07 JAHRESBERICHT

Ludwig Boltzmann Institut
Chronisch obstruktive Lungenkrankheiten

Report
Ludwig Boltzmann Institute for COPD
2006 - 2007

Introduction:

The Ludwig Boltzmann Institute for COPD (LBI – COPD) was initiated in 2002 and is located at the Department of Respiratory and Critical Care Medicine, Otto Wagner Hospital, Vienna. A contract between the hospital authorities (Krankenanstaltenverbund - City of Vienna) and the Ludwig Boltzmann Gesellschaft was assigned with the aim to encourage clinical and translational research within the Competence Center of Pulmonology in Vienna (non - University Community Hospital).

Within the last two years the LBI-COPD comprised 1 head (O.C. Burghuber), 3 group leaders (S.Hartl, A. Valipour, GC. Funk), 5 LBI contracted research fellows (M.K. Breyer, R. Kohansal, I. Mikulic, I. Firlinger, K. Kirchheiner), 3 research associates (P. Eickhoff, L. Cekici, M. Ruis), and 1 secretarial assistance (A. Fink). Head and Group leaders are employees of and payed by the City of Vienna and are staff members of the Department of Respiratory and Critical Care Medicine for many years with specific scientific interest in various aspects of COPD. The average age of our scientific associates is around 25 years and people come from different ethnic backgrounds. The initiation of the LBI-COPD opened a wide range of career opportunities for its researchers, some of which continued international post-doc fellowships in cooperation with the LBI, whereas others pursued their medical careers after a short time employment with the LBI-COPD.

Two of our research fellows (Robab Kohansal, Marie K. Breyer) have recently completed one year fellowships in prestigious institutions in Europe (Spain and in the Netherlands). Robab Kohansal, MD, was working in epidemiology and clinical research at the International Centre for Advanced Respiratory Medicine Caubet - CIMERA in Spain (Prof. A. Agusti) since March 2007. She has received a „long term fellowship for research“ by the European

Respiratory Society, indicating the international recognition of LBI-COPD. Similarly, Marie K. Breyer, who was involved in our rehabilitation programme has worked on a collaborative research project on COPD with Prof. E. Wouters at the Department of Respiratory Medicine, University Hospital Maastricht. Both returned to Vienna this year starting their residency at the Department of Respiratory and Critical Care Medicine at the Otto Wagner Hospital.

Main focus of the LBI – COPD within the last years was a) to study different aspects of COPD as a systemic disease with its substantial comorbidities, particularly focusing on cardiovascular diseases and sleep as well as b) identifying treatment options to improve quality of life in COPD.

Therefore, two research groups, focusing on translational and clinical research in the field of chronic obstructive pulmonary disease (COPD), were assembled. The two research groups work together in two programme lines with three specific projects, each. Programme line 1 focuses on systemic effects of COPD (Cardiovascular effects of COPD, Systemic inflammation in COPD, Effects of COPD on sleep). Programme Line 2 consists of three projects too and deals with investigations related to therapeutic interventions in COPD (Rehabilitation, Non invasive ventilation, Bronchoscopic lung volume reduction,).

Programme Line 1. Systemic effects of COPD

A. Cardiovascular effects of COPD

The **first specific project** arising from this group studied flow-mediated vasodilation in 60 patients with stable COPD and 40 appropriate controls, selected on the basis of clinical examination, medical history, disease severity (lung function impairment), medication and exercise capacity in a cross-sectional study design. The technique of flow mediated dilation enabled to systematically assess endothelial dysfunction, a precursor of coronary heart

disease. We have observed evidence of (clinically silent) significant impairment in the endothelial functioning in patients with COPD compared to age, sex, and body-mass-index matched controls. Our findings further suggest a relationship between airflow limitation, systemic inflammation and endothelial dysfunction. Given the predictive capacity of flow-mediated dilation in cardiovascular risk-stratification, these conclusions may carry a number of potentially important clinical implications, including recommendation of early testing for cardiovascular disease in patients with COPD. This trial has been completed in 2006 and the results have been introduced to the research community at recent national and international congresses (Annual American Thoracic Society Conference 2007, European Respiratory Society Conference 2006, Conference of the Austrian Society of Pneumology 2006). The manuscript is under revision in the American Journal of Respiratory and Critical Care Medicine.

The second specific project prospectively studied left-ventricular diastolic function in patients with COPD and normal or elevated pulmonary arterial pressure. The study design included echocardiographic assessment of left and right ventricular contractility, Doppler-echocardiography, and right heart catheterization. The authors hypothesized that left ventricular diastolic function may be impaired in patients with COPD in the presence of normal pulmonary arterial pressure. This study has commenced in 2006 and has recently been terminated. The main finding was that left ventricular diastolic function is impaired in patients with COPD and normal pulmonary arterial pressure. Left ventricular diastolic dysfunction worsens with increasing right ventricular afterload. Diastolic dysfunction may be one systemic aspect of the disease and this concept may further contribute to an elevated cardiovascular risk in patients with COPD. The manuscript has been accepted for publication in Chest (Funk GC, Lang I, Schenk P, Imkova I, Valipour A, Burghuber OC Left ventricular diastolic dysfunction in patients with COPD in presence and absence of elevated pulmonary arterial pressure Chest 2007, Impact factor 4.0; Topjournal)

The third specific project is an ongoing project that studies the relationship between pathophysiological components of COPD, such as hypoxemia and elevated intrathoracic pressures, and autonomic nervous system activity. The protocol of this study has been awarded additional funding from the "Stiftung zur Förderung der Bekämpfung der Tuberkulose und anderer Lungenerkrankungen" . In a multi-step process this project performed non-invasively obtained hemodynamic measurements of cardiac output, peripheral resistance, beat-to-beat arterial blood pressure, heart rate variability and baroreceptor sensitivity, during simulated pathophysiological conditions, such as laboratory-induced hypoxemia and elevated intrathoracic pressures using positive airway pressures (simulating elevated intrinsic positive end-exspiratory pressure in COPD). In a proof of concept fashion, the study group attempts to translate their findings into patients with severe, emphysematous type of COPD during resting conditions, paced breathing and stress tests. The aim of this project is to gather important information on cardiac autonomic functioning, an important confounder in COPD mortality. This project started in 2006 and is not expected to reach final recruitment until Summer 2008.

B. Systemic inflammation in COPD

Primary aim of this research line is to investigate the profile of systemic inflammatory markers in patients with COPD. Recently published observations share the common interest to assess the extrapulmonary effects of COPD both on a clinical and on a molecular level. Led by the group leaders, our post-doc researchers which were financed by the LBI-COPD (Drs. Eickhoff, Cekici and Schreder) were familiarized with laboratory methods such as HPLC, and enzyme-linked immunonsorbent assay in collaboration with the Department of Clinical Pharmacology at the AKH Wien (Prof. Michael Wolzt). Blood sampels were taken from patients during acute exacerbation and in stable COPD measuring inflammatory proteins such as C-reactive protein and fibrinogen as well as cytokines such as interleukin-6, TNF-Alpha

and vascular endothelial growth factor (VEGF). Supporting recently published data, we observed an increase in pro-inflammatory cytokines in patients with stable COPD, which are upregulated during acute exacerbations of COPD. This project is already completed and the manuscript has been accepted for publication in „Clinical Science“ (Valipour A, Schreder M, Wolzt M, Saliba S, Kapiotis S, Eickhoff P, Burghuber OC. Circulating Levels of Vascular Endothelial Growth Factor and Markers of Systemic Inflammation In Patients With Chronic Obstructive Pulmonary Disease Clin Sci (Lond). 2008, Impact factor 3.2; Topjournal).

A subsequent study explores the relationship between inflammatory markers in blood samples from patients with severe stable COPD and asymmetric dimethyl arginin (ADMA) in order to assess the impact of systemic inflammation on nitric-oxide mediated vasodilation in COPD. The results of this project may help to gain better understanding of the molecular mechanisms involved in the development of cardiovascular failure and pulmonary hypertension in COPD.

C. Effects of COPD on Sleep

Primary aim of this research line is to investigate sleep profiles, nocturnal respiration and symptoms in patients with COPD. Sleep patterns and symptoms associated with sleep breathing disorders in patients with COPD are ill-defined. Patients with COPD have a higher prevalence of insomnia, nightmares and daytime sleepiness than the general population. These sleep disturbances probably contribute to the nonspecific daytime symptoms of chronic fatigue, lethargy and overall impairment in quality of life described by these patients. Unfortunately, sleep impairment is an aspect of COPD that is frequently ignored by many physicians, even in research protocols designed to assess the impact of COPD on quality of life. The aim of this collaborative group project therefore is to assess systematically the relationship between lung function impairment, daytime arterial blood gas analysis, exercise capacity, sleep related symptoms, quality of life, and polysomnographic parameters in patients with stable severe COPD. The LBI-COPD constituted a research collaboration with

another major sleep laboratory in Vienna (Krankenhaus Lainz) and one of the most prestigious international sleep laboratories in - Israel (Prof. Peretz Lavie). - Based on recently published findings of gender-related differences in symptoms of suspected breathing disorders in sleep our group could identify significant differnences between gender (gender-related differences in the severity and profile of nocturnal hypoventilation in COPD). Results of this project has been published recently in "Sleep" (Valipour A, Lothaller H, Rauscher H, Zwick H, Burghuber OC, Lavie P Gender related differences in symptoms of patients with suspected breathing disorders in sleep: a clinical population study using the Sleep Disorders Questionnaire. Sleep 2007; 30: 306 – 313, Impact factor 5.0; top journal)

Programme Line 2: Therapeutic interventions in copd

A. Effects of Rehabilitation on outcome in patients with COPD - Influence of an endurance training and lifestyle coaching on daily life movement-behaviour in patients with COPD (MOVE)

Primary aim of this research line focuses on the translation of rehabilitation programmes in real life of the patients, thus changing life-style of COPD-patients towards more active life. Review of the literature showed that patients suffering from COPD have a more sedendary life style than age matched healthy people and that COPD patients returned to an inactive lifestyle only few month after the end of a rehabilitation programme. The first project investigated the effect of aerobic endurance training on activity levels of daily life of COPD-patients. The LBI-COPD financed our post-doc- researchers carrying out the study.(Marie Breyer and Dominik Hofeneder) We choose an exercise model by Nordic Walking as this is appropriate to reach training goals of heart rate easily and can be done even with reduced performance status. Patients have autonomy of speed control and can maintain aerobic treshold for longer training periods. Thereby patients were acquainted to walking , an activity

of daily living that was experienced as exerting before the study in more severe COPD-patients. The second part of the rehabilitation programme consisted of psychological coaching: patients had a weekly educational session on COPD pathology, diets, smoking cessation and the impact of life style on the course of COPD.

By using a triaxial accelerometer we compared the levels of daily activity before and after 3 and 9 month of the rehabilitation programme. COPD-patients who had weekly education sessions served as controls. Primary outcome was activity level in daily life, secondary outcomes-measure were dyspnoea, overall performance SF36, and physiological data: lung function and 6-min walking distance.The study started in July 2006 and 9 month evaluation has just finished. Results were analyzed indicating significant positive effects of Nordic walking on all outcome parameters studied. Results of this project will be presented during the annual meeting of the European Respiratory Society (ERS) in Berlin 2008 as an oral presentation. Publication is expected by the end of this year.

B. Effects of Ventilatory Support on COPD

The first project is concentrating on mortality as the primary outcome of long term noninvasive ventilation in stable COPD suffering from mild hypercapnia: the NIV-study is an European (German- Austrian- Swiss) Multicenter Study comparing survival in patients with chronic hypercapnia with or without non invasive ventilatory support. The follow up period is one year after initiation of noninvasive ventilation aiming to include 150 patients in each study group.The study will answer the question if there is a benefit in survival if ventilation overts nocturnal blood gas disturbances . Secondary study endpoints address to health related quality of life and performance parameters and clinical stability (rate of exacerbations, clinical resource consumption). Participating Centers provide high expertise in ventilation practice by specific “Respiratory Care Units”, that titrate ventilatory support to sufficient levels to be clinical effective and adapt patients until they are able to use the devices properly at home.

Telephone calls provide support to patients and reinforce compliance with the study therapy. The study started in 2005 and is still ongoing. Interim analysis have not been published yet.

The second project is a controlled trial selecting COPD patients after acute on chronic respiratory failure being ventilated for emergency reasons. NIVEX (Efficacy of nocturnal non invasive ventilation in chronic respiratory failure: withdrawal of non invasive home ventilation in stable hypercapnic COPD patients) is a project of our group leader Hartl Sylvia, supported by the research fellows Marie-Kathrin Breyer and Kirchheiner Katrin. The protocol of this study has been awarded additional funding from the "Stiftung zur Förderung der Bekämpfung der Tuberkulose und anderer Lungenerkrankungen". NIVEX follows clinical stabilization of a severe group of COPD patients - who had to be ventilated because of severe acute on chronic respiratory failure and remained hypercapnic after recompensation - after hospital discharge by noninvasive nocturnal ventilation for 6 month. After this period randomized withdrawal of ventilation is performed (intervention group) or non invasive ventilation continued (control group). Our hypothesis is, that withdrawal of mechanical ventilation after 6 month of non invasive ventilation in selected COPD-patients with poor prognosis leads to clinical instability, elevation of PaCO2 and increase in dyspnoea and/ or disruption in sleep quality. Patients aim to be followed by outcomes of clinical stability. Primary endpoints are time to a certain level (or certain increase) of hypercapnia and increase in dyspnoea. Secondary outcomes are overall disease specific quality of life including cognitive function , number of exacerbations, hospital stays and mortality.

Preliminary analysis of 6 month outcomes on cognitive function showed severe impairment of specific functions (memory and logical reasoning) and only slight improvement after 6 month of ventilation. Comparable results have not yet been published on COPD-patients after respiratory decompensation and were presented for the first time at the annual Congress of the American Thoracic Society 2007 in San Francisco (oral presentation by Marie Breyer,

research fellow of LBI-COPD). These preliminary results are in line with similar results obtained in patients being ventilated and deeply sedated for adult respiratory distress syndrome (ARDS). Data collection presumably will finish at the end of 2008 and at least two publications on different outcomes are expected to be published subsequently.

C. Bronchoscopic lung volume reduction in patients with COPD

Primary aim of this research line is to investigate bronchoscopic lung volume reduction procedures in patients with severe COPD. Bronchoscopic lung volume reduction (BLVR) attempts to achieve the effects of surgical lung volume reduction, by placing bronchial prostheses using a fiberoptic bronchoscope to selectively occlude the airways supplying the most affected hyperinflated regions of the emphysematous lung, while permitting exhaled gas to escape. While the latter treatment option has been developed for the palliation of heterogenous emphysema, a more recent development, the “airway bypass procedure” using the Exhale drug eluting stent, has been introduced for the treatment of homogenous emphysema. Both methods aim to achieve segmental or lobar volume reduction, simulating the effects of surgical lung volume reduction. Recently published reports of BLVR in patients with end-stage emphysema have shown significant improvements in lung function, dyspnea and/or exercise capacity. The treatment algorithm for valve implantations to achieve lung volume reduction, however, varied considerably in these reports as well as clinical and functional response rates. Subset analysis of these studies revealed that particularly, but not exclusively, patients with radiological signs of lung volume reduction treated unilaterally showed significant clinical improvements, whereas most patients without signs of lung volume reduction did not experience these benefits. One of the potential explanations for unsuccessful lobar collapse associated with endobronchial one-way valve implantation is the presence of collateral ventilation.

The group members of the LBI-COPD have been actively involved in three major multicentric, clinical trials, using the above mentioned methods for BLVR:

1. Endobronchial Valve for Emphysema PalliatioN Trial (VENT), completed;

2. A Randomized, Double-blind Study to Evaluate the Safety and Effectiveness of the Exhale Drug-Eluting Stent in Homogeneous Emphysema Subjects with Severe Hyperinflation (EASE), ongoing

3. A multi-center, prospective, clinical trial designed to study the efficacy of one-way valve implantation based on a new treatment algorithm in patients with heterogeneous emphysema.

Our research group contributed a large number of eligible patients to the first two trials (VENT, EASE) and initiated the third trial with support from Emphasys Medical Inc. Accordingly, we have implemented an outpatient clinic for BLVR, thereby laying the ground for cumulating expertise in this field as one of the leading European Research Centers in BLVR for COPD. Due to patenting interests specific details are omitted. The first publications related to the activities in the field of BLVR are expected by the end of 2008/ beginning 2009.

Original papers:

1. Valipour A, Lothaller H, Rauscher H, Zwick H, Burghuber OC, Lavie P
Gender related differences in symptoms of patients with suspected breathing disorders in sleep: a clinical population study using the Sleep Disorders Questionnaire.
Sleep 2007; Impact factor 5.0

2. Valipour A, Schreder M, Wolzt M, Saliba S, Kapiotis S, Eickhoff P, Burghuber OC.
Circulating Levels of Vascular Endothelial Growth Factor and Markers of Systemic Inflammation In Patients With Chronic Obstructive Pulmonary Disease
Clin Sci (Lond) 2008; Impact factor 3.2

3. Funk GC, Lang I, Schenk P, Imkova I, Valipour A, Burghuber OC
Left ventricular diastolic dysfunction in patients with COPD in presence and absence of elevated pulmonary arterial pressure
Chest 2008; Impact factor 4.0

4. Eickhoff P, Kiss D, Schreder M, Kohansal R, Valipour A, Geyer K, Burghuber OC
Endothelial Dysfunction in patients with stable COPD is linked to systemic inflammation
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AJRCCM 2007, Suppl. 300s, p.A516

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