08/09 ANNUAL REPORT

Ludwig Boltzmann Institute
Chronic Obstructive Pulmonary Disease

Ludwig Boltzmann Institute for COPD
2008 - 2009

Introduction:

The Ludwig Boltzmann Institute for COPD (LBI – COPD), initiated in 2002, is located at the Department of Respiratory and Critical Care Medicine, Otto Wagner Hospital, Vienna, with the aim to encourage clinical and translational research within the Competence Center of Pulmonology in Vienna.

Within the last two years the LBI-COPD comprised 1 head (O.C. Burghuber), 3 group leaders (S.Hartl, A. Valipour, GC. Funk,), 5 research fellows (M.K. Breyer, R. Breyer-Kohansal, I.Mikulic, N. Dornhofer, M. Urban) , 4 research associates (S. Ashadi, S. Ashadi, R. Hahn, L.Steindl), and 1 secretarial assistance (J. Eidenberger). Head and Group leaders are employees of and payed by the City of Vienna and are staff members at the Department of Respiratory and Critical Care Medicine with specific scientific interest in various aspects of COPD. Two of our research fellows (Robab Kohansal, Marie K. Breyer) have completed a one year fellowships in prestigious institutions in Europe (Spain and in the Netherlands) and have recently started their pulmonary fellowship at the Department of Respiratory and Critical Care Medicine. Matthias Urban has started a PhD programme on “Vascular Biology” at the Medical University of Vienna. The thesis of his programme has been developed at the LBI – COPD.

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, metabolic diseases and sleep as well as b) identifying non pharmacological 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. Three research groups work

together in two programme lines. Programme line 1 focuses on systemic effects of COPD (Cardiovascular effects of COPD, Metabolic syndrome and COPD, Systemic inflammation in COPD, Effects of COPD on sleep). Programme Line 2 deals with investigations related to therapeutic interventions in COPD (Rehabilitation, invasive and non invasive ventilation, Bronchoscopic lung volume reduction,). In addition, Robab Kohansal, MD, who worked in epidemiology and clinical research at the International Centre for Advanced Respiratory Medicine Caubet - CIMERA in Spain (Prof. A. Agusti) has recently build up a new Programme line (Programme Line 3) focusing on pulmonary epidemiology.

Programme Line 1: Systemic effects of COPD

A. Cardiovascular effects of COPD

1.Endothelial dysfunction is impaired in COPD

The **original project** arising from this program line studied systemic vascular function, markers of systemic inflammation, and lung function in 60 patients with stable COPD and 40 appropriate controls free from traditional cardiovascular risk factors. Study participants were selected on the basis of clinical examination, medical history, disease severity (lung function impairment), medication, and exercise capacity. Systemic vascular function was assessed using flow mediated dilation of the brachial artery. Flow-mediated dilation enables assessing both endothelium-dependent and endothelium-independent vasodilator function of the vasulature. Endothelial dysfunction in turn is a surrogate of subclinical atherosclerosis and cardiovascular disease. Using this technique we observed evidence of endothelial dysfunction in patients with stable COPD compared to age, sex, and body-mass-index matched controls. Furthermore, we were able to detect a relationship between airflow limitation, blood glucose levels, systemic inflammation and endothelial dysfunction. Given the predictive capacity of

flow-mediated dilation in cardiovascular risk-stratification, our findings 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 2008 and the manuscript has been published (Am J Respir Crit Care Med. 2008 Oct 3; IF 9,09 Topjournal)

2. Endothelial dysfunction and systemic inflammation in patients with acute exacerbations of chronic obstructive pulmonary disease

Cumulating data suggest that the inflammatory reaction associated with COPD is not restricted to the lungs but has a systemic component. Additionally patients with COPD have increased cardiovascular morbidity and mortality. The suspected link between increased cardiovascular mortality and systemic inflammation is endothelial dysfunction, which has been demonstrated in patients with COPD. Furthermore there is a close correlation between endothelial dysfunction in coronary and peripheral vessels, which allows assessing flow-mediated dilation (FMD) in the brachial artery via high resolution ultrasound as an early predictor of atherosclerosis. Moreover, systemic inflammatory markers correlate with endothelial dysfunction in patients with stable COPD.

Exacerbations of COPD are episodes of worsening symptoms characterized by increased airway and systemic inflammation. If systemic inflammation is a cause of endothelial dysfunction in COPD, endothelial function would be suspected to be further impaired during exacerbation and recover thereafter. Therefore the purpose of this prospective cohort study in 28 COPD patients is to determine a possible association between the clinical entity of exacerbation, markers of systemic inflammation and endothelial dysfunction.

The study has been approved by the institutional ethics committee and 27 patients have been enrolled and followed up. Early results from these investigations have been presented at the National Society Meeting of the Austrian Society of Pneumology both in 2007 (Kiss D, et al. Wien

Klin Wochenschr Suppl 2007) and 2009 (Urban M, et al. Wien Klin Wochenschr 2009); however, this project has continuously been recruiting patients.

3. Longitudinal study of endothelial function in COPD

In order to assess the disease course of subclinical cardiovascular disease in our study population, a longitudinal follow-up study was initiated in a subset of patients with COPD from the previously described cohort. In this study we determined systemic vascular function, circulating inflammatory markers, lung function parameters, and markers of glucose metabolism at baseline and after 12 months. We observed worsening of endothelial dysfunction and altered glucose metabolism in the presence of preserved lung function values, indicating progression of cardiovascular risk within this cohort. Noteworthy, there was a significant relationship between changes in endothelial function and insulin resistance, suggesting an important role for altered glucose metabolism in the development of cardiovascular disease. Results of this study have been accepted for presentation at various national and international congress meetings including the European Respiratory Society (Cekici L et al, Eur Respir J Suppl 2008) and the American Thoracic Society (Urban M et al, Am J Respir Crit Care Med 2010 Suppl). The manuscript entitled "Insulin resistance may contribute to systemic vascular dysfunction in patients with stable COPD: a longitudinal pilot study" has recently been completed and will be submitted for publication shortly

4. Hyperinflation, altered cardiac filling and systemic inflammation

Ongoing investigations in this field further attempt to delineate the underlying mechanisms for subclinical cardiovascular disease in COPD. In this context biochemical markers of nitric oxide synthase capacity and measurements of systemic vascular function using intima media thickness are within the focus of examinations in order to explore the pathophysiological basis of our observations in a translational research setting.

Most of the above mentioned effects of COPD on the cardiovascular system are considered as systemic effects of the disease, which are primarily caused by systemic inflammation and/or altered glucose metabolism associated with the condition. COPD, however, may also cause insults to the cardiovascular system via a local hyperinflation. In fact, there is cumulating evidence of impaired biventricular preload associated with hyperinflation in patients with COPD. A reduction in cardiac filling pressures may result in unloading of baroreceptors. We therefore investigated baroreceptor sensitivity, an independent predictor of cardiovascular morbidity and mortality, in patients with COPD and controls. 25 patients with COPD free from clinical cardiovascular disease and 12 age, gender, and body-weight matched controls without airflow obstruction were studied for this puprose. Participants underwent comprehensive hemodynamic measurements and assessment of arterial baroreflex modulation of heart rate during resting conditions and mental stress testing. Patients with COPD had significantly lower stroke index, however, significantly higher heart rate and higher total peripheral resistance compared with controls. The mean slope of spontaneous baroreceptor sequences was significantly lower in patients with COPD than controls during both resting conditions and mental stress testing. Importantly, we observed a significant relationship between hemodynamic measurements, baroreceptor sensitivity and lung function parameters of hyperinflation. Thus our results confirm previously reported evidence of impaired cardiac filling related to hyperinflation in patients with COPD. Our findings extend these findings as they also indicate a link between baroreceptor function and increased lung volumes in COPD. Preliminary analysis from this project has recently been accepted to be presented at the European Respiratory Society Meeting 2010 in Barcelona (Wieser V, et al, Eur Respir J 2010 Suppl).

5. Systemic inflammation in COPD

Primary aim of this research line is to investigate the profile of systemic inflammatory markers in patients with COPD. 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.

6. Potential cardiovascular side effect of bronchodilators in COPD

Among our research related to cardiopulmonary interactions in patients with COPD we most recently investigated potential side effects of COPD treatment on the cardiovascular system. Selective b2-agonists, such as salbutamol, are in widespread use for patients with COPD. In addition to their bronchodilating effect, b2-agonists are capable of causing unfavourable effects on the cardiovascular system. In fact, a number of previous reports have described a relationship between oral or inhaled b2-agonist use and increased cardiovascular morbidity and mortality. Thus, we investigated the acute effects of inhaled salbutamol on cardiovascular

autonomic regulation in healthy, non-smoking volunteers, using continuously obtained haemodynamic measurements, blood pressure and heart rate variability, and baroreceptor activity. Using this approach we observed a significant increase in heart rate and cardiac output in response to inhaled salbutamol, which were accompanied by an increase in sympathetically mediated heart rate variability in the absence of significant changes in baroreceptor activity. The observed changes in cardiac autonomic function indicate increased sympathetic activity associated with inhaled beta-2agonists, which may contribute to the increased cardiac risk associated with inhaled b2-agonist treatment. The results of this work has been published in the British Journal of Clinical Pharmacology (Br J Clin Pharmacol 67:394, 2009)

7. Left ventricular filling is impaired in COPD

We 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 published in Chest 2008. (Chest. 2008 Jun;133(6):1354-9, IF: 4,1; Topjournal)

8. Effects of ROFLUMILAST on markers of subclinical atherosclerosis In stable COPD; the ELASTIC-trial

Chronic obstructive pulmonary disease is associated with a low grade systemic inflammatory process. Systemic inflammation is hypothesized to maintain cardiovascular morbidity and mortality in COPD. Early changes of vascular integrity can be detected via markers of subclinical atherosclerosis. Selective inhibition of phosphodiesterase subtype 4 describes a promising therapeutic option in COPD with beneficial impact on lung function and exacerbation rate. Moreover, an anti-inflammatory effect of phosphodiesterase-4 inhibition was confirmed by recent data.

The aim of this study will be to determine the effects of the phosphodiesterase-4 inhibitor Roflumilast on firstly surrogates of subclinical atherosclerosis and secondly markers of systemic inflammation in the peripheral circulation of patients with stable chronic obstructive pulmonary disease.

To investigate these circumstances, we are planning to enrole patients with diagnosed COPD pulmonary disease at GOLD-stage III or IV and history of at least one COPD exacerbation in the previous year. Subjects will be randomized to one of the two treatment arms receiving either Roflumilast or placebo for a study period of six months. Prior to initiation of study medication and after the treatment period patients will undergo measurements of arterial stiffness, systemic inflammation and lung function.

The primary endpoint is defined as a significant improvement of arterial stiffness quantified by means of the so called carotid femoral-Pulse Wave Velocity (cf-PWV). Secondary endpoints include beneficial impacts of study medication on further markers of vascular functional and structural state (i.e. Augmentation Index [Aix], Flow-Mediated Dilation [FMD], brachial artery Intima-Media Thickness [ba-IMT], Matrix Metalloproteinase-9 [MMP-9], asymmetric dimethylarginine [ADMA]) and markers of systemic inflammation (Tumor NecrosisFactor α [TNF-α], C-reactive Protein [CRP]).

The study protocol is authored and currently under preparation for submission to the local Ethics Committee/Institutional Review Board. Study initiation is scheduled for January 2011.

B. Sleep in COPD

1. Sleep profiles in COPD patients with different severity

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. Primary aim of this research line was therefore to prospectively assess differences in symptom profile and polysomnographic parameters in patients with stable mild to moderate COPD and age, gender, and body-mass-index matched controls without airflow obstruction. We observed that patients with COPD compared to controls had overall lower sleep efficiency, a lower total sleep time, and lower mean overnight oxygen saturation. Patients with COPD were furthermore significantly more likely to report symptoms such as insomnia and difficulty in initiating and maintaining sleep. Thus our results indicate clinically relevant impairment in both quantity and quality of sleep in patients with stable mild to moderate chronic obstructive pulmonary disease. The results of this report have been presented both at national and international scientific meetings, the respective manuscript has been submitted for publication.

C. Cerebral effects of COPD

1. Anxiety and depression in COPD

Anxiety and depression are common and treatable risk factors for re-hospitalisation and death in patients with COPD. The degree of lung function impairment does not sufficiently explain anxiety and depression. The BODE index allows a functional classification of COPD beyond FEV_1. Therefore we conducted a cross-sectional study in order (1) to test whether the BODE index is superior to the GOLD classification for prediction of anxiety and depression; and (2) to assess the influence of coping strategies on these psychological disorders in patients with COPD.

COPD was classified according to the GOLD stages based on $FEV_{1\%predicted}$ in 122 stable patients with COPD. An additional four stage classification was constructed based on the quartiles of the BODE index. The hospital anxiety and depression scale was used to assess anxiety and depression. The individual coping with dyspnoea was assessed by a questionnaire.

The overall prevalence of anxiety and depression was 49% and 52%, respectively. The prevalence of anxiety increased with increasing BODE stages but not with increasing GOLD stages. The prevalence of depression increased with both increasing GOLD and BODE stages. The BODE index was superior to $FEV_{1\%predicted}$ for prediction of the presence of anxiety and depression. The individual coping with symptoms was superior to both $FEV_{1\%predicted}$ and BODE index for prediction of anxiety and depression.

We conclude that the BODE index is superior to the GOLD classification for predicting anxiety and depression in COPD patients. A favourable coping strategy may prevent patients from anxiety and depression even in presence of severe dyspnoea.

The data were presented at the American Thoracic Society in 2008 in Toronto and at the Congress of the Austrian Society of Pneumology in September 2008 in Vienna. The paper was published in Respiratory Research (Respir Res. 2009 Jan 9;10(1):1 IF 3.8

D. Metabolism and COPD

1. Body Composition and Systemic Inflammation in COPD

Highly elevated C-reactive protein levels in obese patients with COPD: a fat chance?

COPD has been recognized as a multi component disease in which extra-pulmonary features like exercise intolerance and abnormal changes in body composition may adversely affect health status and survival, irrespective of the degree of airflow limitation. Low-grade systemic inflammation has also been shown to be a systemic feature in patients with clinically stable COPD compared to healthy peers. In particular, elevated C-reactive protein (CRP) levels have been related to adverse clinical outcomes in COPD, like a decreased functional exercise capacity, a reduced daily physical activity level, a decreased health status, an increased risk for cardiac injury, increased arterial stiffness, an increased risk for hospitalizations, and worse survival. Limited data are available about the determining factors of elevated CRP levels in patients with COPD. Currently, elevated CRP levels have been shown to be positively related to the degree of airflow limitation and to body mass index (BMI; body weight in kilograms divided by squared height in meters) in patients with COPD. Nevertheless, the positive relationship between highly elevated CRP levels and increased BMI in COPD has only been studied in limited sample sizes and has not been corrected for all confounding variables together, like the degree of airflow limitation and age. Therefore, the aim of the study was to determine whether and to what extent COPD patients with a low, high or obese BMI are more likely to have elevated CRP levels compared to normal-weight COPD patients and to explore the effects of clinically relevant covariates like age, sex, disease severity, long-term oxygen therapy (LTOT), co-morbidities and current pharmacological therapy, on the likelihood of having elevated CRP levels. This study was carried out by Marie-Kathrin Breyer at the Department of Respiratory Medicine, University Hospital Maastricht, Maastricht, the

Netherlands in 2007. The LBI-COPD funded MKB. In this cross-sectional study a total of 628 COPD patients were investigated. Results have shown, COPD patients with an obese BMI being more likely to have highly elevated CRP levels compared to normal weight COPD patients. Moreover, COPD patients with a low BMI are less likely to have highly elevated CRP levels compared to normal weight COPD patients. These findings are suggestive for an adipocyte-induced systemic inflammation in COPD. Results have been presented during the annual meeting of the European Respiratory Society (ERS) in Munich 2007 as an oral presentation. The full length article has been published (Clin Nutr. 2009 Dec; 28(6):642-7, IF: 3,203

2. Adipokines and Systemic Inflammation in COPD (Gender related differences of circulating leptin in COPD)

Gender related differences in the extra-pulmonary manifestations of COPD are barely investigated. Interestingly, a recent study showed that systemic effects of smoking differ between men and women. The authors demonstrated decreased plasma concentrations of the anti-inflammatory adipokine adiponectin in women. In addition, the same authors reported increased plasma levels of high sensitive C - reactive protein (hsCRP) in men. These differences may contribute to a different aetiology of COPD among men and women. Circulating leptin is another adipokine that is involved in limiting food intake, systemic inflammatory processes and its concentration has shown to be positively related to cardiovascular disease. Additionally, circulating leptin levels are gender related and higher in healthy women compared to healthy men, independent of body mass index (BMI; weight divided by squared height in meters). Furthermore, for the same amount of fat mass, women have higher circulating leptin levels compared to men. The role of circulating leptin and other adipokines in the involvement of the systemic inflammation in COPD is only studied scarcely and mainly in male COPD patients with a low BMI (< 21 kg/m²). Therefore, the present study

primarily aimed to unravel gender related differences in the adipokine metabolism in clinically stable subjects with COPD. Based on the higher production of leptin in women, we hypothesized that women have higher circulating leptin levels and leptin/fat mass ratio compared to men with COPD. Secondarily, additional plasma adipokines (adiponectin and resistin) as well as systemic inflammatory biomarkers, such as hsCRP, interleukin 6 (IL6), tumour necrosis factor α (TNFα), and its soluble receptors R55 and R75 (sTNFα-R55, R75) were analyzed in subjects with COPD as well as in healthy subjects. This study was carried out by Marie-Kathrin Breyer at the Department of Respiratory Medicine, University Hospital Maastricht, Maastricht, the Netherlands in 2007. The LBI-COPD funded MKB. Data were collected from 91 subjects with COPD, stratified in 4 groups by BMI and matched for age, gender and disease severity. Additionally, 35 healthy subjects were studied. The healthy subjects were age and BMI matched with the COPD patients. The results of the present study underscore a gender difference in the systemic pathology of COPD. In men, leptin, adiponectin and resistin appear to be physiologically regulated in clinically stable COPD, while in women, leptin metabolism is disturbed. Leptin production is increased in women with COPD when compared to healthy women and to men with COPD. Moreover, the present study revealed that subjects with COPD are characterized by low grade systemic inflammation reflected in increased levels of CRP and IL-6. Results have been presented during the annual meeting of the American Thoracic Society (ATS) in Toronto 2008 as a poster discussion as well as results will be presented during the annual meeting of the European Respiratory Society (ERS) in Vienna 2009 as an oral presentation. The full length article has been submitted for publication.

3. Metabolic Syndrome in Patients with COPD

Only recently, an increased body weight in COPD is gaining more interest after it has been shown to be highly prevalent in patients with COPD. An increased body weight seems to be

somewhat overlooked when investigating body composition in COPD. An increased waist circumference (as a marker of increased central abdominal obesity) is one of the components of the metabolic syndrome, which is a 'composite score' of various cardiovascular risk factors. Patients with the metabolic syndrome have been identified to be at increased risk of developing type 2 diabetes and cardiovascular disease as well as having an increased cardiovascular and all-cause mortality (even when initially without cardiovascular disease or diabetes) compared to healthy subjects without the metabolic syndrome. In COPD, both, type 2 diabetes and cardiovascular disease are of growing interest as both occur with an increased incidence. It therefore may be clinically relevant to assess the prevalence of COPD patients with the metabolic syndrome. We aimed to prospectively evaluate the prevalence of the metabolic syndrome and its individual components as defined by the International Diabetes Federation (IDF) in a large consecutive COPD sample. This study was carried out by Marie-Kathrin Breyer at the Department of Respiratory Medicine, University Hospital Maastricht, Maastricht, the Netherlands in 2008. The LBI-COPD funded MKB. Data were collected prospectively in 358 consecutive COPD patients. Results have shown, according to the IDF definition, 41% of the present COPD patients were identified having the metabolic syndrome. Results have been presented during the annual meeting of the American Thoracic Society (ATS) in Toronto 2008 as a poster discussion as well as during the annual meeting of the European Respiratory Society (ERS) in Berlin 2008 as an oral presentation. The full length article has been submitted for publication.

Programme Line 2: Therapeutic interventions in COPD

A. Pulmonary Rehabilitation

1. Nordic Walking Improves Daily Physical Activities in COPD - a Randomised Controlled Trial

Despite optimal pulmonary drug treatment, patients with chronic obstructive pulmonary disease (COPD) frequently experience dyspnoea and fatigue during everyday life, which, in turn may result in daily physical inactivity. Indeed, we and others have shown patients with stable COPD being significantly more inactive in their daily life compared to healthy subjects, spending most of the day sitting or lying down. Therefore, it seems clinically relevant to reduce daily symptoms and to maintain or even improve patients' daily physical activity level. We chose an exercise-based training modality, Nordic Walking as it has been shown to be a safe and effective exercise method for patients entering cardiac rehabilitation. Moreover, Nordic Walking is appropriate to reach training goals of heart frequency easily and can be done even with reduced performance status. Patients have autonomy of speed control and can maintain aerobic threshold for longer training periods. The primary aim of the study was to determine whether and to what extent Nordic Walking is able to impact on the daily physical activity pattern (measured by a tri-axial accelerometer) of COPD patients under short- and long-term observation. Secondarily, we aimed to explore the effects of Nordic Walking on the functional exercise capacity (using the 6 minute walking test), exercise-induced dyspnoea (using the modified BORG-Dyspnoea score) and mood status (using the Hospital Anxiety and Depression Scale) of COPD patients. All parameters were assessed at baseline, after 3, 6, and after 9 month. The LBI-COPD funded our post-doc- researcher carrying out the study (MarieKathrin Breyer). After recruitment of study participants, follow-up procedures and analyses of data, Nordic Walking has been proven to have a positive impact on COPD patients' daily physical activities and to be as effective in improving the patients' exercise

performance as other training methods that are commonly used in COPD rehabilitation. In addition, the exercise training had a striking effect that was translated into the patients' daily physical activity pattern, which verified a change in the patients' behaviour. Results have been presented during the annual meeting of the American Thoracic Society (ATS) in Toronto 2008 as a poster discussion as well as during the annual meeting of the European Respiratory Society (ERS) in Berlin 2008 as an oral presentation. The full length article has is under revision in "Respiratory Research".

2. COPD and Long-term Oxygen Therapy: Influence of a standardized training.

Long-term oxygen therapy (LTOT) is the treatment proven to improve survival in chronic obstructive pulmonary disease (COPD) patients with chronic respiratory failure. It also appears to reduce the number of hospitalizations, increase effort capacity, and improve health-related quality of life. Standard LTOT criteria are related to COPD patients who have PaO2 < 55 mmHg, are in a clinical stable situation, and are receiving optimal pharmacological treatment. The benefits of LTOT depend on correction of hypoxemia.

Since the introduction of oxygen in COPD as a therapeutic agent 70 years ago, much has been learned regarding the detrimental effects of hypoxemia and the beneficial impact of oxygen therapy. The large numbers of patients receiving supplemental oxygen as treatment and the high costs incurred in providing oxygen therapy necessitate the practitioner to know the indications for LTOT as well its effects on survival, pulmonary hemodynamics, sleep, and exercise capacity. The benefits of oxygen therapy in those with mild to moderate hypoxemia, although they may not include a reduction in mortality, may include improvements in mood, neurocognitive function, and quality of life. Further randomized controlled studies are needed to confirm or refute prior data in this patient group. It is recognized that the basis for LTOT prescription for all patients is founded on data that are over 25 years old and that only involve a very select cohort of patients. It is clear that further studies are required to assess the effects

of oxygen on patients with COPD. Recently a review about LTOT in COPD has shown that data about the adherence to this treatment are widely evaluated but investigations on influences of this treatment on patient's behaviour and knowledge about both, disease and therapy, are still missing. Moreover, contrary to other chronic diseases as Diabetes, data about a standardized professional education for the correct use of home oxygen therapy were never evaluated because standardized training is not available yet.

Therefore the aim of our study is to evaluate effects of a standardized training including practical and theoretical education performed by chest physicians and physiotherapists on COPD patient's behaviour, knowledge and compliance to this treatment. Study design is prospective, randomized, controlled, single centred and will start in 2010 and is not expected to reach final recruitment until summer 2012.

B. Effects of Ventilatory Support on COPD

1. Multicenter NIV Study

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.

2. Ventilatory support in COPD patients who remain hypercapnic after one episode of acute respiratory failure requiring mechanical ventilation (NIVEX trial)

The 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 clinical worsening or death. A secondary end-point is the change in the six-minute walking distance.

Withdrawal of non-invasive ventilation decreased the time to clinical worsening and decreased the six-minute walking distance. We conclude that following acute respiratory failure in COPD patients with sustained hypercapnia non-invasive ventilation should be considered.

The study has been successfully completed. The data have been presented at the European Respiratory Congress 2008 in Berlin as an oral presentation winning the „Noninvasive Ventilation Award“ of the ERS (€1.500). Additionally the data have been presented at the Congress of the Austrian Society of Pneumology in September 2008 in Vienna winning a poster award (€2.000). The paper is currently under revision in "Respiratory Medicine"

3. Classification of weaning from mechanical ventilation

Patients with COPD frequently require long episodes of weaning after intubation due to acute respiratory failure. Weaning from mechanical ventilation was categorized as simple, difficult, or prolonged by an international task force of the ATS/ERS/ESICM/SCCM/SRLF in 2007. This new classification has not been tested in clinical practice. The objective of our study was to determine the incidence and outcome of weaning according to the new categories.

We included medical and surgical patients who required mechanical ventilation in a prospective, multicenter, six month cohort study.

From an initial cohort of 510 patients, 257 intubated patients started weaning. Of these patients, the cumulative incidences of simple, difficult, and prolonged weaning were 152 (59%), 68 (26%), and 37 (14%), respectively. Hospital mortality was increased in patients with prolonged (32%) but not difficult (9%) weaning in comparison to those with simple weaning (13%), overall p=0.0205. In a multivariate logistic regression model, prolonged but not difficult weaning was associated with an increased risk of death. Ventilator-free days and ICU-free days were decreased in both difficult and prolonged weaning.

We concluded that the new weaning category ‘prolonged weaning’ is associated with increased mortality and morbidity in the ICU. The new category ’difficult to wean’ was associated with increased morbidity, but not mortality.

The data were presented at the American Thoracic Society in 2009 in San Diego and at the Congress of the Austrian Society of Pneumology in June 2009 in Vienna winning the first poster award (€4,000). The paper was published in the European Respiratory Journal .

(Eur Respir J 2010;35:88-94, IF 5.5; Topjournal)

4. Physiological effects of extracorporeal CO2 removal in hypercapnic COPD patients with acute respiratory failure – the COPDECAP study

Acute hypercapnic respiratory failure requiring mechanical ventilation is a life-threatening crisis for a patient with COPD. It is associated with prolonged weaning and substantial mortality. In stable COPD hypercapnia is the result of a compensatory mechanism aiming at unloading the ventilatory muscle pump. More specifically, the effective work of breathing is reduced due to rapid shallow breathing thus preventing ventilatory muscle fatigue. The cost of this breathing pattern is hypercapnia resulting from lower tidal volumes and increased death space ventilation.

In acute-on-chronic respiratory failure this compensational mechanism becomes insufficient due to the extra load imposed on the ventilator pump. Hypercapnia aggravates and overt respiratory acidosis develops imposing the need for non-invasive or invasive or mechanical ventilation.

Arterial-venous driven extracorporeal elimination of CO2 is an emerging alternative strategy for treating hypercapnia in respiratory failure. The feasibility and safety of this method has been shown in patients with acute respiratory distress syndrome (ARDS) and in patients awaiting lung transplantation. Recently, pump driven venous-venous circuits have become available, which may cause fewer local complications than the arterial-venous devices. Emerging data suggest that lung protective ventilation can be accomplished in ARDS using venous-venous driven extracorporeal elimination of CO2.

Consequently extracorporeal CO2 elimination is a candidate for treating hypercapnic respiratory failure in patients with COPD. On the one hand, it has been suggested as a supportive strategy during non-invasive ventilation in acute-on-chronic respiratory failure, potentially avoiding intubation. On the other hand, COPD patients might be weaned from mechanical ventilation more rapidly with the support of the extracorporeal CO2 elimination. Both scenarios implicate that the extracorporeal elimination of CO2 has a favorable effect on the respiratory function in COPD. However, so far the physiologic consequences of extracorporeal CO2 elimination in COPD patients with respiratory failure are unknown. More specifically two major questions should be answered:

(1) What is the effect of extracorporeal CO2 removal on the control of breathing? It is known that acute lowering paCO2 with concomitant increase in blood pH can cause a reduced respiratory drive with consecutive hypopnoea or apnoea.

(2) Does lowering paCO2 have favorable consequences for the ventilatory muscle pump? On the one hand, reducing hypercapnia does not *per se* change the mechanics of the respiratory system. On the other hand, a lower paCO2 may allow breathing with very low tidal volumes thus deflating the hyperinflated lungs and further unloading ventilatory muscle pump.

A positive physiologic effect of a therapeutic intervention is the scientific basis for trials studying clinical endpoints. Therefore we aim to study the consequences of extracorporeal CO_2 removal on the ventilatory muscle pump, on the pattern of breathing and on the control of breathing in COPD patients with acute hypercapnic respiratory failure.

We plan a randomized, prospective, unmasked, controlled clinical trial in 28 COPD patients with acute hypercapnic respiratory failure treated with non-invasive ventilation. Patients will be randomized in a 1:1 manner to an intervention group (=DECAP group) and a control group. Extracorporeal CO2 removal will be accomplished via a pump-driven veno-venous membrane lung and respiratory mechanics will be obtained via an esophageal balloon catheter

during 24 hours. Primary endpoints are the change in the $P_{O.1}$ due to extracorporeal CO2 removal and the change in the pressure time product due to extracorporeal CO2 removal.

The study is conducted in conjunction with the Department of Anesthesiology of the University of Torino, Italy. A study protocol is currently at the ethics committee. We plan to start enrolling patients in summer 2010.

C. Bronchoscopic lung volume reduction in patients with COPD

Primary aim of this research line was to investigate bronchoscopic lung volume reduction (BLVR) procedures in patients with severe emphysematous type of COPD. 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, the so-called “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. The investigators of this program line have been engaged in two major clinical multi-centre trials of this field, the “Endobronchial Valve for Emphysema PalliatioN Trial (VENT)” and the “EASE trial: 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)”. The results of the VENT trial have been presented at the European Respiratory Society Meeting in 2007. On the basis of these, the rate of success for lung volume reduction varied considerably. Subset analysis of these studies revealed that particularly, but not exclusively, patients with radiological signs of complete lobar fissure showed significant clinical improvements, whereas most patients with incomplete fissures did not experience these benefits. These findings suggest presence of collateral ventilation across

interlobar fissures, which may prevent desired lobar collapse associated with endobronchial one-way valve implantation. On the basis of these findings we have initiated a prospective multi-center trial designed to study the efficacy of one-way valve implantation in patients with heterogeneous emphysema using a new treatment algorithm based on information of emphysema heterogeneity, destruction score, and fissure analysis. This report recruited a total of 15 patients at 3 different centres (Vienna, Brussels, Antwerp). The study has been terminated in December 2008. The first set of data will be presented to the European Respiratory Society Meeting 2010 in Barcelona.

Lung volume reduction may also be achieved via instillation of synthetic polymeric sealant that produces volume reduction by collapsing hyperinflated lung. The investigators participate in another multi-center trial (AERISeal study) involving patients with persisting dyspnea due to severe emphysema. Initial experiences with this technique in patients with advanced homogeneous emphysema appear promising with patients demonstrating improvements in spirometry, gas trapping and exercise capacity. These results will be presented as an abstract to the European Respiratory Society Meeting 2010 in Barcelona. Longer term follow-up is currently pending.

Finally, in order to determine the impact of BLVR treatment on predicted mortality in patients with emphysema we calculated mortality prediction scores prior to and 6 month after polymeric BLVR treatment. We observed a significant reduction in both the BODE Index and the NETT mortality prediction index, which corresponds to clinically significant mean reductions in predicted 24 and 48 month mortality rates.

Programme Line 3: Pulmonary Epidemiology

1. The natural history of chronic airflow obstruction revisited:

An analysis of the Framingham Offspring cohort

Understanding normal lung development and ageing in health and disease, both in men and women, is essential to interpret any therapeutic intervention. Therefore this study aimed to describe lung function changes in healthy never smoking males and females, from adolescence to old age; and, to determine the effects of smoking and those derived from quitting. We investigated a prospective cohort study within of all participants of the Framingham Offspring cohort who had two or more valid spirometry measurements during follow-up (n=4,391; age range at baseline 13 to 71 yrs), with a median follow up time of 23 yrs. Result have shown that: (1) healthy never smoker females achieve full lung growth earlier than males, and their rate of decline with age was slightly but significantly lower; (2) smoking increases the rate of lung function decline, both in males and females; (3) there is a range of susceptibility to the effects of smoking. The presence of respiratory symptoms at baseline and/or a respiratory diagnosis during follow up appears to identify a group of susceptible smokers; and, (4) quitting smoking has a beneficial effect at any age, but it is more pronounced in earlier quitters.

This original manuscript was published in collaboration with the LBI for COPD by Robab Kohansal and Pablo Martinez-Camblor, Alvar Agusti, A. Sonia Buist, David M. Mannino and Joan B. Soriano during the European respiratory society (ERS) long term fellowship of Robab Kohansal in Mallorca/Spain 2007 and was published in the American Journal of Respiratory and Critical Care Medicine. (Am J Respir Crit Care Med. 2009 Jul 1;180(1):3-10; Topjournal)

2. Investigations/Publications in collaboration with other institutes/investigators

Investigating the natural history of lung function: facts, pitfalls and opportunities

Eleven years ago, a workshop from the National Heart, Lung and Blood Institute – National Institutes of Health (NHLBI-NIH) reviewed the already huge amount of lung function data in NHLBI sponsored cohorts to highlight the availability of these data and to publish recommendations for future data collection and analytic efforts. We aimed to update this work, including European evidence. Therefore, the objectives of this review are to *(1)* briefly summarize studies investigating the natural history of lung function decline and/or studies with serial pulmonary function testing holding the potential for further investigations on the natural history of COPD; *(2)* identify and discuss the main methodological limitations in studies carried out to date; and, *(3)* propose a number of characteristics that the "ideal" study on natural history of lung function decline should consider.

This systemic review was published in collaboration with the LBI for COPD by Robab Kohansal and Joan B. Soriano and Alvar Agusti during the European respiratory society long term fellowship of Robab Kohansal in Mallorca/Spain 2007 and was published in CHEST May 2009.

3. The Austrian LEAD Study (Lung**,** H**e**art**,** Br**a**in**,** Bo**d**y**) –**

A longitudinal study investigating health challenges in Pulmonology

While data for mortality and morbidity of COPD is missing in Austria, a recent cross-sectional study in the city of Salzburg, Austria showed that the overall prevalence of GOLD stage I or higher COPD was 26.1% (similar for women and men). Moreover this study revealed that the prevalence of GOLD stage II or higher COPD was 10.7% and 1% of the population met the criteria for GOLD stage III or IV. Although the study protocol showed limitations, e.g male and female were older than 40 years, this investigation emphasised the impact of this disease in Austria.

While the raw number of burden was investigated sufficient over time the Natural History of this disease is still under-evaluated in terms of investigating the development and aging of the lung in order to gather important information regarding the progression and prognosis of COPD and therefore to improve the assessment of ongoing strategies aimed at the early detection and treatment of COPD. The British Thoracic Society recommended in December 2006 seven priorities for respiratory research. Not surprisingly, the number one in the list was to study "… the natural history of early development of the respiratory tract and immune system and the techniques needed to understand normal air growth, development and decline in health and disease" . Epidemiology of the natural decline of lung function is indeed a hot topic in medical research. Greater knowledge of the early development of the respiratory tract is necessary, the normal growth and development of the airway and its decline with age, factors that influence the development, remission, relapse, progression and severity of the disease, the response to treatment, and on intermediate clinical events and potential biomarkers. This involves the development of non-invasive imaging and physiological techniques, the improvement of histological, biochemical, molecular and microbiological characterization of the pulmonary tissues, and the study of cohorts of subjects at different ages and stages of disease. The heterogeneity in the pathogenic processes, clinical expressions and responses to treatment can largely be explained in terms of the development of different phenotypes which reflect diverse interactions between environmental and genetic factors. Identification of these phenotypes and the study of their implications in the susceptibility, prevention, treatment and prognosis of COPD are very important areas of research in translational terms.

Epidemiological and longitudinal, multidisciplinary studies are necessary to help us to understand the variability in the prevalence of COPD between different areas as well as the importance of non-diagnosed COPD as a predictor of morbid-mortality and disability, evaluating the convenience of phenotyping the disease to make more correct epidemiological

measurements, investigating co-morbidities and both their impact in the severity of the disease and the convenience of extending the prevention to them, evaluating the impact of early detection.

Accepting the natural course of lung function and associated development of COPD caused by aging of the human body, other increasing or highly prevalent diseases in our society as the metabolic syndrome, dementia and asthma may be associated comorbidities linked with COPD.

Therefore the aim of our investigation is to investigate the natural course of COPD based on the natural decline in lung function and co morbid conditions in both health and disease. Study design will be prospective, longitudinal, observational, family clustered including Austrian population from adolescence to senescence. This investigation aims to provide information on lung function and influencing factors including comorbidities and chronic diseases in male and female. This epidemiologic project will start in 2011 and first round of recruitment and examinations are expected until 2013. We aim to re-invite study population every three years for follow up in order to gather longitudinal data.

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