drug for adults and older children for achieving overall treatment goals*.[1] At the more severe end of the management spectrum, in patients who remain 'high risk' (in terms of asthma exacerbations) and sub-optimally controlled despite use of medium- or high-dose ICS plus LABA therapy or LTRA plus sustained-release theophylline (Step 3), the guidelines recommend possible use of add-on therapies, including lowest-dose oral steroids and anti-IgE therapy, alone or in combination (Step 4).[1–3]

What 'Real-life' Complementary Studies Suggest

LTRAs are not commonly prescribed as first-line or add-on anti-inflammatory therapy in the UK because of limited RCT data to support their efficacy as compared with that of ICS (in mild persistent asthma) and with that of LABA add-on therapy (in moderate asthma).[49–54] Yet the UK Health Technology Assessment Programme commissioned ELEVATE — two separate, 2-year pragmatic trials to investigate the real-life effectiveness of LTRA therapy compared with ICS for patients initiating maintenance asthma therapy (GINA Step 2), and LTRA add-on compared with LABA add-on therapy in patients with uncontrolled asthma despite maintenance ICS therapy (GINA Step 3).[24]

ELEVATE's pragmatic design differed from that of a classical RCT by using broad inclusion criteria and evaluating effectiveness outcomes over an initial 2-month period, but also over a longer-term, 2-year period.[24] The primary endpoint was asthma-related quality of life—a patient-oriented measure of effectiveness—assessed by the Mini Asthma Quality of Life Questionnaire (MiniAQLQ). Patients continued to participate in the study even if they did not receive and complete the full, prescribed regimen, thus it was a true intention-to-treat (ITT) study. As a result of the ITT approach, the 2-year dropout rate was only 4%, which compares favourably with dropout rates seen in some of the larger asthma RCTs (e.g., 25% in GOAL[16] and 16% in IMPACT[15]). As patients continued to receive care at their usual practices, ELEVATE achieved high levels of complete data – more than 90% of patients had 2-year data for the primary endpoint, and more than 95% for healthcare resource and asthma exacerbations.

At 2 months, LTRAs were equivalent to the guideline-recommended reference alternative treatment strategies in terms of the MiniAQLQ. At 2 years, true equivalence was not shown, but there were no significant differences between LTRAs and the alternative treatment strategies for primary or secondary outcome measures. Also of note was that, in contrast to ICS, the benefit of LTRA therapy at 2 months remained largely consistent irrespective of smoking status.[24]

As yet, the results of ELEVATE have not been repeated in further pragmatic, or classical, trials. The differences seen in ELEVATE and those of classical RCTs could be explained by several factors including patient characteristics (presence of smokers or overweight patients), adherence and inhaler technique (see below). However, the ELEVATE authors concluded that their findings suggest a need for caution when extrapolating results from RCTs to the broad population of patients with asthma who are treated in community settings and that clinical decisions should take into account data from RCTs and pragmatic trials.

Another UK study explored the implementation of guideline-recommended strategies to characterise real-life prescribing patterns in patients with more severe asthma (GINA Step 4).[55] This cross-sectional study using the GPRD evaluated the use of recommended add-on therapy in asthma patients who remained inadequately controlled or high-risk despite high-dose ICS (≥800mcg beclometasone-equivalent daily dose) plus LABA therapy. Inadequate control was defined as evidence of ≥1 exacerbation in the prior year, and high-risk as ≥2 exacerbations in the prior year. Eighteen percent (18%) of this population were categorised as being high-risk, yet (of these) less than one-third (30%) were being prescribed therapy in addition to high-dose ICS plus LABA. The study findings suggest there is limited implementation of asthma guidelines in routine UK primary care and, possibly as a result, potential sub-optimal asthma management (evidenced by recurrent asthma exacerbations) among high-risk patients.

Adherence

What the RCT-based Guidelines Say

Asthma guidelines make no differentiation between relative adherence rates for different therapeutic options and recommend only that a patient's adherence to their prescribed regimen and level of asthma control be assessed prior to stepping up existing therapy. Yet adherence is a well-recognised management challenge across all chronic diseases; adherence to asthma medication in developed countries is estimated at only 50%.[56–61] Suboptimal adherence can result in impaired health-

related quality of life; unnecessary costs to healthcare systems due to medication wastage and emergency healthcare utilisation resulting from poorly controlled disease.[62–65]

RCTs' selection of only highly-adherent patients (often ≥90% adherent), to maximise causation between trial therapies and measured outcomes, coupled with the fact that RCT interventions may drive adherence, can potentially bias and over-estimate treatment-related outcomes.

What 'Real-life' Complementary Studies Suggest

Pragmatic trials offer the possibility of evaluating adherence in a more naturalistic setting than RCTs.[66, 67] One such approach was used in a pragmatic study designed to compare adherence to once-daily and twice-daily mometasone furoate. Adherence data was captured using patient self-report and dose counters.[67] Patients with poor adherence remained in the study and were included in the final analysis. Using this pragmatic approach, a discernible difference in rates was measured with greater adherence recorded for the once-daily regimen.[67]

In the aforementioned ELEVATE pragmatic study, differential adherence rates were reported for LTRA compared with the alternative treatment strategies. The authors concluded that the significantly higher adherence rates recorded for LTRA compared with the alternative treatment strategies (65% vs 41% for ICS, and 74% vs 46% for add-on LABA) were realities of real-world prescribing and, thus, part of the true, overall treatment effect.[24]

In observational, clinical database studies, adherence is frequently evaluated using proxy measures, such as the medication possession ratio (MPR). The MPR provides a percentage representation of the number of days a patient's collected therapy would last them over the course of a year. The MPR provides an indication of a patient's maximum possible compliance, with the caveat that there are no data available on whether patients actually take prescribed therapies. In a real-life comparative effectiveness study of two ICS therapies (extrafine hydrofluoroalkane belcometasone dipropionate [EF HFA-BDP] and fluticasone propionate [FP]) widely used in the United States (US), median MPR was low in both cohorts; less than 10% of patients in any treatment group had an MPR of 80% or above.[68]

Inhaler Device Type

What the RCT-based Guidelines Say

Available devices used to deliver inhaled asthma therapies include pressurised metered-dose inhalers (pMDIs), breath-actuated pMDIs (BAIs) and dry powder inhalers (DPIs). Device preparation and handling vary greatly according to device type, and even inhaler brand. Many real-life asthma patients use their inhaler devices incorrectly, and proper inhaler technique is not consistently or regularly reinforced.[69, 70] The effectiveness of inhaler device and their suitability for a patient is paramount in ensuring inhaled asthma therapies reach the lungs and target the key sites of asthmatic inflammation. Ensuring patients use their inhaler devices correctly remains a challenge for physicians.

Prescribing of asthma inhalers differs substantially among countries, likely influenced by 'tradition' as well as device availability, relationships with pharmaceutical companies and local guidelines. RCTs have typically concluded that outcomes for different devices delivering ICS monotherapy are comparable. Similarly, the handful of trials comparing inhalers for license-equivalent fixed dose combination (FDC) ICS/LABA report similar outcomes with different types of inhaler device.[71–73] Yet those patients included in RCTs are typically trained in inhaler technique and frequently monitored to ensure they maintain proper inhalation technique throughout.[1–3] As a result, there are limited unequivocal data on the true role of the different inhaler types available and guidelines offer little steerage on inhaler selection. Indeed, in the UK, the British Thoracic Society / Scottish Intercollegiate Guidelines Network (BTS/SIGN) assign their highest evidence grade to a statement on their lack of difference: *In adults, there is no clinical difference in effectiveness of pMDI ± spacer v DPI. Breath-actuated MDI is as effective as pMDI. More recent DPIs are as effective as older DPIs*.[1]

What 'Real-life' Complementary Studies Suggest

The non-interventional nature of observational studies can provide useful insight into the role of inhaler devices in real-life asthma management.

The REALITY study used the UK's GPRD to evaluate the comparative effectiveness of different inhaler types as used by asthma patients managed on maintenance ICS in routine care.[74, 75] Participating patients initiated or increased ICS therapy via pMDIs, BAIs, or DPIs. No requirements were placed, or indeed were discernible, on patients' inhaler technique training. Significantly higher odds of achieving the proxy asthma control outcome (defined as no prescriptions for acute oral steroids for asthma, antibiotics for lower respiratory infections and no emergency healthcare utilisation for asthma) were found for both BAI and DPI inhalers compared with pMDIs.[75] The results had significant health economic implications, with BAIs (on average) being more cost-effective than pMDIs.[74]

A second GPRD study using a robust, retrospective, matched cohort design, considered the role of inhaler device in FDC ICS/LABA therapy.[76] One-year comparative outcomes were evaluated for patients initiating FDC ICS/LABA as fluticasone/salmeterol delivered via pMDI or DPI devices. Compared with the DPI cohort, patients receiving therapy via pMDI had significantly greater odds of achieving asthma control (as per the REALITY study definition, above) during the outcome year and numerically (but not significantly) lower exacerbation rates. This finding challenges the guidelines statement of equivalence of pMDI and DPI devices, and received clinical opinion of the possible superiority of DPI devices. The authors speculated on the reasons for their findings and noted that DPIs are less frequently prescribed in the UK than pMDIs, which may have led to less

proficient teaching of DPI handling techniques or to an indiscernible selection / prescribing bias despite the use of patient matching to minimise potential biases. Moreover, the authors hypothesised that the bronchodilator within the combination therapy might have helped patients with pMDI coordination errors to recognise and auto-correct their coordination issues, resulting in more proficient usage than with pMDI ICS monotherapy.

Whatever the underlying reason, or combination of reasons, for the better outcomes associated with pMDI compared with DPI in the FDC ICS/LABA study population, the findings highlight the role that observational studies can play in differentiating between real-life treatment options considered to be equivalent in the RCT setting.

The Role of Particle Size

What the RCT-based Guidelines Say

When the Montreal Protocol recommended the phasing out of chlorofluorocarbons (CFC) in medical devices, manufacturers typically replaced CFC with an alternative propellant, hydrofluoroalkane (HFA), without making any adjustments to the ICS formulation. Yet some took the opportunity to refine the formulation to allow delivery of ICS with a greater extrafine particle fraction. Extrafine particle (EF) HFA beclometasone (BDP), for example, has a mass median aerodynamic diameter of 1.1µm compared to the larger 3.5–4.0µm for traditional CFC BDP.[77] Dose-ranging studies suggest that EF HFA-BDP has: significantly greater effects on lung function than CFC-BDP on a microgram-for-microgram basis;[78] significantly better, and more even, lung deposition (55–60% compared with 4–7% for CFC-BDP in healthy volunteers), and reduced oropharyngeal deposition (29–30% versus 90–94%).[79–81] As a result, guidelines recommend EF HFA-BDP for use at half the dose of larger-particle BDP formulations.[82]

What 'Real-life' Complementary Studies Suggest

A series of observational studies have investigated the potential role of particle size in the effective management of real-life asthma. The observational studies compared EF HFA-BDP to larger particle ICS alternatives using a matched cohort design and observational data from three national datasets—the clinical GPRD and OPCRD databases in the UK, and the insurance Ingenix Normative Healthcare Database in the US. To minimise potential confounding of results due to inhaler device types (see earlier discussion), patients in all studies were limited to those receiving therapy via pMDI only. For consistency, standard asthma control outcome measures were used across all the studies.[68, 83, 84]

In the UK, EF HFA-BDP was compared with CFC-BDP and with the commonly prescribed ICS fluticasone propionate (FP).[83, 84] In the US, where CFC-BDP was not used during the study period, EF HFA-BDP was

	EF HFA-BDP vs CFC-BDP[a] CFC-BDP as the reference group (OR, 1.00)	
	Invitation population	Step-up population
	EF HFA-BDP (N=2,882)	EF HFA-BDP (N=258)
Primary measure of asthma control, adjusted OR (95% CI)	1.15 (1.02-1.28)[b]	1.72 (1.14-2.56)[c]
Exacerbation during the outcome year, adjusted rate ratio (95% CI)	0.95 (0.81-1.12)[d]	0.64 (0.39-1.05)[e]
	EF HFA-BDP vs FP[a] FP as the reference group (OR, 1.00)	
	Invitation population	Step-up population
	EF HFA-BDP (N=1,319)	EF HFA-BDP (N=250)
Primary measure of asthma control, adjusted OR (95% CI)	1.30 (1.02-1.65)[f]	1.22 (0.66-2.26)[g]
Exacerbation during the outcome year, adjusted rate ratio (95% CI)	0.96 (0.85-1.08)[f]	1.08 (082-1.43)[g]

[a] 2-way matched analyses of EF HFA-BDP vs FP, and EF HFA-BDP vs CFC-BDP, respectively, outcomes for the matched treatment arms were adjusted for residual baseline difference

[b] Adjusted for age and baseline paracetamol prescriptions, antibiotics, and number of non-asthma-related consultations

[c] Adjusted for number of non-asthma-related consultations

[d] Adjusted for age and baseline antibiotics and number of non-asthma related consultations

[e] No significant effects (unadjusted OR)

[f] Adjusted for year of index date, acetaminophen, asthma consultations, rhinitis diagnosis, and cardiac disease diagnosis

[g] Adjusted for year of index date, acetetaminophen, asthma consultations and rhinitis diagnosis CFC-BDP: chlorofluorofluorocarbon beclomethasone dipropionate; EF HFA-BDP: extra-fine hydrofluoroalkane beclomethasone diproprionate; FP: fluticasone propionate

Figure 4A. Extrafine particle formulation of HFA-BDP demonstrated consistently comparable, or better, asthma control outcomes than larger particle BDP and FP across asthma steps (ICS initiation or step-up).

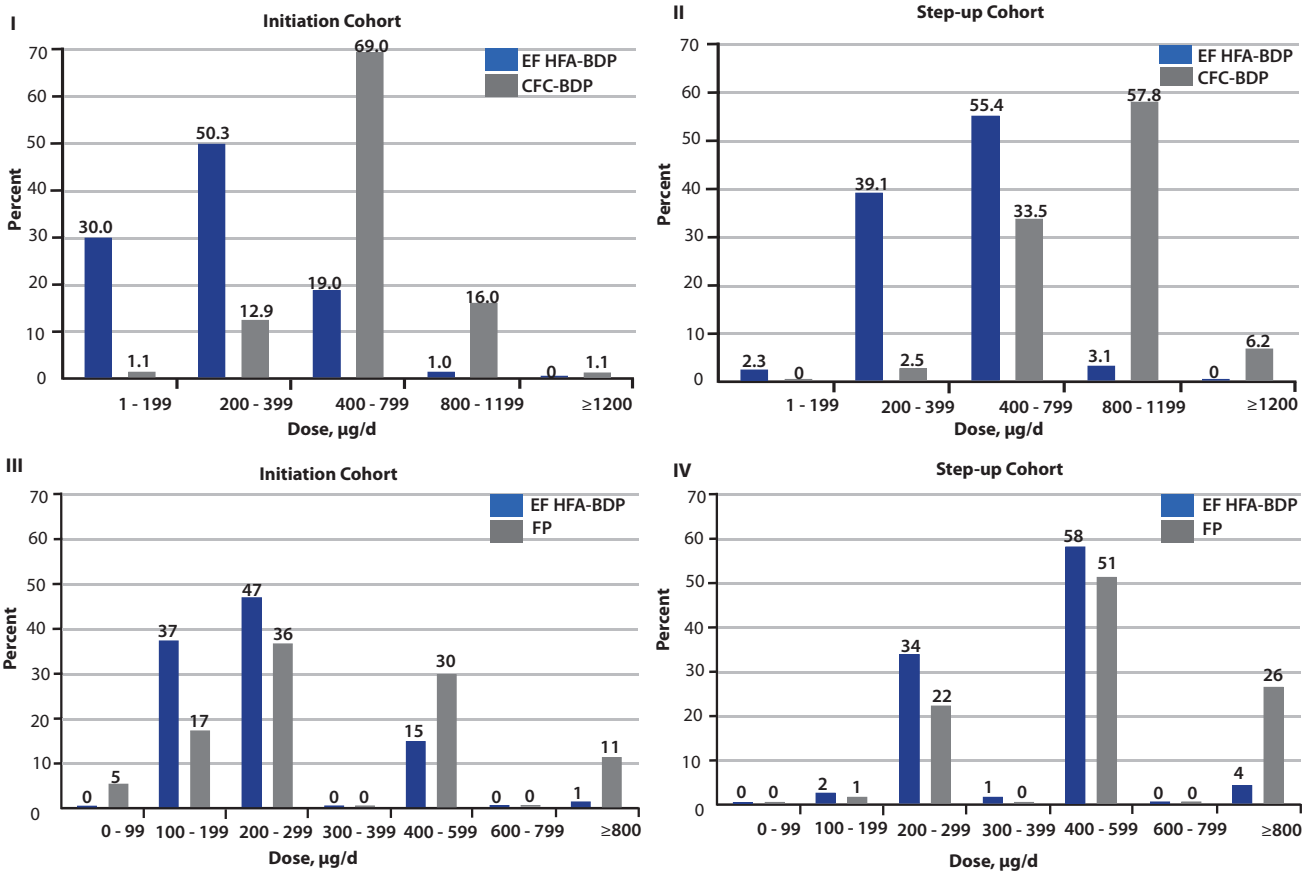

Figure 4B. The extrafine HFA-BDP achieved at least as good outcomes as FP despite being prescribed at significantly lower dose (when guidelines recommend equivalent mg-mg dosing).[83–85]

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compared with FP only.[68] Patients receiving EF HFA-BDP consistently achieved similar or better asthma control outcomes than FP and CFC-BDP, despite significantly lower microgram-per-microgram dosing of EF HFA-BDP (see Figure 4). The robustness of the results was reinforced by similar outcomes across mirrored unmatched cohort analyses and across age and smoking status sub-analyses, making any remaining systematic bias (i.e., confounding by severity) unlikely to be relevant.

The consistency of the outcomes across three national datasets, and independent of management step, age or smoking status, provides compelling data to suggest that ICS formulation characteristics, including particle size and resulting action site within the lung, may play an important role in achieving effective real-life asthma control. Moreover, the consistently higher dosing of FP, despite guideline recommendations for equivalent EF HFA-BDP and FP dosing suggests a possible misunderstanding of the dose-equivalents of commonly prescribed ICS and poor implementation of the dosing ratios recommended by asthma guidelines.

Conclusions

The studies discussed in this review, at points, reinforce the validity of guideline-recommended treatment strategies, but they also provide useful supplementary data on the comparative effectiveness of therapies. They look more closely at outcomes achievable in real-life (less selected) patients and relevant subgroups and on the potential role of inhaler device, particle size and dosing frequency on achieving asthma control outcomes in routine primary care.

The real-life and pragmatic studies contained within this review offer data that (i) provoke thought about the most appropriate controller therapy in patients with mild and moderate asthma (especially among those who smoke); (ii) suggest ICS particle size and asthma inhaler device may play important roles in achieving effective real-life asthma control, and (iii) demonstrate a potential interaction between dosing frequency and treatment compliance.

While pragmatic and observational studies lack the internal validity of RCTs, their broader inclusion criteria increase external validity and reduce the potential outcome bias associated with highly-selective classical RCT populations. Furthermore, limitations in the internal validity of pragmatic trials and observational studies can be improved by detailed a priori analysis planning, rational hypotheses, independent

review and by seeking consistency of results across relevant subgroups (see Figure 3). When adhering to these best practice standards, pragmatic and observational studies generate valuable data on longer-term (comparative) effectiveness and safety outcomes of therapies that can be evaluated across diverse patient populations, or within particular subgroups of interest that are often excluded by classical RCTs. In this way, they can shed light on aspects of asthma care either omitted from, or potentially un-evaluable in, the RCT setting.

The important role of classical RCTs in providing the safety and efficacy data used to evaluate and license new therapies remains unequivocal. While their strict inclusion criteria and protocols provide the most robust cause-and-effect data available on treatment-related outcomes, such selection criteria may artificially inflate, or bias outcomes. Furthermore, the reluctance by pharmaceutical companies to provide easy access to placebo for trials, other than their own, is a major obstacle to the performance of independent research; research that might generate data quite different to that originating from the highly-selective funded RCTs.

No study design is without its limitations, and with sparse head-to-head drug comparisons and growing recognition of the need to understand how therapies compare and perform in routine care, pragmatic trials and observational studies can provide valuable safety and effectiveness data to complement that from RCTs.[85] As proposed by ARIA (Allergic Rhinitis and its Impact on Asthma) and GA2LEN (Global Allergy and Asthma European Network), a combination of all these approaches is probably needed because all have advantages and drawbacks and they are not designed to answer the same questions.[86]

Clinicians must continue to use best practice guidelines to inform their prescribing decisions, but must also challenge the robustness and completeness of the supporting data in order to maintain and improve outcomes for their patients.

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Telehealth Helps Improve Care for Patients with COPD

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Telehealth services are expected to grow significantly over the next decade, driven by a trio of major healthcare pressures - the rising prevalence of chronic diseases, an ageing population and budget restraints. For patients with long-term conditions such as COPD, remote monitoring is proving to be a valuable approach, with the latest research showing hospitalisations and Accident & Emergency (A&E) visits reduced by more than half.

The 2012 ERS congress was the ideal venue to showcase the latest developments in remote patient monitoring – a growing specialist area. Globally, the entire telehealth market has been calculated to be worth $US3.5 billion in 2011[1] and the prediction is that this will almost treble by 2016 to $US9.7 billion.

The service allows clinicians to observe patients' physiological data remotely, using telecommunication and wireless technology. The home-based devices measure and monitor vital signs including temperature, blood pressure, weight and oxygen saturation, and forwards the data electronically for review by the clinical team. Clinicians can diagnose exacerbations in existing conditions at an early stage, as well as monitoring chronic conditions.

How it Works

The telehealth service is backed up by a team of highly-trained nurses and technicians, at dedicated national call centres and centrally located workshops. The equipment is provided and installed in the patient's home, including a hub and peripherals such as pulse oximeters or blood pressure cuffs. Trained staff install the equipment and provide patients with education and training. They also handle equipment cleaning and verification, on-going monitoring, follow-up, a support helpline and removal of equipment when required.

Why it Matters

Telehealth is a research-proven solution to the demographic and financial pressures facing today's healthcare organisations. In the UK, for example, there are currently 15.4 million people with a long-term condition. This is set to rise to 18 million by 2025, forcing a shift in healthcare towards earlier detection and better prevention. Estimates by the United Nations suggest the population aged 60 and over will increase 50% by 2050. An older population will place higher demands on public services. Increasingly, individuals are likely to have less support from an extended family network but will still expect, and should have access to, a good, quality service. Other factors influencing healthcare include declining birth rates, which will mean fewer recruits to take up care roles, and the ever-growing demand for efficiency savings.

Latest Research

The PROMETE study,[2] a randomised controlled trial to establish the efficacy of a home telehealth service was presented at ERS congress. The trial was conducted in Spain at the Pneumology Department, Hospital Unversitario La Princesa, Madrid, and four local primary care centres at Goya, Montesa, Lagasca and Castello. Telehealth equipment, homecare assistance and a clinical call centre were provided by Linde Healthcare, a global business unit of The Linde Group.

Sixty patients with severe COPD were split into two groups - the intervention group received the home telehealth service and the control group received conventional healthcare. Patients included in the trial had severe COPD, GOLD stage IV, were on home oxygen therapy and had experienced at least one exacerbation episode leading to hospitalisation in the previous year. Vital signs including blood pressure, heart rate, blood oxygen saturation and peak-flow were monitored daily.

The results showed the telehealth group experienced a decrease of more than 60% in the number of hospitalised days, a 65% decrease in A&E visits and a 60% decrease in hospitalisations due to COPD exacerbations. The control group experienced one hospitalisation in ICU and eight patients required further treatment with non-invasive ventilation. None of the patients in telehealth group required this treatment. The researchers also found patients' acceptance of the home telehealth service was high, with an average 8.95 score on a scale of 10 (Table 1).

The team concluded: "Home telehealth services are effective in the follow-up of patients with severe COPD, and considerably reduce the number of hospital admissions, days of hospital stays and A&E visits, as

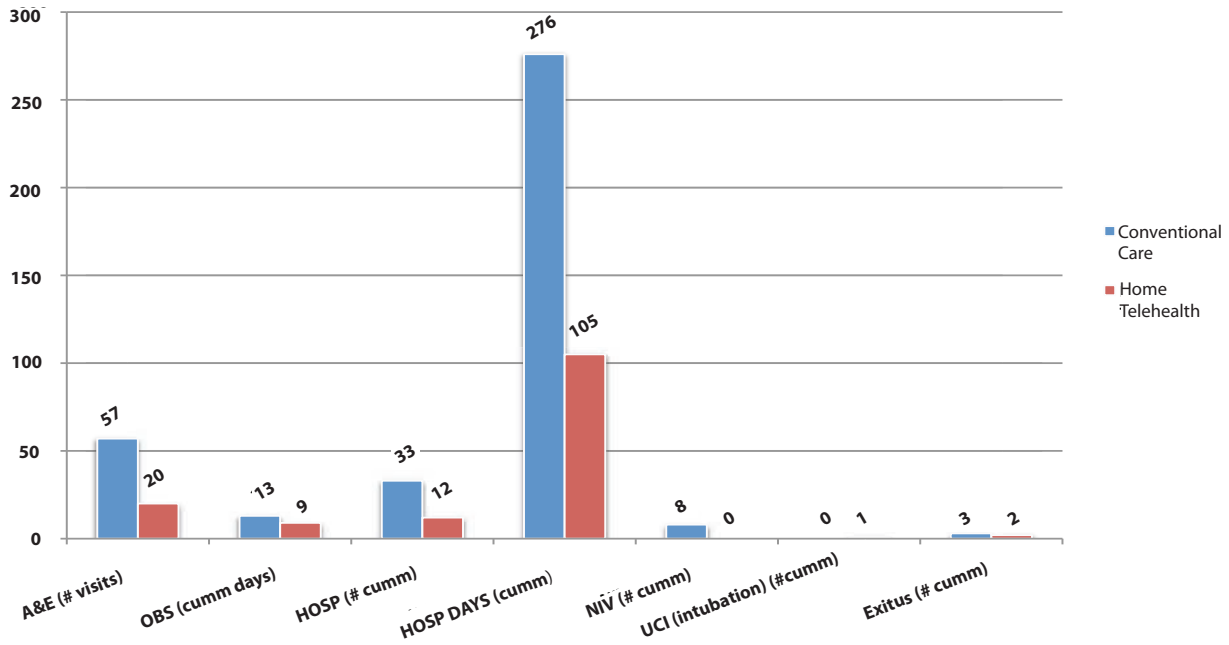

Table 1. Hospital resources usage for both Home Telehealth and Conventional Care groups: The results of the PROMETE study showed the telehealth group experienced a decrease of more than 60% in the number of hospitalised days, a 65% decrease in A&E visits, and a 60% decrease in hospitalisations due to COPD exacerbations.

compared with the control group. Patients adapted well to the telehealth service, and no withdrawals have been observed related to difficulty in the use of the telehealth equipment."

The study has been reported in independent publications, such as the Journal of Telemedicine & Telehealth, and has won the 2012 sustainable innovation award from the Spanish Federation for Health Technologies.

Comprehensive Service

In order to generate maximum value from telehealth, it is important to provide a comprehensive service, where patients receive consistent and ongoing support. Only after this is in place can the benefits - including improved quality of life for patients and cost-savings - and potential of telehealth be fully harnessed. The service needs to integrate all the non-clinical elements, combining homecare technology with end-to-end service support for patients, clinicians and commissioners. This includes: providing the equipment; installation; patient education and reference material; asset management and equipment care; technical triage - consisting of a technical support helpline and home-visiting technician; clinical triage, which includes identifying at-risk patients through threshold monitoring; an easy-to-use web-based portal for clinicians supported by one-to-one training; and 24-hour technical support and user manuals. (Figure 1)

Fig 1. An example of homecare technology

A fully-integrated telehealth service means supporting patients' understanding and adherence, as well as providing a friendly voice at the end of the phone if they have questions or concerns. This gives patients consistency and reassurance. But while patients' needs are paramount, the telehealth service is built around the needs of clinicians, freeing them up to concentrate on their clinical work.

Shift to Home-Based Care

The cost of treating chronic conditions is inexorable. In world rankings, COPD was the sixth cause of death in 1990 and is expected to jump to fourth position by 2030, due to increases in smoking and demographic changes. Linde Healthcare sees telehealth as a vital part of the move towards more home-based care, helping clinicians and managers to strike the right balance between hospital and primary care spending and make the best possible use of scarce

Fig 2. The use of technology can help people manage their own health, while maintaining their independance.

clinical resources.

It's a view being picked up on by more than individual healthcare organisations. In the UK, the government has responded by setting up a major project, the Whole System Demonstrator (WSD) programme, to investigate how technology can help people manage their own health, while maintaining their independence (Figure 2). The WSD programme is believed to be the largest randomised control trial of telecare and telehealth in the world to date, involving over 6,000 people across three sites. Headline findings show these services can substantially reduce mortality, hospital admissions, the number of days spent in hospital and time spent in A&E.

ERS Congress

This year's congress was the first opportunity for Linde Healthcare and its newly-acquired Air Products continental European homecare business to meet under the same banner to demonstrate its range of combined services for chronic respiratory care. These included: LISA® (Leading Independent Sleep Aide) a programme to help patients cope with sleep-disordered breathing; VisionOx®, a monitoring device that attaches to patients' equipment to measure breathing frequency, oxygen flow and usage duration helping predict exacerbations and monitor patients' adherence to home oxygen therapy; Adherence Management online tools, that allows clinicians to access therapy-related information for patients and make timely decisions to increase therapy adherence; REMEO®, for long-term ventilation care; and a pulmonary rehabilitation exercise and education programme for patients with COPD.

The ERS congress provided a useful platform to demonstrate Linde Healthcare's competence far beyond just delivering medical gases, and allowed Linde Healthcare to demonstrate its significant experience, expertise and active involvement in home respiratory services. World-class telehealth services are a must for today and tomorrow's healthcare organisations and, if expertly provided, they will deliver high levels of patient satisfaction and significant benefits and cost savings.

Key Telehealth Benefits

For Patients

• Improves patient outcomes by avoiding exacerbations and hospitalisations.
• Increases quality of life for patients who are able to stay at home.
• Helps patients to understand more about their condition and enables them to be more involved in their ongoing treatment and care.
• All elements of the service come from Linde Healthcare, so patients have contact with one organisation for equipment installation, education and training, telephone support and equipment removal. Help is just a phone call away, 24 hours a day.

For Clinicians

• The telehealth service is simple and easy to use.
• Large numbers of patients can be managed. With easy access to patient data, clinicians can manage their patients efficiently and workloads are reduced.
• Access to ongoing patient history allows the clinical team to anticipate and identify acute events.
• Clinical resources can be firmly focused on caseload prioritisation and patient management. Day-to-day management of the telehealth service is handled by Linde Healthcare.
• Non-compliance and technical issues are followed up by Linde Healthcare.

For the Health Service

• Case loads can be more effectively managed.
• Unplanned hospital admissions are reduced due to earlier interventions and preventative measures.
• Earlier discharge is possible.
• Early detection allows proactive action before a situation develops into a full medical emergency.

Linde Healthcare

Linde Healthcare is part of the Linde Group, a world-leading gases and engineering company. Linde's focus on healthcare – as one of its three strategic pillars – has led it to become the second largest supplier of medical gases and related services in the world. It is this on-going commitment to expanding its competencies and scaling up its product and services in this field – alongside the company's belief in the role of home-based chronic disease monitoring and management – that led Linde Healthcare to recently acquire Air Products' homecare business in continental Europe.

Linde now delivers quality care to a further 250,000 patients, and the acquisition makes the company one of the market leaders in the European respiratory homecare business, significantly strengthening its position in this growing healthcare market. The move also puts Linde in a strong position to drive innovation and develop new

services, which will, among other developments, help boost the uptake of telehealth services worldwide.

For more information, visit: http://www.linde-healthcare.com.

The Linde Group

The Linde Group is a world-leading gases and engineering company with around 51,000 employees in more than 100 countries worldwide. In the 2011 financial year, it generated revenue of EUR 13.787 bn. The strategy of The Linde Group is geared towards long-term profitable growth and focuses on the expansion of its international business with forward-looking products and services. Linde acts responsibly towards its shareholders, business partners, employees, society and the environment – in every one of its business areas, regions and locations across the globe. The Group is committed to technologies and products that unite the goals of customer value and sustainable development.

For more information, see The Linde Group online at http://www.linde.com.

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Dual Virus-bacteria Infections in COPD Exacerbations

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Introduction

Chronic obstructive pulmonary disease (COPD) is predicted to be the 4th most common cause of death by 2030. It is characterised by poorly reversible lung function, airways inflammation and impaired health status, and the occurrence of acute exacerbations that become more common as the disease progresses. Acute exacerbations are associated with accelerated loss of lung function, impaired quality of life and enormous morbidity and mortality. Therefore, preventing exacerbations is a major therapeutic goal that has not been achieved with currently available treatments. The major causes of exacerbations are respiratory infections with both viruses (predominantly rhinoviruses) and bacteria implicated, although the relative contribution of these remains debated. Rhinovirus infection can increase susceptibility to bacterial infection in *in vitro* models but it is not known whether this occurs *in vivo* and whether dual infection contributes to COPD exacerbations. New data from an experimental rhinovirus infection model of COPD exacerbation has provided new evidence that dual viral/bacterial infection may be important in COPD and should provide a new impetus for the development of antiviral therapies as novel treatments for COPD exacerbations.

Infection and COPD exacerbations

Bacterial infection has long been considered the main cause of COPD exacerbations. Numerous studies have reported high rates of bacterial infection in samples collected during exacerbations, but bacteria can also be present in stable COPD patients.[1] Studies comparing rates of bacterial detection in stable and exacerbated patients have generally reported higher infection rates in exacerbations, providing evidence for a causative role of bacteria in exacerbations.[1-4] The most common bacteria detected in COPD exacerbations are *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*. The perceived role of bacteria in COPD exacerbations has underpinned the use of antibiotics as a mainstay of treatment, however the effect of antibiotics and the role of bacteria in COPD exacerbations continues to be debated.[5]

The greater frequency of exacerbations in the winter months,[6] and the occurrence of upper respiratory symptoms preceding exacerbations suggest a link between respiratory virus infections and COPD exacerbations.[7] Older studies investigating the role of viruses in COPD exacerbations reported detection rates of ~10-20% of exacerbations,[8,9] casting doubt on the role of virus infection. However the diagnostic methods used in these studies had low sensitivities for virus detection, especially for rhinoviruses that are the commonest cause of viral upper respiratory tract infections. The application of molecular diagnostic techniques such as PCR led to a re-evaluation of the role of viruses in COPD exacerbations. Studies using PCR have detected viruses in up to 47-56% of exacerbations[1, 10-13] with picornaviruses (predominantly rhinoviruses) the most frequently detected viruses.[14] However, the role of virus infection in COPD exacerbations continues to be debated as PCR detects very small amounts of viral nucleic acid, and therefore does not definitively prove the presence of live virus. However it is equally possible that the role of viral infections in COPD exacerbations has been underestimated, as patients are evaluated at the time of presentation which may occur considerably later than the initial viral infection. As rapid diagnostic methods and antiviral agents become available, the relationship between virus infections and COPD will no longer be of just academic interest but will have potential therapeutic implications, and therefore warrants further study.

Bacteria-virus Interactions

In Vitro Studies

Viral and bacterial infections can modulate host immunity and thereby alter immune responses to subsequent infections. It is well established that influenza infection can impair host antibacterial immune responses, and this can result in secondary bacterial pneumonia.[15, 16] However although the most common viruses detected in COPD exacerbations are rhinoviruses, little is known about the relationship between rhinovirus infection and bacterial infection. A number of studies have evaluated the effects of rhinovirus on bacterial infection in *in vitro* models. Rhinovirus infection of nasal epithelial cells results in increased adherence of *Streptococcus pneumonia*, *Staphylococcus aureus* and *Haemophilus influenzae*,[17] and rhinovirus also increases adherence of *Streptococcus pneumoniae* to human tracheal epithelial cells.[18] Rhinovirus infection upregulated the expression of several surface molecules including fibronectin, platelet-activating factor receptor, and carcinoembryonic antigen-related cell adhesion molecule[17] that mediate bacterial

adherence to cells. Another mechanism whereby rhinovirus infection may predispose to secondary bacterial infections is disruption of the airway epithelial barrier function. Rhinovirus infection *in vitro* reduces transepithelial resistance, induces tight junction breakdown and facilitates bacterial transmigration across polarised airway epithelial cells.[19, 20] In addition to effects on epithelial cells rhinovirus infection of macrophages impairs their responses to bacterial products.[21] Most research has focussed on primary viral infection and secondary bacterial infection, but one study has suggested that bacterial infection can also influence immune responses to viral infection. Infection of epithelial cells by *Haemophilus influenzae* increases susceptibility to infection by rhinovirus, possibly by up-regulation of ICAM-1.[22] As chronic infection with *Haemophilus influenzae* is common in COPD this may be a mechanism of increased susceptibility to virus infection in COPD.

Clinical Studies

In vitro studies have highlighted a number of mechanisms whereby rhinovirus infection may increase susceptibility to bacterial infection, but it is not known whether these are relevant *in vivo*. Biopsy studies have revealed that in human infections, very few epithelial cells are actually infected with rhinovirus and there is minimal cytopathic effect unlike influenza,[23] with the pathological features and symptoms of infection resulting from the host inflammatory response. Therefore the relevance of *in vitro* models to *in vivo* infection is debatable.

Both bacterial and viral infections are common in COPD, but few studies have examined the role of dual infection in COPD exacerbations. The studies that are available have reported dual infection in a minority of exacerbations (average 13%), casting doubt on whether it plays any significant role in COPD exacerbations.[24, 25] However these studies may underestimate the true prevalence of dual infection, as samples were collected at a single time whereas viral and bacterial infections may occur at different time points. Hutchinson *et al*. sampled patients at the onset of exacerbation and again 5-7 days later, and found that 36% of exacerbations in which a virus was detected at onset developed secondary bacterial infection.[26] 71% of patients with bacterial exacerbations had reported symptoms of a viral upper respiratory tract infection prior to onset, so the true association may be even higher. Determining the role of dual infection in COPD exacerbations is difficult in naturally-occurring exacerbations due to variation in times to presentation, the effects of treatment and the difficulty in collecting clinical samples in acutely unwell patients.

Experimental Rhinovirus Infection in COPD

We have developed a model of COPD exacerbation using experimental rhinovirus infection. Inoculation of COPD subjects with rhinovirus induced the typical symptomatic, physiological and inflammatory features of a COPD exacerbation.[27, 28] Using this model to study viral/bacterial interactions in COPD overcomes many of the difficulties previously described that are difficult to resolve with naturally-occurring exacerbations. As the time of onset of exacerbation is known, samples can be collected at pre-determined time points so removing any variability in time to presentation. Multiple samples can be collected during the course of the exacerbation and treatment can be withheld. Therefore the rhinovirus infection model is ideal for examining the relationships between virus and bacterial infection in COPD. Following rhinovirus infection we found that 60% of the COPD patients developed secondary bacterial infections, predominantly *Streptococcus pneumoniae* and *Haemophilus influenzae*.[29] There was no increased incidence of bacterial infection in non-obstructed smokers and non-smokers also inoculated with rhinovirus. Moreover, there was a temporal sequence of rhinovirus infection occurring first with a peak in virus load on days 5-9 post-inoculation, followed by bacterial infection that peaked on day 15 post-inoculation. The incidence of secondary bacterial infection was related to deficiencies in the antimicrobial peptides secretory leukoprotease inhibitor (SLPI) and elafin.

These results suggest that dual infection is more common than was previously thought in COPD exacerbations, but because the viral and bacterial infections occur at different time points, collecting samples on a single occasion will underestimate the true prevalence of dual infection. Furthermore deficiency of antimicrobial peptides may be a novel mechanism of susceptibility to bacterial infection following rhinovirus infection.

Therapeutic Implications

Current therapy for COPD exacerbations consists of supportive treatments (controlled oxygen therapy and nebulised bronchodilators), together with corticosteroids and antibiotics. Corticosteroids have been shown to improve outcomes overall in COPD exacerbations but recent data has suggested that in some patients corticosteroids may have adverse effects.[30] The role of antibiotics is also controversial, with both studies showing no effect and others showing clinical benefit published. A study using procalcitonin as a marker of bacterial infection found that antibiotic use could be reduced from 72% of exacerbations to 40% with no difference in outcomes.[31] Therefore it is likely that antibiotics are overprescribed in COPD exacerbations and this may be due to use of antibiotics in viral exacerbations. The data from our experimental rhinovirus infection studies implicates virus infection as a cause of exacerbations and also contributing to bacterial infections in COPD. Therefore treatment of viral infections may not only prevent viral exacerbations but may also have an impact on secondary bacterial infections. Currently, there are no drugs licensed for treatment of rhinovirus infections. A capsid binding inhibitor (pleconaril) was developed for treatment of rhinovirus infections and shown to have clinical efficacy,[32] but was not approved for use as a treatment for the common cold. There have been no trials of pleconaril in COPD so it is not known whether it is effective in treating rhinovirus induced COPD exacerbations. Other drugs for the treatment of rhinovirus infections are in development, and trials of antiviral agents in COPD are awaited.

A number of *in vitro* studies have suggested treatments that may be of benefit in viral and bacterial infections and therefore may be potential treatments for COPD exacerbations. The antihistamine levocetirizine reduced adhesion of *Staphylococcus aureus* and *Haemophilus influenza* to primary human nasal epithelial cells, probably by reducing expression of fibronectin and CEACAM,[33] and similar effects were seen with the macrolide clarithromycin.[34] Studies have suggested that macrolides can reduce both colds[35] and COPD exacerbations[36] in clinical trials. Macrolides have antibacterial, antiviral[37] and anti-inflammatory effects and all these mechanisms may be important in reducing COPD exacerbations.

Conclusions

COPD exacerbations are a major cause of morbidity and mortality and new treatments are urgently required. Virus and bacterial infections are the main causes of exacerbations and, although dual infection is not commonly detected, evidence from *in vitro* studies and experimental rhinovirus infections suggests this may be more common than was previously thought. Antiviral agents and drugs that reduce bacterial adherence have potential as new treatments for COPD exacerbations.

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Pulmonary Hypertension in Cystic Fibrosis

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Introduction

Cystic fibrosis (CF) is one of the most common genetic diseases in Caucasians and among the leading causes of chronic respiratory insufficiency in adolescents and young adults. Although the majority of patients with CF survive into adulthood, the disease is still associated with a reduced survival due to progressive destruction of the lung by a combined infectious and exaggerated inflammatory process. The forced expiratory volume in one second (FEV1) has been shown to be the best marker of lung disease severity and a major predictor of respiratory morbidity and mortality.[1] However, other factors such as nutritional status, gender, diabetes, liver disease, and chronic infection by pathogens such as multiresistant *Pseudomonas aeruginosa*, *Burkholderia cepacia* or *Mycobacterium abscessus* may also affect survival.

Hemodynamic, right ventricle and pulmonary structural alteration due to pulmonary hypertension (PH) have been reported several decades ago in cardiac catheterisation[2] and autopsy studies.[3-5] Nevertheless, patients with CF are not systematically screened in daily practice for PH, and morbidity associated with PH may have been underestimated. Indeed, recent data, as discussed below, report the pejorative role of PH in patients with CF and the importance of a systematic screening of PH in these patients.

Definition of Pulmonary Hypertension

Right heart catheterisation is considered the reference standard for mean pulmonary artery pressure (mPAP) determination, with a value above 25 mmHg defining PH. However, this procedure is often considered too invasive to be suitable for screening or monitoring over time.[6] As such, in routine practice, noninvasive echocardiography is used as an alternative to estimate systolic PAP (sPAP) from the peak tricuspid regurgitation velocity (TRV) using the modified Bernouilly equation[7] and the estimation of the right atria pressure using different formula.[8] With this technique, PH is defined as a sPAP value greater than 35 mmHg. However, sPAP estimation by echocardiography may be difficult in CF because of lung hyperinflation, the absence of tricuspid regurgitation in some patients, and variations in TRV depending on respiration time, regurgitation severity,[9] and difficulty to estimate right atrial pressure. As the pulmonary artery acceleration time (PAT) has been shown to correlate strongly with mPAP measured on the Doppler pulmonary artery flow,[10] some authors have used this parameter to define PH. The advantage of the PAT is that it can be measured in most children and adults.[10, 11] Indeed, in our experience, sPAP could not be determined in only 17/67 (25%) patients, whereas PAT could be measured in all patients.[12] Most importantly, parameters associated with PH such as FEV1, vital capacity (VC), and nocturnal gas exchange, correlated with PAT but not with sPAP.[12] PAT is known to be inversely correlated to heart rate, which may be increased in patients with CF. However, correcting PAT for heart rate did not improve the correlation with sPAP in a series of studies.[13-16] In conclusion, right heart catheterisation remains the gold standard for the measurement and diagnosis of PAP, but the PAT may be an interesting alternative for the screening and follow-up evaluation of large groups of patients.[10, 12] However, to date no study has evaluated the correlation between PAT and mPAP measured by right heart catheterisation in CF patients.

Prevalence of Pulmonary Hypertension

The prevalence of PH varies according to the technique used to define PH and the type of population. Right heart catheterisation has been used in the most severe patients, i.e. mainly patients on the lung transplant waiting list. In these patients with end-stage lung disease, the prevalence of PH ranged from 38 to 63%.[2, 17-19] In another study of 18 patients with a FEV1 < 40% predicted, the prevalence of PH, defined as a sPAP > 35 mmHg, was 39%.[7] By using the TRV in a study of 40 patients, the prevalence of PH ranged between 49% and 30% according to a TRV value exceeding 2.5 or 2.8 m/s, respectively.[20] Finally, in a recent study from our group which analysed 67 pediatric and adult patients with a FEV1 < 60% predicted in a stable condition, the prevalence was 33% when PH was defined as PAT < 101 ms and 15% when PH was defined as sPAP > 35 mmHg.[12] Of note, in patients

with CF, PH is generally moderate and to our knowledge, no episodes of acute life-threatening PH have been reported.[12, 18, 19]

Risk Factors for PH

As FEV1 has been shown to be the best marker of lung disease severity and a major predictor of respiratory morbidity and mortality in CF,[1] it is not surprising that most studies observed a correlation between FEV1 and the presence and/or severity of PH.[7,12, 20] Several studies found a significant negative correlation between the level of daytime oxygenation and the presence or the severity of PH.[2, 7, 20] Other parameters, such as VC,[12, 19, 20] partial arterial carbon dioxide pressure ($PaCO_2$),[19] but also a clinical severity and a radiological score,[20] have also been shown to be significant predictors of PH. The effect of nocturnal oxygenation, and in particular the desaturation index, has been poorly evaluated. Nocturnal hypoxia induced by obstructive sleep apnoea (OSA) by itself originates PH and the application of continuous positive airway pressure (CPAP) can reduce pulmonary pressure.[21] Daytime and sleep pulse oximetry (SpO_2) values have been recorded in 33 adult patients with CF.[7] By multivariate analysis, echocardiographic sPAP correlated only with awake SpO_2 and not with nocturnal SpO_2,[7] as in agreement with another study.[20] However, in our experience of 67 stable CF patients with a FEV1 < 60% predicted, nocturnal desaturation emerged as a strong predictor of PH in a multivariate analysis, at the same level as FEV1.[12]

As in COPD patients (see classical papers of Fletcher E *et al.*), one can hypotheses that nocturnal hypoxemia, that occurs before daytime chronic respiratory failure, may be able to induce acute increases in PAP during REM sleep. This can participate to arterial remodeling and secondary lead to permanent PT. The vicious circle of excessive and uncontrollable pulmonary inflammation and infection is a hallmark of CF lung disease and could also play a major role in the development of PH, especially in patients who have episodes of hypoxemia. As such, bacterial infection may trigger or precipitate PH by means of an excessive local inflammatory response. Indeed, an earlier study by our group showed that PH was more frequent and more severe in patients with *Burkholderia multivorans* infection than in patients with infections due to other bacteria despite a similar level of blood oxygenation, lung function and bronchiectasis.[22]

Prognosis of PH

PH is appearing as a major factor associated with a decreased survival. In CF, even if factors such as microbiology, nutritional status, age, female sex, pancreatic insufficiency, CF-related diabetes mellitus, liver disease, number of respiratory exacerbations, and environmental and center-related factors have been shown to affect survival, PH has emerged as an important prognostic factor.[1] Indeed, even if PH is generally mild, most studies have observed an independent association between PH and an increased mortality in patients with CF.[6, 7, 22] In a large cohort of 149 CF patients who were listed for lung transplantation, a higher sPAP value measured during cardiac catheterisation was associated with higher mortality before transplantation.[6] In a large retrospective cohort of 179 consecutive CF patients evaluated for lung transplantation, PH determined on right cardiac catheterisation (mPAP ≥ 25 mmHg) was observed in 38.5% of the patients.[19] The median survival (free of lung transplantation) was 13.4 months. After adjusting for several covariates, the presence of PH significantly increased mortality ($p< 0.001$). Pulmonary vascular resistance (PVR) was associated with mortality ($p=0.03$) but when both PH and PVR were included in the model, only PH predicted mortality. As the performance of a right cardiac catheterisation in CF patients with less severe lung disease may raise some ethical and practical issues, the use of noninvasive measures for the estimation of PH is important. The presence of PH evaluated on an echocardiography, was significantly higher in the group of CF patients with *chronic B. cepacia* infection and PH than in those without these risk factors.[22]

In another recent study from our group, we evaluated the prognostic value of the PAT in a group of 67 stable CF patients.[12] As none of the patients died during the follow up, time to lung transplantation was used to assess prognosis. Of the 8/67 patients who underwent lung transplant during the follow up, only 3 had sPAP ≥ 35 mmHg and 5 had sPAP < 35 mmHg, whereas 7 had PAT < 101 ms. The Kaplan Meier curves for time to lung transplantation showed that the time to lung transplantation did not differ significantly between the two sPAP categories. In contrast, patients with a PAT < 101 ms had significantly shorter times to lung transplantation than the patients in the two other tertiles pooled. This finding suggests that individual patients with PAT < 101 ms may deserve consideration for inclusion on the lung transplant waiting list.

PH and Quality of Life and Exercise Capacity

PH has also been shown to be associated with an impairment of exercise capacity.[23] In a case-control study, 17 adults with mild-to-moderate CF without PH on echocardiography at rest were compared to 10 healthy, nonsmoking, age and height matched controls. All subjects underwent maximal cardiopulmonary exercise testing with echocardiography before and within 1 minute after stopping exercise. Exercise ventilation parameters were similar in the two groups; however, cases as compared to controls, had higher post exercise sPAP and had decreased exercise capacity. Importantly, the change in sPAP values before and after exercise correlated strongly to the parameters of exercise capacity among cases but not among controls.

To our knowledge, the effect of PH on the quality of life and quality of sleep in patients with CF has not been evaluated but could be worth to be analysed.

Conclusion

Moderate levels of PH are common in patients with advanced CF

lung disease and are associated with an increased mortality. As right cardiac catheterisation is often considered too invasive, noninvasive techniques are warranted for routine screening and repetitive assessment of PH in CF patients. Echocardiography represents the logical alternative to cardiac catheterisation but the classical determination of the sPAP from the peak TRV may fail in a certain number of patients, and may not be well correlated to measurements obtained during right heart catheterisation. The determination of the PAT may be a valuable alternative with a recent study showing the greater clinical relevance of PAT compared to echocardiographic sPAP.[12, 16]

The management of PH presents a major challenge in CF. The optimal timing and method for screening for PH needs to be determined. Moreover, we do not know if long term oxygen therapy, eventually with noninvasive ventilation, may reverse PH. As PH seems to be correlated to the desaturation index, may nocturnal oxygen therapy be sufficient, in other words, what may be the optimal duration and level of oxygen therapy? May a reduced PAT be considered as a useful tool for the optimal timing for lung transplantation in patients with CF? Future large prospective studies should confirm the prognostic value of PAT together with the ability of oxygen therapy with or without noninvasive ventilation to decrease or stabilie the level of PH in patients with CF.

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Improvements in Lung Cancer

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Introduction

The Cancer Registry of Norway is a nation-wide institution. It is regulated by law that all clinical and pathology departments submit standardised reports on cancer patients to the Registry. Furthermore, the Registry has a law-regulated authority to collect supplementary information on the diagnosis, treatment and outcome of all cancer patients from hospitals. The surgical registry is one of the most detailed in the world. Furthermore, data from the registry includes important contributions to the new TNM classification for lung cancer, determined by the International Association for Study of Lung Cancer (IASLC).

Several European and other Western countries have reported differences in the surgical treatment of lung cancer. With regards to the resection rate, the situation in Norway seems favourable. Great Britain and Ireland report 9-11% resection rate, in contrast to 17-20% in Norway. In some other European countries, the rate is more than 20%. The increased surgical activity in Norway in the last few years, with increased resection rate and lower postoperative mortality in 2000-2005, is a potential explanation for the improvement in the treatment of lung cancer.

However, in Norway there has been a remarkable difference in the treatment from one part of the country to the other. Following the centralisation of evaluation and treatment, the waiting time from diagnosis to operation has increased by 9 days.[1]

Lung cancer is annually diagnosed in 2,000-2,500 persons in Norway, and of those 300-500 are referred for surgical treatment, which means a resection rate of 15-20%. Since surgery is known to be the only treatment modality to cure lung cancer, our research over the last 10 years has been focused upon various aspects of the surgical treatment of lung cancer. Therefore, in 2002 we published the results of a survey of more than 1000 patients in Norway who were being treated conservately, to find out if some of these patients could have been operable and thus treated surgically.[2] After the exclusion of 166 patients for various reasons, almost 400 were found inoperable due to advanced disease. Of the remaining patients, 270 were classified as being operable, and 127 possibly operable. We concluded that the policy in Norway concerning evaluation and treatment of lung cancer patients was inadequate, and requested lung physicians to be more aggressive for this group of patients. We have communicated this opinion in numerous international fora and journals.

In the following years, we have mainly concentrated on population based surgical treatment of various aspects of lung cancer.

A study of adolescent smoking and trends in lung cancer incidence among young adults in Norway from 1954-58 concluded that lung cancer incidence rate in young Norwegians was almost identical in both men and women.[3] The lung cancer risk at age 40-44 was closely associated with teenage smoking.

The mean waiting time for surgery from the point of diagnosis to the point of operation in Norway was 26 days. However, patients who had their preoperative evaluation and surgery at the same hospital had a waiting time nine days shorter than those being referred to another hospital for surgery.[1]

A population-based evaluation of the seventh edition of the TNM system in 1,885 operated lung cancer patients concluded[4] that this edition did not improve the overall predictive ability of the TNM system; however, the new classification implies changes in treatment for nearly one-fifth of these cases. The implication of the seventh TNM edition for the outcomes of patients needs further research.

Resected Synchronous Primary Malignant Lung Tumours.[5]

This study of 94 patients was published in an American journal. Synchronous malignant tumours were found in 94 patients: 66 had two tumours, and the remaining 28 had three or more. The tumours were of similar histology in 85 cases. The 5-year relative survival rate was 31.4% for patients with squamous cell carcinomas, 23.2% for adenocarcinomas and 42.7% for patients with tumours of other histology (two carcinoids).

It was concluded that survival rates in patients with synchronous lung tumours is good compared with historical reports of patients with

distant metastases or other variants of T4 tumours; thus, they should be considered for surgery.

Carcinoid Lung Tumours

Incidence, Treatment and Outcomes in a Population-Based Study[6]

Of 26,665 patients diagnosed with lung cancer in the period 1993-2005, 265 (1%) had carcinoid tumours, of which 11 were diagnosed incidentally at autopsy. In the remaining 254 patients, typical carcinoids were found in 188, atypical in 59 and unclassified in seven cases. Of the 217 resected tumours, 173 (80%) were typical. General surgeons performed 94 resections, including 11 of 17 pneumonectomies. All six bronchial resections were performed by thoracic surgeons. Of the 33 operated patients who died during follow-up, 18 had metastatic carcinoid tumours, of which 10 (56%) were atypical tumours. In 37 non-resected patients (15 with atypical and seven with unclassified histology), metastatic or locally advanced disease (N=21,12 of which were atypical) was the main cause of inoperability and death. Five year survival for all patients was 92% for typical and 66% for atypical; for resected patients, the survival rates were 96% and 79%, respectively. It was concluded that carcinoids are rare malignant tumours and are, in most cases, resectable; the typical subgroup had better prognosis than atypical in univariate analyses. The main cause of death was metastases/locally advanced tumour at presentation or recurrent disease following resection; both situations were three times more common in patients with atypical carcinoids.

Small Cell Lung Cancer in Norway

Should More Patients have been Offered Surgical Therapy?[7]

Small cell lung cancers (SCLC) account for 15-20% of all lung cancers. Because symptoms are generally unspecific, the disease is often diagnosed late, with 70% of patients already in stage IIIb of IV at the time of diagnosis. Therefore, the final outcome of these patients is poor, with an overall 5-year survival rate of less than 10%. However, surgery has a place in therapy in stage I SCLC.

In the period between 1993-99, 2,442 individuals with SCLC were identified. The majority were treated with convential chemotherapy or concurrent chemoradiotherapy, while 38 underwent surgical therapy. The 5-year survival rate was 11.3% in patients treated conservatively compared to 44.9% for those who underwent surgical resection. The conclusion was that patients with peripherally located small cell lung cancer should be referred to surgery.

Small Cell Lung Cancer: Better than its Reputation?[8]

However, despite the depressing fate in patients with SCLC, we could see some improvement in a small group of patients. This investigation included all patients with a diagnosis of SCLC, limited or disseminated disease, between 2000-2005 (N-94), and who were alive 5 years or more after the diagnosis. All pathological specimens from 18 different hospitals were revised by the local pathologist. After this, 72 diagnoses were maintained while 15 changed to other lung malignancies (12) or benign lesions (3). Seven patients had disseminated and 93 patients had limited disease. It is concluded that the favourable survival of 72 patients was most likely caused by the high percentage of limited disease.

Lung Cancer Surgery: The First 60 Days[9]

In the period between 1993-2002, lung cancer was diagnosed in 19,582 patients, 3,224 (16.5%) of which were treated by surgery. The main preoperative risk factors were coronary artery disease, chronic pulmonary disease and peripheral artery disease. The postoperative mortality after pneumonectomy was up to 20%, and this procedure in elderly patients should not be recommended.

Complications and early death after surgical resection was studied in 2000 and 2010.[10] During that period, the number of operating centres was reduced from 25 to eight. Pre- and postoperative fatal bleeding episodes were eight in the first period and two in the last. Similarly, broncho-pleural fistula occurred in three patients in 2000 and in 1 in 2010.

Survival after Resection for Primary Lung Cancer; A Study of 3,211 Resected Patients.[11]

The five year relative survival was 46.4%. Both observed and relative survival after sublobar resection was less favourable when compared to other resections except pneumonectomy. A possible reason for this may be that sublobar resection means that only a peripheral part of the lung is removed and no hilar lymph node dissection is performed. Consequently, early local recurrence may occur. Nevertheless, the relatively favourable results could stimulate to a more aggressive approach in the selection of patients for surgery.

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Prolonged Overcirculation-induced Pulmonary Arterial Hypertension in Piglets, as a Cause of Right Ventricular Failure

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Introduction

Pulmonary arterial hypertension (PAH) is a rare and fatal dyspnoea-fatigue syndrome caused by a progressive increase in pulmonary vascular resistance, eventually leading to a right ventricular (RV) failure.[1] In spite of recent advances achieved in PAH therapies with the use of vasodilator therapies based on the administration of prostacyclin analogues, endothelin-1 receptor antagonists and phosphodiesterase type-5 inhibitors, the prognosis of PAH patients remains poor, with a low quality of life and a high mortality rate in the majority of them.[2] The patient outcome is predominantly determined by the adaptative response of the RV function to the increased afterload.[3,4] However, the pathophysiology and the cellular and molecular mechanisms underlying the development of RV failure on increased afterload remain largely unknown. The development of realistic experimental models of advanced PAH might therefore contribute to a better understanding of the pathobiolgy of load-induced RV failure, and secondary to the discovery of potential cardioprotective treatment strategy aiming improved RV function.

PAH is a classically described complication of congenital cardiac malformations with left-to-right shunting.[5] The severity of shunt-induced PAH depends on the duration and the magnitude of shunt flow and pressure. Shunt-induced PAH is associated with adaptative RV hypertrophy and eventual failure, with increased atrial and/or ventricular pressures as a cause of shunt reversal. Viktor Eisenmenger first reported the pathology of congenital cardiac shunt- induced PAH in 1897.[6] The clinical and hemodynamic picture of shunt-induced PAH with RV failure-induced shunt reversal was described by Paul Wood, who first defined the term "Eisenmenger syndrome".[7] The pathology of cardiac shunt-induced PAH became better understood with the advent of corrective surgical procedures in the1950s. It soon became apparent from pre-operative biopsy material, and eventually post-mortem studies, that shunt- induced PAH would be reversible after shunt closure when the pulmonary arteriolar remodelling was limited to medial hypertrophy and minimal intimal thickening. More advanced lesions including intimal laminar sclerosis, fibrinoid necrosis and plexiform lesions were shown to be irreversible. These observations appear to be transposable to any cause of PAH, as this entity is histopathologically homogeneous, and acutely reversible forms have been shown to be characterised by exclusive or dominant medial hypertrophy (Figure 1).[8,9]

Experimental Model of Pulmonary Arterial Hypertension: Three-month Overcirculation in Piglets

Left-to-right shunt-induced PAH can be experimentally reproduced in piglets which is the preferred species due to its highly reactive pulmonary circulation prone to remodelling, especially during the first weeks and months of life. It has been estimated that shunted piglets would reproduce, in a few months, a natural history of the disease that would require decades in the human species.[10]

The experimental model of overcirculation-induced PAH is obtained by the surgical anastomosis of the subclavian artery or the innominate artery to the pulmonary arterial trunk, which corresponds to the Blalock-Taussig operation. The modified Blalock-Taussig shunt increases with the growth of the animals, maintaining a maximum mechanical stress as a cause of pulmonary arteriolar remodelling and increased pulmonary vascular resistance. It has indeed been shown that 3-month systemic-to-pulmonary shunting increases mean pulmonary artery pressure to 30-40 mmHg at a normalised cardiac output (measured after shunt closure), and approximately doubles pulmonary vascular resistances. After 3-month shunting, RV function adaptation to afterload, evaluated by the ratio of end-systolic to pulmonary arterial elastances (Ees/Ea), appears to be preserved (Figure 2). Histopathological studies revealed pulmonary arteriolar remodelling, with pronounced medial hypertrophy after 3-month systemic-to-pulmonary shunting (Figures 2A and 2C).[11,12] All these hemodynamic and histological features are compatible with changes seen in early still-reversible stages of PAH.

At the pathobiological level, overcirculation-induced PAH is associated with increased circulating endothelin-1 levels, together with increased pulmonary expressions of endothelin (ET)-1 and endothelin receptor type B (ETB), inducible nitric oxide (NO)-synthase, vascular endothelial growth factor (VEGF), serotonin receptor-1B, angiopoietin-1, angiotensin II and its angiotensin A T1 and A T2 receptors, phosphodiesterase-5 and tenascin-C.[11-15] Pulmonary expressions of bone morphogenetic protein receptor (BMPR)-2 and BMPR-1A decrease,[13] while there are no changes in the expressions of the

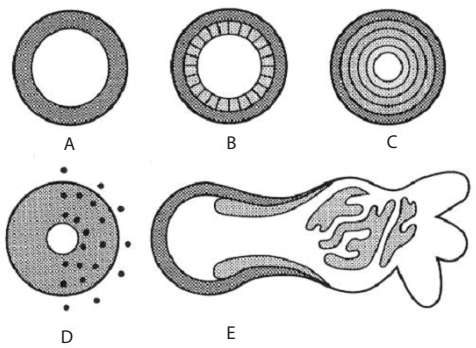

Figure 1. Progressive remodelling of the pulmonary arterioles in congenital heart disease-associated pulmonary arterial hypertension: (A) medial hypertrophy; (B) medial hypertrophy and intimal proliferation; (C) medial hypertrophy and concentric laminar sclerosis; (D) medial hypertrophy and fibrinoid necrosis; (E) plexiform lesion. Stages A and B are reversible after surgical closure of the shunt (adapted from reference 8).

endothelin receptor type A (ETA), endothelin converting enzyme-1, endothelial NO-synthase, Tie2 receptor, angiopoietin-2, serotonin transporter and serotonin receptor-2B.[11-15]

Left-to-right shunt-induced pulmonary hypertension represents a realistic PAH model, which has been shown to reproduce experimentally most of the biological determinants implicated in the pathogenesis of the early stages of the pulmonary hypertensive disease in PAH and thus potentially interesting for the search of its *primum movens*.

Experimental Model of Right Ventricular Failure: Six-month Overcirculation in Piglets

In the overcirculated piglet model, prolonged systemic-to-pulmonary shunting (doubling it to 6 months) has been tested, aiming at a model of more advanced PAH. After 6 months, systemic-to-pulmonary shunting induces a similar increase in pulmonary vascular resistance, which is

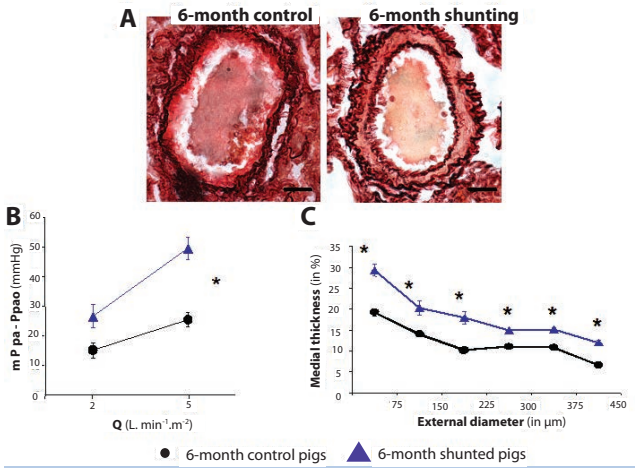

Figure 3. Pulmonary arterioles of sham-operated (6-month control pigs) and 6-month shunted pigs (A). Six-month systemic-to-pulmonary shunting induces a shift of the pulmonary artery pressure (Ppa) versus flow curves (Q) to higher pressures (B) and an upwards shift of medial thickness versus arteriolar diameter curves (C), mainly in smallest pulmonary resistive arterioles (adapted from reference 16). Values are expressed as mean ± SEM. * p<0.05, 6- month sham (control)-operated versus 6-month shunted pigs.

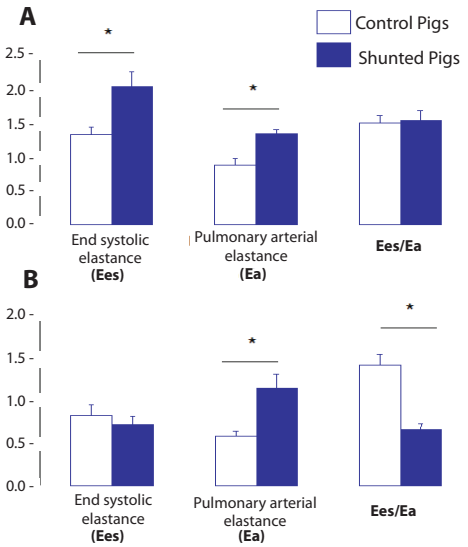

Figure 2. End-systolic elastance (Ees, assessing the contractility of the right ventricle), pulmonary arterial elastance (Ea, assessing the right ventricular afterload) and the ratio of Ees to Ea in sham-operated piglets (controls) and in piglets with systemic-to-pulmonary shunting maintained during three (A) and six months (B) (adapted from references 11 and 16). Values are expressed as mean ± SEM. * p<0.05, sham (control)-operated versus shunted pigs.

approximately doubled (Figure 3B), medial hyperplasia with increased medial thickness (Figures 3A and 3C) and similar up-regulation of ET-1/ETB, angiopoietin- 1/Tie2 and VEGF signalling pathways and decreased BMPR-2 expression,[16] as compared to 3-month shunting.[11-15] However, the increase in mean pulmonary artery pressure is less prominent than previously reported after 3-month shunting, but refined measure of resistance obtained by multipoint composite plots of mean pulmonary artery pressure versus blood flow shows that this is entirely explained by a decreased cardiac output (Figure 3B).[16] After 6-month systemic-to-pulmonary shunting, the decrease in the ratio of RV end-systolic to pulmonary arterial elastances (Ees/Ea), evaluated by the "single- beat method"[17] and evaluating the systolic adaptation of the RV function to afterload, suggests an uncoupling of RV function from the hypertensive pulmonary circulation[16], which was not observed after 3-month shunting[11-15] (Figure 2). Decreased pulmonary blood flow probably limits the mechanical stress on the pulmonary circulation, thereby slowing or even halting the progression of the pulmonary hypertensive disease.

In this prolonged shunted piglet model, RV failure is associated with the myocardial activation of apoptotic pathways, as assessed by the increased pro-apoptotic Bax/Bcl-2 ratio (Figure 4A) and the activation of the final enzymatic executioner of apoptosis, the caspase-3. Moreover, there is a significant inverse correlation between RV-pulmonary arterial coupling (assessed by Ees/Ea) and the apoptosis within the RV (evaluated by Bax/Bcl-2) (Figure 4B), suggesting that apoptosis of cardiac cells (i.e. cardiomyocytes) could play a role in RV- arterial uncoupling in this experimental model of RV failure.[16] Prolonged exposure to afterload also induces an increase in cardiomocyte size in the RV, but also in the left ventricle (LV).[16] Moreover, gene expressions of different factors potentially implicated in cardiomyocyte hypertrophy, such as atrial and

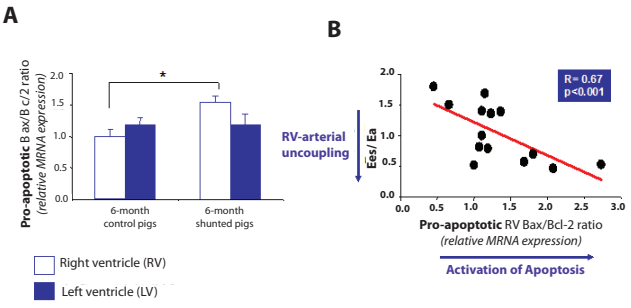

Figure 4. Relative myocardial mRNA content for pro- and anti-apoptotic mitochondrial members of Bcl-2 protein family, as the pro-apoptotic Bax to Bcl-2 ratio in right (white bars) and left ventricles (blue bars) from 6-month sham (control)–operated and 6-month shunted pigs (A). Values are expressed as mean ± SEM. * p<0.05, 6-month sham (control)-operated versus 6-month shunted pigs. Correlation between Ees/Ea (assessing the systolic function adaptation of the RV against increased right ventricular afterload) and right ventricular (RV) pro-apoptotic Bax/Bcl-2 ratio (B) (adapted from reference 16).

brain natriuretic peptide precursors (ANP and BNP) and insulin growth factor signalling pathway (i.e. IGF-1 and IGF-1 receptor), are increased in the failing RV compared to the healthy one.[16] Increased accumulation of extracellular matrix is also present in the failing RV.[16] In this experimental model, a global hypertrophic response seems to be consistent with conditions of chronic overload, with increased preload and afterload for the RV, but also an increased preload of the LV required for chronically shunt-related increase in cardiac output.

In the 6-month overcirculated piglet model, the failing RV does not present with altered capillary density, but decreased expressions of angiogenic factors, including angiopoietin-2 and VEGF, are observed in the failing RV.[16] In this experimental model, RV failure is associated with increased expressions of pro-inflammatory cytokines, such as interleukin-1 alpha and -1 beta within the RV and LV, but also of tumour necrosis factor (TNF)-alpha at both RV and seric levels,[16] suggesting potential implication of inflammatory processes in the development and progression of RV failure. Moreover, increased expressions of interleukins also in the LV may be indicative of the biological changes within the LV towards the progression of severe global failure.

Translational Use of Experimental Models to the Human PAH Disease

The "perfect" animal model of PAH does not exist yet. All currently available models remain of limited translational relevance. However, the natural evolution of the overcirculation-induced PAH in growing piglets, from a pulmonary hypertensive disease alone to afterload-induced RV failure gives a strong rationale to suggest that this model mimics in few months what happens in humans in decades. Moreover, hemodynamic, morphometric and pathobiological data obtained in this model are in accordance with results obtained in patients with PAH.

The 3-month overcirculated piglet model has already been used to study the signalling pathways involved in the pulmonary hypertensive disease at most early stages of the disease (thus for the search of its *primum movens*). Moreover, the prolonged (6-month) overcirculated piglet model, as an experimental model of RV failure on increased afterload, seems very promising to search biological determinants responsible for the RV failure induced by increased afterload and potential cardioprotective therapeutic intervention.

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Treatment Strategy in Patients with Pulmonary Arterial Hypertension Associated with Connective Tissue Disease

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Introduction

Pulmonary arterial hypertension (PAH - Group 1 of the classification of pulmonary hypertension [PH]) is a severe and chronic disease characterised by a progressive obstructive remodelling of the pulmonary vasculature, which results in increased pulmonary vascular resistance and pressure. If left untreated, PAH causes right heart failure and premature death.[1] PAH includes a heterogeneous group of clinical entities: idiopathic PAH (IPAH), heritable PAH, drug and toxin induced PAH and PAH associated with other diseases (A-PAH) such as connective tissue disease (CTDs), human immunodeficiency virus (HIV) infection, portal hypertension, congenital heart disease (CHD), schistosomiasis, and chronic haemolytic anaemia.[1]

PAH associated with CTDs (CTD-PAH) represents a relevant clinical subgroup of A-PAH: looking at the population of adults with any PAH, up to 30% has been estimated to have CTD-PAH.[2] In registries, CTD-PAH is the second most prevalent type of PAH after IPAH.[3, 4] Among CTDs, PAH is most frequently observed in systemic sclerosis (SSc),[2] particularly in its limited variant (formerly named CREST syndrome). However, PAH may also occur in other CTDs, including systemic lupus erythematosus (SLE) and mixed CTD (MCTD), and less frequently, in rheumatoid arthritis, dermatomyositis, and Sjögren's syndrome.

Epidemiology

The exact prevalence of PAH in CTDs is unknown. Most data is available for PAH associated to SSc (SSc-PAH): in large cohorts of patients with SSc the prevalence of haemodynamically proven PAH varies between 7% and 12%.[2, 5] The prevalence in other forms of CTD is lower, ranging from 1 to 5% in SLE and MCTD and is <1% in rheumatoid arthritis, dermatomyositis, and Sjögren's syndrome. Previous assessments based on echocardiographic measurements[6-9] have overestimated the true prevalence of SSc-PAH, and should not be relied on to establish the diagnosis and initiate treatment. In fact, in these patients PH may occur as a result of an isolated pulmonary arteriopathy (PAH) or in association with interstitial fibrosis. Furthermore, PH from left heart disease (pulmonary venous hypertension) may be present and cannot be excluded with certainty by echocardiography. It is imperative to determine which mechanism is operative (or prevalent) in any single patient with SSc, since this impacts prognosis and dictates treatment.

Pathology and Pathophysiology

Remodelling and obliteration of the pulmonary distal vessels represent the histological substrate that characterises all forms of PAH (Group 1 of PH classification): structural vascular changes consist in a combination of medial hypertrophy, intimal fibrosis (concentric, eccentric), adventitial thickening, perivascular inflammatory infiltrates, complex lesions (plexiform, dilated lesions) and thrombotic lesions. Besides these general similarities, two recent studies[10, 11] outline some characteristic features of obstructive vascular remodelling in SSc-PAH: compared to IPAH, a higher degree of intimal fibrosis, a more pronounced perivascular and interstitial inflammation/fibrosis, and a more frequent involvement of the small pulmonary veins were documented. These histological peculiarities may partly explain the poorer response to therapy and the significantly worse survival observed in SSc-PAH compared with IPAH patients.

While the histological changes in PAH have been well characterised, the cellular and molecular workings underlying vascular remodelling remain vastly unknown. Immunological and inflammatory mechanisms may play a role in the development of pulmonary vascular remodelling, as suggested by the evidence of circulating antibodies, immunoglobulin-G, pro-inflammatory cytokines, and by the presence of complement fraction deposits in the pulmonary vessels wall. In patients with SSc, early vascular changes (markers of specific

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endothelial injury) have been documented,[12] including gaps between endothelial cells, apoptosis, endothelial activation with expression of cell adhesion molecules, inflammatory cell recruitment and a procoagulant state. In SSc-PAH, dysregulated angiogenesis is reflected by increased levels of circulating vascular endothelial growth factor (VEGF),[13] a glycoprotein with potent angiogenic and vascular permeability-enhancing properties that could be a potential candidate for therapeutic targeting.

Clinical Features

From a clinical standpoint, despite the similarities in pathogenesis and histopathological phenotype, CTD-PAH differs significantly from other forms of PAH. Compared with IPAH, patients with CTD-PAH are predominantly women (female/male ratio 4:1), are older (mean age at diagnosis 66 years), may present concomitant disorders (pulmonary fibrosis, left heart disease, renal dysfunction, musculoskeletal complications), have significantly lower exercise tolerance, and have worse prognosis.[2] The unadjusted risk of death for SSc-PAH compared to IPAH is 2.9[14] and the predictors of survival are the same as for IPAH. Moreover, the outcome of SSc-PAH is significantly worse even when compared with other forms of CTD-PAH.[15] Symptoms and clinical presentation are very similar to IPAH and occasional patients thought to have IPAH can be identified as having an associated CTD via immunological screening tests.

Because of a relatively high prevalence of PAH in SSc, there is an opportunity for early diagnosis in this population: the detection at an early stage with less haemodynamic impairment[5] could lead to prompt therapeutic intervention, which may theoretically be beneficial from a prognostic standpoint. Currently, echocardiographic screening for the detection of PH has been recommended annually in asymptomatic patients with the SSc spectrum of diseases, and only in presence of symptoms in other CTDs.[16] However, the cost-effectiveness of this strategy has not been clarified as compared to symptom-based screening: in fact, whether this approach leads to improved outcomes or merely reflects a so-called "lead-bias" remains to be determined in larger prospective studies. As in other forms of PAH, right heart catheterisation is recommended in all cases of suspected CTD-PAH to confirm the diagnosis, determine severity, and rule out left heart disease. Moreover, RHC is mandatory if targeted treatments are being considered. In patients with CTD-PAH, the role of acute vasodilator test to assess pulmonary vasoreactivity is less clear than in IPAH: in fact, the proportion of acute responders is significantly lower and, in the event of a positive acute response, the usefulness of long-term treatment with high-dose of calcium-channel blockers (CCB) is less established. Therefore, current guidelines recommend that vasodilator testing be performed on an individual basis in this subgroup of PAH patients.

Treatments

In the past 15 years, huge therapeutic progress has been made in the PAH field and seven drugs belonging to three pharmacological classes (endothelin receptor antagonists [ERAs], phosphodiesterase type-5 inhibitors [PDE5-I] and prostanoids) have currently been approved by the Food and Drug Administration (FDA) and by the European Medicine Agency (EMA). CTD-PAH subjects have been enrolled in most of the major randomised controlled trials (RCTs) for regulatory approval of PAH-specific therapies, including those with combination therapy. Overall, CTD-PAH subjects constitute approximately 30% of the PAH patient population included in RCTs,[17] and is the second largest group after IPAH. The availability of these specific therapies targeting different pathobiologic pathways implicated in the disease process[18] significantly improved symptoms, exercise capacity, haemodynamics and also survival in PAH patients.[17]

Despite these important therapeutic advances, morbidity and mortality rates in PAH are still considerably high,[19] particularly in the group of subjects affected by CTD-PAH who tend to have a poorer response to therapy and a significantly worse prognosis compared with IPAH patients.[15] These findings may be linked to different factors, including the older age of CTD-PAH patients, the more severe right ventricular and pulmonary vascular dysfunction leading to a lower efficacy for PAH-approved treatments and, above all, the systemic nature of CTDs with the propensity to involve multiple organ systems such as the gastrointestinal tract, heart, kidney and lungs. In addition, in the majority of RCTs and long-term continuation studies performed in PAH, the drug-related side effects were higher in CTD-PAH patients.

Therefore, treatment strategy of patients with CTD-PAH appears more complex than that of patients with IPAH. As compared to IPAH, there are some differences on the background treatment approach of CTD-PAH patients:

- High-dose CCB therapy is usually not indicated for these patients; however, CCB treatment is commonly used (at low dosage) for Raynaud phenomenon.
- Anti-inflammatory drugs: immune and inflammatory mechanisms may play an important role in the pathogenesis of CTD-PAH, mainly in SLE- and MCTD-PAH. The evidence of inflammatory cell infiltrates in the plexiform lesions, and immunoglobulin and complement deposits in the pulmonary arterial walls of these patients supports the use of anti-inflammatory and/or immunosuppressive therapies. Several uncontrolled and open-label studies evaluated the role of these treatments in patients with CTD-PAH: it has been reported that treatment with glucocorticosteroids and/or cyclophosphamide may result in dramatic clinical and haemodynamic improvement in patients with SLE- and MCTD-PAH;[20, 21] unfortunately, it has also been shown that immunosuppressive drugs are absolutely ineffective in patients with SSc-PAH.[22]
- Anticoagulants: based on pathologic evidence of pulmonary vascular thrombotic lesions[23] and on retrospective data showing a favourable effect on survival,[24] anticoagulation is routinely recommended in IPAH patients. However, the role of anticoagulation is much less clear in

CTD-PAH patients. In fact, in this group of PAH there is the potential for increased gastrointestinal bleeding, particularly in SSc patients in whom gastro-intestinal telangiectasias may be common. Therefore, the use of these drugs should be considered in more severe CTD-PAH patients who have no contraindications, and in those receiving continuous intravenous PAH drugs.[25]

As far as targeted therapies are concerned, given that subjects with CTD-PAH contribute substantially to the patient population included in most of the RCTs that have led to the approval of PAH therapies, they should follow the same treatment strategy as in IPAH.[16] However, it must be highlighted that most CTD-PAH subjects enrolled in RCTs were SSc-PAH patients and, given the differences in survival and potential differences in response to immunosuppressive therapy between the various forms of CTD-PAH, the overall results of the RCTs should only be applied to SSc-PAH. In any case, targeted therapies are commonly used in all forms of CTD- PAH, despite the lack of real evidence for diseases other than SSc.

Subgroup analysis of CTD-PAH patients enrolled in the major RCTs to assess the efficacy and tolerability of PAH-targeted drugs have shown favourable effects.

Endothelin-1 (ET-1) seems to play an important role in the pathogenesis of vascular lesions in CTD-PAH. ET-1 is a potent vasoconstrictor, exerts mitogenic effect on fibroblast and vascular smooth muscle cells, causes the release of pro-inflammatory cytokines and modulates cell surface adhesion molecule expression, thus contributing to vascular damage and fibrosis. Furthermore, ET-1 is an important mediator in SSc, and there is a correlation between ET-1 plasma concentration and disease severity.[26] Therefore, as well as targeting PAH in patients with CTDs, ERAs may also potentially influence the pathogenetic processes in SSc, acting against both the vascular and the fibrotic components. Taken together, these observations confirm that blocking the endothelin system remains a logical therapeutic strategy in CTD-PAH.

Bosentan therapy was shown to have beneficial effects on functional class, exercise capacity, time to clinical worsening, and haemodynamics in PAH patients.[27, 28] In the BREATHE-1 study,[28] the subgroup analysis of CTD-PAH patients (mainly SSc) showed a non-significant trend toward a positive treatment effect on 6-minute walk distance (6MWD). Furthermore, it has been highlighted that the favourable effects observed were mainly due to deterioration prevention: in fact, in the SSc-PAH subgroup, baseline 6MWD improved only by 3 metres in the bosentan arm, while a 40-metre decline was observed in placebo recipients. On the other hand, in the IPAH subgroup, bosentan therapy improved 6MWD by 46 metres versus a decline of only 5 metres in placebo recipients. More recently, an analysis of CTD-PAH patients included in several RCTs of bosentan showed a trend toward improvement in 6MWD and improved survival compared with historical cohorts.[29] Ambrisentan is the only selective ERA (for ETA receptors) currently approved by regulatory agencies (FDA and EMA). In a large RCT, ambrisentan improved 6MWD in PAH patients and the treatment effect was less pronounced compared with IPAH[30] in the CTD-PAH patient subgroup.

Aside from improving PAH, ERAs (specifically bosentan) cause significant reductions in the occurrence of new digital ulcerations without, however, evidence of healing of pre-existing ulcers.[31]

Changes in nitric oxide (NO) pathways have been detected in PAH patients. The pulmonary vasodilating effects of NO are mediated through its second messenger, cyclic guanosine monophosphate (cGMP), which is rapidly broken down by phosphodiesterases (PDE). PDE type 5 (PDE5) is the predominant PDE isoform in the lung that metabolises cGMP, and it has been shown to be up-regulated in conditions associated with PH. By selectively inhibiting PDE5, the PDE5-I promote the accumulation of intracellular cGMP, thereby enhancing NO-mediated vasodilatation and reducing smooth muscle cell proliferation.

Sildenafil is the first PDE5-I approved for PAH treatment. The pivotal SUPER-1 study investigated sildenafil treatment in 278 PAH patients randomised to receive either 20, 40 or 80 mg of sildenafil or placebo 3 times daily (TID) for 12 weeks.[32] All three doses tested significantly improved exercise capacity, WHO functional class, and haemodynamics. The current FDA recommended dose is 20 mg TID, because there were no significant differences in clinical effects and time to clinical worsening at week 12 among all active-treatment groups. However, the maintenance of effect up to one year has been demonstrated only with the dose of 80 mg TID. A *post hoc* analysis of the SUPER-1 trial assessed the effects of sildenafil specifically in the subgroup of 84 patients with CTD-PAH (30% of the entire patient population), 45% of whom had SSc-PAH. Improvements in all efficacy outcomes (6MWD, hemodynamics, and functional class) were documented only with the 20 mg dose, suggesting that oral sildenafil 20 mg TID is a rational treatment dose for patients with SSc-PAH (as well as for patients with other forms of CTD-PAH).[33]

Tadalafil, is a once-daily (OD) dispensed PDE5-I. The PHIRST study assessed the effects of tadalafil on exercise capacity and other clinical endpoints in patients with IPAH and APAH (including CTD-PAH) who were either treatment-naïve or on background therapy with bosentan.[34] Patients were randomised to receive tadalafil 2.5, 10, 20 or 40 mg or placebo. The study showed that tadalafil 40 mg was well-tolerated and improved exercise capacity and quality of life measures and reduced clinical worsening. In the subgroup of CTD-PAH patients, the treatment effect on 6MWD was slightly lower than those seen in the overall patient population for the tadalafil 2.5 and 10 mg doses, whereas for the higher two doses, improvements in CTD-PAH patients were greater. The

recommended dose for tadalafil is 40 mg OD regardless PAH etiology. Prostanoids have played a prominent role in the treatment of PAH. In fact, prostacyclin is a potent vasodilator in both the pulmonary and systemic circulations, and has antiproliferative and antiplatelet aggregatory activity. Dysregulation of prostacyclin metabolic pathways has been shown in patients with PAH as assessed by reduction of prostacyclin synthase expression in the pulmonary arteries and of prostacyclin urinary metabolites. Exogenously administered prostanoid analogues might help to overcome the adverse effects of decreased endogenously produced prostacyclin.

Several compounds and methods of administration have been studied. Chronic intravenous epoprostenol therapy has had a substantial impact on the clinical management of patients with severe PAH. It improves exercise capacity, hemodynamics, and survival in patients with IPAH. In SSc-PAH, epoprostenol improves exercise capacity, symptoms and haemodynamics[35] and may have long-term beneficial effects,[36] although a clear effect on survival in these patients has yet to be demonstrated. The complexity of epoprostenol therapy (permanent tunnelled catheters, portable infusion pumps, reconstitution of the drug, etc.) and the potential for serious adverse events related to the delivery system, has led to attempts to develop other prostanoids with simpler administration.

Treprostinil is an epoprostenol analogue suitable for continuous subcutaneous (sc) administration. The favourable effects of sc treprostinil on symptoms, exercise capacity and hemodynamics in PAH patients were documented in a RCT performed in 470 PAH patients;[37] a post hoc analysis of the trial confirmed the favourable effects of sc treprostinil in the subgroup of 90 CTD-PAH patients.[38] Treprostinil is also approved in the US for intravenous use: the effects appear comparable with those of epoprostenol but require a significantly higher maintenance dose, usually twice as much as for epoprostenol. However, treprostinil does not require refrigeration with ice packing and the drug reservoir can be replaced every 48 hours (as compared to 12 for epoprostenol): these practical aspects may represent a significant advantage for patients with SSc-PAH and often frequent digital problems and severe Raynaud phenomenon.

As previously highlighted, in most RCTs and long-term PAH continuation studies[17] the magnitude of the response in the CTD-PAH subgroup was lower than in IPAH. It is, therefore, imperative to elaborate new treatment strategies in PAH-CTD patients to try to optimise the effects of available resources. First of all, care of these complex patients requires a multidisciplinary approach in order to ensure the best therapeutic strategy and monitoring. Then, considering the multiple pathways which contribute to PAH, the combination of PAH-specific classes of drugs might lead to greater benefit. Combination therapy has become the standard of care in many PAH centres, although long-term safety and efficacy have not yet been amply explored. Current treatment guidelines for PAH recommend a sequential add-on approach to combination therapy in which the timing of treatment escalation is determined by the relevance of clinical response. The evaluation of clinical response is based on pre-defined therapeutic targets which are also known prognostic indicators. Results of a few RCTs evaluating combination therapy for PAH have been published showing that various drug combinations appear to be safe and effective. None of these studies has been specifically performed in CTD-PAH but these patients have been included in some of them.[39, 40, 41] Although no specific subgroup analysis is provided for these studies, the improvement observed in the CTD-PAH population was apparently less relevant compared with IPAH patients; furthermore, significantly more patients with CTD-PAH had adverse effects, including ERA related-hepatotoxicity, than IPAH patients.

Another possible way to optimise treatment approach in PAH is upfront combination treatment strategy. This approach may provide an aggressive and hopefully effective new way to maximise drug effects. A long-term event-driven study (AMBITION) is currently ongoing and it will compare the effects of ambrisentan or tadalafil monotherapies with the upfront combination of both compounds.[42] This study will provide the opportunity to analyse the efficacy of this new strategy in the CTD-PAH patient sub-group, in particular in those with the SSc disease spectrum.

Lung transplantation (LT) is typically offered as a last resort to patients with PAH who fail medical therapy. The presence of a CTD is not a contraindication for lung transplantation per sè; however, patients with CTD-PAH frequently have associated morbidity and organ dysfunction other than the lung, which places them at a significantly increased risk for LT. For example, motility disorder of the esophagus and gastroesophageal reflux in patients with SSc significantly enhance the postoperative potential of aspiration and damage to the recipient lung. For these reasons, it is extremely important for LT candidates to be evaluated on an individual basis.

Conclusions

PAH is a common complication of CTDs, particularly of SSc. When associated to CTDs, PAH significantly worsens survival and is a leading cause of death in these patients. There are several possible pathogenetic mechanisms leading to PH in CTD: interstitial fibrosis (Group 3 of PH classification), left ventricular dysfunction (Group 2) and isolated pulmonary arteriopathy (CTD-PAH, belonging to Group 1). It is imperative to determine which mechanism is operative since this dictates treatment. Despite the favourable results observed in RCTs, the efficacy of PAH-specific therapy is reduced in CTD-PAH and the overall survival of this patient population remains unacceptably low. Furthermore, immunosuppressant therapy is generally ineffective on the pulmonary vascular disease with the exception of some forms of PAH associated with SLE or MCTD. Whether early diagnosis and treatment of CTD-PAH patients improves outcomes is still uncertain and needs to be confirmed in properly designed studies.

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Recent Advances and Perspectives of Telemedicine in Sleep and Sleep-related Disorders Monitoring

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The use of assistive technology and telemedicine, with increasingly faster rates of data transfer, is likely to continue to shape our medical practice in the future, mostly in developed countries. The main domains of potential expansion for these technologies are patient's monitoring in hospital wards, nursing homes, and at home. Information and communication technologies also allow data transmission from the patient's home to hospital, for diagnosis or therapeutic and follow-up purposes, avoiding in some case patients displacement, something welcome when patients live far away from the hospital.[1] Telemedicine involves bi-directional interaction between patients and healthcare providers. It has been demonstrated to increase quality of life and decrease health-related costs in chronic respiratory failure patients.[2] Sleep medicine represents a huge potential for the development of tele-health technologies.

Indeed, the population suffering from Obstructive Sleep Apnoea syndrome (OSA) and chronic respiratory failure is growing, and the diseases related treatments include complex technical devices (CPAP, BIPAP) that form a large investigation field for data transmission analyses through informatics interface.

During the last decade, several telemonitoring investigations have been conducted in this domain, in two specific conditions. Devices allowing telemetric transmission of physiological parameters during sleep have been studied, with the purpose of sleep monitoring, as the Heasys® sheet,[3] or to enhance diagnosis accessibility for sleep disorders.
In our centre, we have tested, in a pilot-study,[3] new flat bed multi-sensor monitoring equipment, the Heasys® sheet (Figure 1), that has been developed to detect the presence of subjects in bed as well as body movements, and allow measurement of body temperature and urine saturation. The purpose of our study was to assess whether Heasys® was efficient to detect bed egresses, and if the detection of movements by Heasys® effectively corresponds to body position changes. We recorded 5 healthy volunteers and 12 patients from the sleep lab with both Heasys® and polysomnography (PSG). The sheet includes sensors that measure *body temperature*, *body movements* and *body presence*. Positive presence signal requires the activation of at least one of the 3 sensors. Recorded signals are sent at a frequency of 8-measurements/minute to a web browser that analyses data to obtain the mean value per minute.

We found that Heasys® is a very good tool, allowing presence assessment in bed as well as measurement of body motions in both normal subjects and in patients. All the bed-exit events were associated with a lack of signal from the presence detector. It not only recorded most of the body position changes during the night, but also additional motions associated with respiratory events; arousals or leg movements that frequently occur during normal sleep or sleep disordered breathing. Altogether, these observations suggest that this tool might be of interest to monitor, for example, in real-time, nursing home residents when they stay in bed at night. Several bed-exit alarms have been developed in order to prevent falls that occur mainly in resident's room, but unfortunately, troubles are frequent when these systems are used in real-life, including delayed signal of absence, false absence signal in low weight patients or false alarms due to patient's motions, such that their capability to prevent falls is a subject of concern.[4, 5]

The main interest of Heasys® is the possible combination of three signals (presence, motion and temperature) that allows extracting accurate information on bed exit events. Potentially, this could largely minimise false alarms signals. To date, such technologic innovations are not yet a routine aspect of nursing care, and further studies in nursing homes or geriatric wards are required to confirm that their use will effectively result into a decrease in the number of falls, an increase in resident's quality of sleep, a better efficiency of nursing staff work or reduced costs.

Other research teams are working on the development of new sleep monitors, potentially useful to help nurses in their daily practice. Kogure *et al.*[6] have developed a nonwear actigraphy device, placed under the mattress, able to differentiate "in-bed/out-of-bed" state and sleep/wake schedules. It has been tested, and compared with conventional actigraphy, on 12 nursing-home residents, and the correlation between both systems was very good. Hayes *et al.*[7] used a different method to capture both in-bed activity and activity everywhere in the home by equipping each room with passive infrared motions sensors. Combining

Figure 1. Heasys®, a wireless bed monitoring. The box is placed under the bed during night recording.

data from multiple sensors, they developed an algorithm able to determine the state of the subject (awake in bed, asleep in bed, out of bed, asleep out of bed). They tested it successfully in 8 elders.

Another part of sleep monitoring includes diagnosis of sleep disordered breathing (SDB), where telemedicine can be very useful. Effectively, with the development of sleep medicine, sleep lab have to face a large demand for sleep studies and waiting lists are often long. To overcome this problem, a lot of simplified portable monitoring devices have been developed and are now widely used to decrease the delay of SDB diagnosis and related costs.[8] The major problem encountered with these devices is the potential loss of data, observed with unattended polysomnographic procedures (4.7 to 20%)[9] as well as with polygraphic procedures (up to 24%)[10] leading to less cost-savings than expected.

In order to enhance the quality of the home-based sleep recordings, real-time telematic data transmission have been tested. A research team in Cleveland performed an interesting preliminary study in 10 fibromyalgic patients. They described an easily deployable home monitor, PSG@Home, which permits complete sleep evaluation in the patients' homes under direct remote supervision of a sleep specialist. The PSG is transmitted by a cell phone-based in real-time. All 10 studies were successful and generated high-fidelity recording.[11]

The team of Fleury *et al.*[12] have studied 99 patients who underwent home-unattended and in-hospital unattended but telemonitored polysomnography (TM-PSG). For TM-PSG, nurses from the sleep lab checked every 30 min the quality of the recording and were instructed to replace electrodes giving faulty signals. They obtained 2 times less failure rate with the TM-PSG.

We have recently performed a feasibility study on 21 patients with the Sleepbox®. The purpose was to attend (real-time) home-PSG, from the sleep lab, and to react in case of defective signal. Sleepbox® is a wireless system able to communicate with the Dream® polysomnograph, and with Internet through a wi-fi/3G interface. It is equipped with a digital infrared camera, and with a speaker/microphone system for bidirectional audio/video communication via Skype®. The Sleep Lab nurse performed a discontinue monitoring of the PSG. In case of loss of sensors, she called the patient who had been previously educated to replace the probes. As it was a feasibility study, we faced several technical problems, mainly with Skype®, but 2 interventions have been done during the PSG recordings and were successful. Patients replaced the sensors correctly. The Sleepbox® could be an interesting perspective to decrease the failure rate of home-PSG[13] but further studies are ongoing to confirm the interest of this technology.

The second main domain of telemedicine development in sleep medicine concerns therapy. In OSA patients, new CPAP devices allow telematic data transmission on an easy way, and their use becomes widespread. Several studies have demonstrated the interest of these techniques: in the study of Stepnowsky *et al.*,[14] the addition of a telemonitoring program to the usual educational program highlighted an improvement of CPAP compliance of 46% after 2 months.

Smith *et al.*[15] showed also a positive impact of additional educational program delivered by nurses via teleconference in 19 non-compliant OSA patients. The larger study[16] was performed on 250 patients. They were randomised to use a theory-driven interactive voice response system designed to improve CPAP adherence or to placebo for 12 months. Median observed CPAP use in patients randomised to intervention arm was approximately 1 h/night higher than in the control subjects at 6 months and 2 h/night higher at 12 months. These results are really encouraging and stress the interest of telemedicine in treatment follow-up.

Recently, Dellaca *et al.*[17] performed home-based CPAP therapy trial (with automatic devices), with real-time teleassistance and analyses from the sleep lab. 20 OSA patients have been recorded. A telemetric unit based on the conventional GPRS mobile phone network and connected to a commercial CPAP device, allowed the hospital technician to monitor flow, pressure and air leaks by remote control, and to titrate CPAP in real time. After 1 week, a full hospital PSG was performed for a conventional attended CPAP trial. The in-lab CPAP value was virtually the same as the pressure obtained at home, such that a simple telemetric system, requiring neither a special telemedicine network nor any infrastructure in the patient's home, made it possible to perform effective remote CPAP titration on OSA patients. Once again, these results reflect the future possibilities to centre more and more diagnosis and treatment of sleep disorders on a domiciliary basis.

In chronic respiratory failure patients, Vitacca *et al.*[2] were able to demonstrate, in a randomised study performed on 240 patients, that intensive telemonitoring during one year results in a decrease of hospitalisation rate (-36%) and of urgent GP calls (-65%), an increase in days without exacerbations (+71%) and finally decreased global

health costs despite the additional cost of telemonitoring.

Till now, none of these devices have been largely implanted, because some barriers persist and slow their implementation. First of all, these telemonitoring devices are very complex and the heterogeneity of the systems is the same that these we can observe in the computer market, with possible compatibility problems with the other programs used in hospitals.

Secondly, the high cost (patient's home must be equipped with a computer and an internet connection, high specifications of computer programs) brakes the implementation of these systems, and no reimbursement from the social security is foreseen. However, investigations using solely the integrated circuits available on the market (mobile telephone) are conducted to simplify access to these technologies for both patients and hospitals.[17, 18]

Lastly, a lot of problems related to privacy protection and security of medical data transmission have not been solved, and EU commission is currently working to adapt existing rules to face e-health needs.[19] However, we expect that the recent technical progresses and future advances in the development of telecommunication technologies will arise to routine use of telemedicine in daily practice.

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Patient Ventilator Asyncronies in Neuromuscular Disease During Nocturnal Non-Invasive Ventilation

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Introduction

Over the years, non-invasive ventilation (NIV) has evolved towards a standard of care in neuromuscular diseases (NMD). When applying NIV in NMD patients, clinicians must pay close attention not only to reduce respiratory work performed by patients and to improve nocturnal and diurnal PaCO2, but also to avoid the possible negative effects of an improper setting. Among them, ventilator asynchrony has been defined as a faulty interaction between the patient and the ventilator. To achieve these goals, paying particular attention to the setting is imperative. Additionally, as NIV in chronic respiratory failure, and especially in neuromuscular diseases, is mainly used during the night, settings which seem appropriate for ventilating patients during wakefulness may not work appropriately during the night.[1] Thus, it is now evident that diurnal observation is not sufficient for a correct evaluation of NIV, and that the monitoring of breathing during sleep, either with a cardio-respiratory polygraphy or a polysomnography, is essential to identify the proper ventilator setting.[2-3] In fact, patient-ventilator asynchronies (PVA) may be clinically silent and may be identified only with a careful inspection of nocturnal recordings. Moreover, significant changes in transcutaneous PCO2 and oxygen saturation are not often evident.[4] Recent reviews have stressed the importance to identify PVA under NIV, and to adjust ventilator settings accordingly.[5-7] Their recognition is important, as most PVA cause sleep disruption.[8, 1] In this article, we will describe the main asynchronies occuring during NIV in NMD patients and their consequences on sleep quality.

We will separately discuss patient–ventilator asynchronies during the triggering phase, during the inspiratory and cycling off phases.

Asynchronies in the Triggering Phase

Ineffective Efforts

The most important asynchronies during the triggering phase are ineffective efforts (IE), defined as the failure of a patient's inspiratory effort to trigger a ventilator breath. In a polygraphic recording they appear as thoraco-abdominal displacements not assisted by the ventilator positive pressure boost.

The first studies on this kind of asynchrony were performed on COPD patients, since they were believed more frequent in patients with obstructive airway disease than in those with restrictive diseases.[9] In COPD patients the principal cause of IE is intrinsic PEEP (PEEPi). It results from incomplete expiration, which leads to dynamic hyperinflation, a common abnormality in these patients. Incomplete expiration may be also worsened during NIV, due to a too short expiratory time or to an excessive duration of pressure insufflation. When dynamic hyperinflation is present, the inspiratory effort of the patient fails to overcome the load induced by PEEPi and IE occur.

However, in the last years IE during NIV have also been described in neuromuscular patients.[1, 10] In NMD patients, Fanfulla *et al*. showed that setting the ventilatory parameters on an empirical basis during wakefulness often led to IE during sleep. In fact, in their study, IE did not appear during the day but were frequent at night. As most of NMD patients hardly have PEEPi, other mechanisms must be involved in their occurrence. During the night, major changes in the control of breathing occur, most notably the loss of waking neural drive to respiration.[11] As an effect of the lower drive, the patient's effort is not enough to trigger the ventilator breath. Vitacca *et al*.[12] showed that the likelihood of experiencing IE statistically and linearly decreased, reducing the level of assistance in different kinds of patients. In fact, an excess in assistance (pressure support), in addition to causing lung hyperinflation and the appearance of PEEPi, may further depress the respiratory drive. Accordingly, in the already cited study by Fanfulla, the patients with the most advanced diseases, who received a high pressure support, had a high rate of IE, which decreased after a reduction in the inspiratory pressure, with no deterioration of blood gases.

In addition to inspiratory pressure, the level of expiratory pressure (EPAP) proved inappropriate for most of patients, and the number of IE decreased after its reduction. In fact, in subjects without PEEPi, even a low level of EPAP can cause an activation of expiratory muscles and reduce triggering capacity. The recruitment of the expiratory muscles interferes with the ability of the next inspiratory effort to trigger the ventilator favouring IE.[13] In some patients even a very low level of EPAP

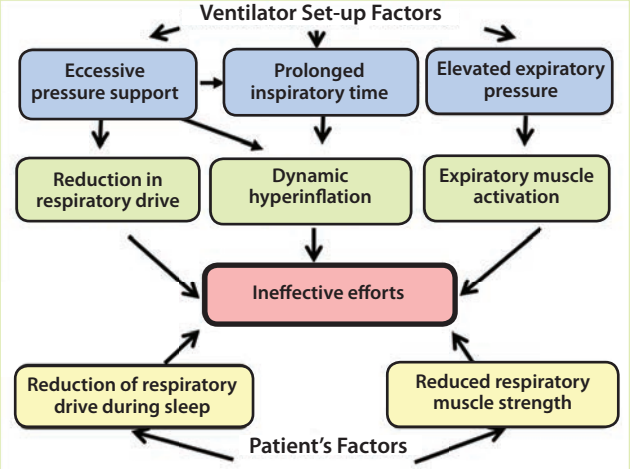

Figure 1. Factors related to ventilator setting or to patients' respiratory system that may enhance the occurrence of ineffective efforts

may be of danger, so that it is important to reduce the EPAP administered as much as possible, even to zero (Figure 1).

One more possible cause of IE is an inappropriate kind or a low sensitivity of the trigger. Some studies have showed that flow triggering slightly reduces the effort needed to trigger the ventilator as compared with pressure triggering, but the overall effect of flow trigger on total patient effort is small, and its clinical benefit appears much less than commonly stated.[14] For this reason, flow and pressure trigger are both used in clinical practice. On the other hand, triggers of modern ventilators are all quite sensitive, and adult neuromuscular patients, during the day, are able to trigger their ventilator without significant efforts. The situation may be different during the night, if leaks occur. Leaks may greatly affect the trigger preventing the detection of patient inspiratory effort. This mechanism may also lead to IE.[15]

The mode of NIV may influence the occurrence of IE.[16] We have recently documented that some modes of NIV may cause IE in NMD.[17] In fact, we compared pressure support ventilation (PSV) with and without guaranteed volume in a group of stable NMD, and we found a high prevalence of IE when we used the PSV mode with guaranteed volume. Although we do not have a clear explanation for this event, we hypothesise that IE could result from persisting mechanical insufflation during the neural expiratory phase as a result of supplemental inspiratory flow.

Autotriggerings

Other major asynchronies during the triggering phase include auto-triggerings (AUTO), consisting of close repeated inspiratory pressure boosts delivered by the ventilator that are not started by the patient. As we have recently documented[18] this kind of asynchrony is common in NMD patients under NIV. AUTO may be easily recognised in nocturnal polygraphic traces as the occurrence of at least three rapid successions of pressurisation clearly overcoming the patient's respiratory rate. While some authors found that IE are the most frequent PVA in NMD patients, in our experience AUTO is more frequent. In fact, as we previously reported, we always perform nocturnal polygraphic monitorings to improve ventilator setting, and we try to keep inspiratory pressure low enough to prevent IE but not so low as to cause alveolar hypoventilation. Additionally, we eliminate expiratory pressure in most of patients. AUTO are mainly caused by expiratory leaks and may be enhanced by a low respiratory drive and by the absence of hyperinflation,[19] which are often observed in patients with NMD disease. In our study, we documented an increase of these asynchronies when NIV was applied at home in comparison to hospital in a group of NMD patients, which was proportional to an increase in air leaks. Unfortunately, as AUTO are related to expiratory leaks, and expiratory leaks are related to mouth opening, they are rather difficult to manage. The few measures to reduce expiratory leaks, like application of a chinstrap or of an oro-nasal mask, are not easily accepted by NMD patients. Ventilators able to modify trigger sensitivity in relation to variation of the amount of leaks will probably help us to manage them better in the near future.

Asynchronies in the Inspiratory and Cycling off Phases

Prolonged insufflations

Less common asynchronies such as prolonged insufflation (PI) during pressure-support ventilation may also occur in NMD during NIV. During PSV, PI occurs when the ventilator continues the insufflation beyond the beginning of the patient's expiration. In polygraphic recordings it may be recognised as a prolongation of the mechanical insufflation beyond the end of patient inspiration, evaluated on the thoracic and/or abdominal traces. This kind of asynchrony is related to inspiratory leaks, and in our experience may be minimised by reducing inspiratory leaks and setting a maximum inspiratory time. During PSV, the ventilator tends to compensate large inspiratory leaks with a prolongation of the insufflation, and the delivered flow may remain above the value of the expiratory trigger, so that cycling off does not occur. In this situation, the patient attempts to expire, and may fight against the ventilator because the expiratory valve remains closed. A reduction of the pressure support level decreases the leaks and the incidence of PI. Additionally, the ventilator insufflation time may be limited with an increase in the expiratory trigger threshold and/or a reduction in the maximal inspiratory time. Calderini *et al.*[20] reported that adjusting the maximal inspiratory time to 0.8 - 1.2 seconds improved patient-ventilator synchrony, reducing the work of breathing, and improving comfort.

The use of a time cycled mode may be another alternative. In our institution, to avoid prolonged insufflations, the assist-pressure control of ventilation (APCV), that works with a preset fixed inspiratory time, is frequently used in neuromuscular patients

Asynchrony	Main Causes	Polygraphic Traces
Ineffective efforts (IE)	Reduction of respiratory strength; reduction of respiratory drive; intrinsic PEEP; insensitive trigger	Thoracic-abdominal movements without a positive pressure boost
Autotriggerings (AUTO)	Expiratory leaks	Occurrence of at least three rapid successions of pressurisation clearly above that of the patient's respiratory rate
Prolonged insufflation (PI)	Inspiratory leaks	Inspiratory pressure lasting more patient's inspiration detected on the respiratory bands

Table 1. A summary of the main asynchronies, their cause and their appearance in polygraphic recordings.

instead of the flow cycled mode. We also found that NMD patients preferred this mode of ventilation although no differences in gas exchange between flow cycled and time cycled mode were found. The kind and the size of the mask should be also carefully chosen and the position of the mask often readjusted in order to minimise inspiratory leaks that can occur around the mask. Table 1 summarises the main asynchronies, their cause and their appearance in polygraphic recordings.

Consequences of PVA

Most of the described nocturnal asynchronies follow air leaks either during inspiration (PI) or during expiration (AUTO), and occur more often in NREM sleep, although no significant differences between leaks during NREM and REM sleep have been found. Previous studies have already demonstrated a correlation between asynchronies and Arousal/Awakening Index,[19] which is also consistent with our findings. Although in our study we found a very low frequency of PVA, especially in the hospital setting, the analysis of asynchronies and arousals demonstrated that they were temporally associated, confirming the close relationship between imperfect coordination and altered quality of sleep. PVA may have negative effects on sleep quality, favouring permanence in light NREM sleep and decreasing stable stage N3. In addition, as we also evaluated the frequency of association between every kind of asynchrony and the associated arousal, we could conclude that IE and AUTO, that are more often associated with arousals, deserve more attention than PI as possible cause of sleep disruption.

In conclusion, as PVA have a negative impact of sleep they should be carefully detected and minimised. Further studies to better define the nomenclature of asynchronies and to understand their long term clinical effects are necessary.

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Upcoming Congresses and Meetings

The 2012 Isocyanates and Health: Past, Present and Future Conference

01 – 02 November 2012

Maryland, United States

This is an international, multidisciplinary conference which aims to share the latest knowledge and most important issues on the health effects of isocyanates. Areas include exposure monitoring, environmental controls and clinical management. The meeting hosts a variety of different sessions, including scientific, plenary and panel sessions, as well as posters and exhibitions, which will present the most current research and initiatives across different industry sectors.

COPD 2012: From Evidence to Practice

08 - 09 November 2012

London, United Kingdom

COPD 2012 is aimed at all medical professionals with an interest in respiratory medicine, and will feature sessions which offer updates on the epidemiology, biomarkers and pathophysiology of COPD, as well as an evaluation of emerging COPD therapies and the chance to share and exchange ideas with leading practitioners in the field.

British Thorac Society Winter Meeting 2012

05 - 07 December 2012

London, United Kingdom

The British Thoracic Society was formed in 1982 by the amalgamation of the British Thoracic & Tuberculosis Association and the Thoracic Society. Members include doctors, nurses, respiratory physiotherapists, scientists and other professionals with an interest in respiratory disease. The BTS' main objective is to improve the care of people with respiratory disorders. The Winter Meeting attracts over 2000 delegates and is the UK's primary respiratory scientific meeting, with a focus upon presenting updates on current research and symposia from leading researchers.

The Intensive Care Society (ICS) State-of-the-Art Meeting 2012

10 - 12 December 2012

London, United Kingdom

The Intensive Care Society is the representative body in the UK for intensive care professionals and patients, and is dedicated to the delivery of the highest quality of critical care to patients. The State-of-the-Art meeting is the UK's largest gathering for intensive care professionals, and will feature both international experts and speakers from the UK, as well as an exhibition, poster presentations and research awards and grants.

11th Annual British Thoracic Oncology Group Conference 2013

23 - 25 January 2013

Dublin, Ireland

BTOG aims to improve the care of patients with thoracic malignancies through multidisciplinary education and clinical and scientific research. BTOG represents all the disciplines involved in the care of lung cancer and mesothelioma throughout the UK, and includes medical and clinical oncologists, respiratory physicians, surgeons, radiotherapists, radiologists, nurses, pharmacists and scientists. The annual conference features scientific symposiums, plenary sessions, state-of-the-art presentations and workshops.

Association for Respiratory Technology and Physiology (ARTP) Annual Conference 2013

07 - 09 Feburary 2013

Leicestershire, United Kingdom

The Association for Respiratory Technology and Physiology (ARTP) are the professional guardians of physiological measurement issues in respiratory medicine in the UK. The ARTP aims to deliver and promote education and training programmes, as well as promoting advances in diagnostic, treatment and care of patients with respiratory disease. Additionally, the organisation represents the interests of practitioners at all levels. Led by experts within the field, the conference features plenary lectures, meet the expert sessions and workshops.

14th European Congress: Perspectives in Lung Cancer

08 - 09 March 2013

Torino, Italy

This conference program has been created with health care professionals involved in the therapeutic managements of lung cancer in mind, providing both current and emerging information on the diagnosis and treatment of patients with lung cancer and other thoracic malignancies. The meeting features didactic presentations and interactive case presentations which will focus upon the upcoming trends treatments, as well as updating professional's knowledge and expertise.

11th ERS Lung Science Conference

15 - 17 March 2013

Estoril, Portugal

The theme for the 11th ERS Lung Science Conference is 'Early origins and mechanisms

of chronic lung disease.' The scientific programme will provide up-to-date sessions on microbiota in chronic lung disease, early origins of chronic lung disease and bridging innate and adaptive immune pathways in disease inception.

Sleep and Breathing

11 - 13 April 2013

Berlin, Germany

The Sleep and Breathing conference is the largest pan-European meeting of its kind, and the only meeting to offer an integrated approach to the investigation and treatment of sleep disorders. In 2013, the focus will remain predominantly on sleep breathing disorders. However, the programme will also cover sleep-related areas of paediatrics, obesity, cardiovascular disorders, diabetes, psychology, psychiatry and neurology. These areas will be explored through case studies, plenary sessions, debates and specialised symposia.

Association of Respiratory Nurse Specialists (ARNS) Annual Conference 2013

09 - 10 May 2013

Warwick, United Kingdom

The ARNS Annual Conference promises something for all those working in respiratory nursing and allied health professional roles. The conference includes a variety of workshops and sessions which cover a wide range of areas within respiratory illness. This course is aimed at doctors, nurses and physiotherapists who would like to feel more confident with managing end of life issues in respiratory disease.

3rd International Primary Care Respiratory Group (IPCRG) Scientific Meeting

23 - 24 May 2013

Upsala, Sweden

The 2nd Scientific IPCRG Meeting was a great success, with over 160 delegates from 18 different countries. The meeting focused upon both research ideas and clinical research, and included an in-depth overview of the IPCRG's ongoing research as well as many networking opportunities. The 3rd Scientific Meeting looks set to produce another interesting and thought provoking programme.

21st European Conference on General Thoracic Surgery

26 - 29 May 2013

Birmingham, United Kingdom

According to its pure tradition, the European Society of Thoracic Surgeons (ESTS) intends to set up a scientific programme of the highest quality. While the scientific sessions will include the very best of recent work, rewarded by many ESTS Prizes, the collaborative ESTS-AATS-STS postgraduate course, the techno-meeting, breakfast sessions and numerous symposia will gather a large number of leading experts in order to update attendee's knowledge on the various aspects of Thoracic Surgery.

3rd World Congress of Thoracic Imaging

08 - 11 June 2013

Seoul, South Korea

At the 3rd World Congress of Thoracic Imagining, a large number of professors, doctors and distinguished leaders in the field from all over the world, as well as five member societies, will come together to discuss recently emerging issues and the latest information in the field of thoracic radiology. The congress is designed to offer a programme filled with comprehensive and substantial scientific sessions and symposia as well as offering the most relevant and practical education. These sessions will cover topics such as lung cancer, cardiac imagining, COPD and airway disease and interstitial lung disease.

36th European Cystic Fibrosis Conference

12 - 15 June 2013

Lisbon, Portugal

The objective of this conference is to provide a forum for the discussion of the best basic and applied science, and facilitate translation of the latest knowledge into daily clinical practice. The programme will reflect these priorities and bring together scientific and clinical teams. You can expect a high quality programme of plenary sessions, symposia and workshops, with international experts in cystic fibrosis invited to present lectures. The Conference will provide a social platform and a great opportunity for making or renewing contacts with colleagues in the field.

EAACI – WAO World Allergy and Asthma Congress 2013

22 - 26 June 2013

Milan, Italy

The European Academy of Allergy and Clinical Immunology is a non-profit organisation which aims to promote basic and clinical research, as well as collect, assess and disseminate scientific information. It further aims to encourage and provide training and continuous education. The World Allergy Organisation is an international umbrella organisation which provides direct educational outreach programmes, symposia and lectures to members in nearly 100 countries around the globe. The combined knowledge and expertise of these two organisations ensures that the congress will be one not to miss.

European Respiratory Society Annual Conference 2013

07 - 11 September 2013

Barcelona, Spain

The ERS is the leading professional organisation in its field in Europe, and has around 10,000 members from over 100 countries. It is broad-based, and its scope covers both basic science and clinical medicine. ERS seeks to alleviate suffering from respiratory disease and promote lung health through research, sharing of knowledge and through medical and public education. The ERS congress adheres closely to these principles, and offers a range of sessions including symposia, workshops, seminars and abstract presentations, as well as lectures given by leading experts in the field.

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