The Annual Scientific Meeting
Israel Society of Pulmonology

June 30 - July 2, 2011
Venue: Hotel Pastoral, Kfar Blum

Scientific Organizing Committee:
Yochai Adir, Amnon P. Ariel, Zvi G. Fridlender, Israel E. Priel
WELCOME NOTE

Dear Participant / Guest,

On behalf of the Executive Committee of the Israel Society of Pulmonary Medicine and the Organizing Committee of the Meeting we are pleased to welcome you at the Annual Scientific Meeting of the Society at one of the most charming locations in Northern Israel – Kfar Blum, 2011.

The Scientific Committee has made a conscious effort to allow multiple presentations, although, not all submitted abstracts could be accepted.

This year, we decided to avoid parallel sessions in an effort to enable us all to become familiar with the current scientific activity in Pulmonary Medicine in Israel.

We deliberately chose a tight time schedule, thus avoiding unnecessary rejections. We hope that with due cooperation of presenters and audience this will allow fruitful discussion within the allocated time limits.

We are all looking forward to an exciting meeting, based on the abstracts accepted. The Agenda reflects original work done in various fields of pulmonology, both in basic science and at the bedside. This achievement is remarkable given the objective difficulties and the very heavy routine workload.

We wish you a pleasant and enriching experience.

Looking forward to seeing you in Kfar Blum!

With kind regards

The Scientific Organizing Committee

Yochai Adir  Amnon P. Ariel  Zvi G. Fridlender  Israel E. Priel
MD, FCCP     MD, MHA, FCCP     MD, MSc       MD, FCCP
Member       Member             Member       Chair
We’ve just celebrated **Shavuot**, one of the three major Jewish holidays. This holiday is about the Giving of the Torah (Matan Torah) on Mount Sinai. But it also has non-religious, social meaning. This holiday’s other names include the holiday of Harvest (Hag HaKatzir - the holiday of First Fruit - Hag HaBikurim)

At Shavuot the scroll of Ruth is read. Among other things the story speaks of mercy, of the way to treat those who are less fortunate and of the great reward in doing so. Mercy is celebrated in quiet deed.
The Seven Species: wheat, barley, dates, grapes, figs, pomegranates, olives.
### PROGRAM

**Thursday, June 30, 2011**

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<td>EVENING PROGRAM:</td>
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<td>DANNY SANDERSON &quot;FROM THEN TILL NOW&quot;</td>
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<td>A show of stand-up and rock &amp; roll in one smile!</td>
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<td>Accompanied by his rock band, performing his best all time hits including those from &quot;Kaveret&quot;</td>
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<td>High Dose INH Therapy in MDR-XDR TB: a Preliminary Study</td>
<td>Bendayan D, Litman K, Hendler A, Polansky V</td>
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<td>Complications of Influenza A/H1N1</td>
<td>Ayanon L, Munteanu D, Smoliakov A, Almog Y, Barski L</td>
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<td>The Impact of Fluoroquinolone Resistance of Gram Negative Bacteria in Respiratory Secretions on the Outcome of Lung Transplant (non CF) Recipients</td>
<td>Shteinberg M, Raviv Y, Bishara J, Stein N, Rosengarten D, Bakal I, Kramer MR</td>
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<td>Metallic Stent Placement for Airway Complications after Lung Transplantation – Long Term Follow up</td>
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<td>“Autoimmunity” Fights Fibrosis; FasL – Positive Immune Cells Dissipate Myofibroblasts with Low FLIP Levels</td>
<td>Wallach-Dayan S, Elkayam L, Golan-Gersh R, Arish N and Breuer R</td>
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<td>Airway Hyperresponsiveness and Remodeling in Asthma: Clues from the Mouse</td>
<td>Kohan M, Muro AF, Bader R, Berkman N</td>
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<td>10:15-10:25</td>
<td>Oncostatin M in BAL Correlated with the Severity of Sarcoidosis</td>
<td>Guber A, Jawad A, Salamon P, Mekori YA, Shtritt D</td>
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Friday, July 1, 2011

11:15 – 12:15 PULMONARY HYPERTENSION & VENOUS THROMBOEMBOLISM

Sharshevsky Y, Noyman Y, Shitrit D

11:25 – 11:35 Out of Proportion Pulmonary Hypertension and Heart Failure with Preserved Systolic Function
Adir Y, Wolff R, Amir O

11:35 – 11:45 The Role of Left Atrial Size in the Assessment of Pulmonary Hypertension
Maimon N, Zikrin G, Regev A, Novack V, Heimer D, Smoliakov A, Cafri C

11:45 – 11:55 The Clinical Characteristics and Outcomes of Patients with Clinically Unexpected Pulmonary Embolism Versus Patients with Clinically Suspected Pulmonary Embolism
Shteinberg M, Adir Y, Segal-Trabelsy M, Laor A, Bitterman H

11:55 – 12:15 Q & A

12:15 – 13:30 PHYSIOLOGY, EXERCISE, AIRFLOW LIMITATION & NONINVASIVE VENTILATION

Gaides M, Ben Dov I, Bogomazov S, Vagner R

12:25 – 12:35 What Limits Patients with Mild to Severe Cystic Fibrosis During Exercise?
Reuveny R

12:35 -12:45 Determinants of Elevated Health Care Utilization in COPD
Simon-Tuval T, Tarasiuk A, Scharf SM, Bernhard-Scharf BJ, Reuveni H, Maimon N

12:45– 12:55 Incidence of Hospitalization among Severe COPD Patients Treated with Home Non-Invasive Ventilation
Guetta O, Heimer D, Daniel S, Avnon L, Avriel A, Maimon N

12:55 – 13:05 Transcutaneous Capnography Measurement and BiPAP Titration
Fukas L, Fruchter O, Rosengarten D, Raviv Y, Abdel Rachman N, Russanov V, Madan S, Kramer MR

13:05 – 13:30 Q & A

13:30 LIGHT BUFFET LUNCH – EXHIBIT AREA
Registrants only

17:00 – 18:30 GUIDED SPORT WALK IN THE NATURE
Sponsored by GlaxoSmithKline

19:00 – 21:00 DINNER

21:00 EVENING HOTEL PROGRAM
DAVID & PATRICIA singing Israeli and Latin classics

Saturday, July 2, 2011

07:00 – 10:00 BREAKFAST

10:00 MORNING PROGRAM in the Serenade 2 Hall (2 floor, above reception desk):
"STAND-UP WITH SARA SHAMIR, actress and comedian talking about life full of humor"

13:00 – 14:30 LUNCH
SPONSORSHIP

AstraZeneca
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Novartis
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SLEEP RELATED BREATHING DISORDERS

PRINCE FLORIMOND FINDS THE SLEEPING BEAUTY

Painting by Gutenburg
Abnormal Sleep Predicts Quality of Life in Chronic Obstructive Pulmonary Disease

Nimrod Maimon MD¹, Steven M Scharf MD PhD², Tzahit Simon-Tuval PhD³, Barbara J Bernhard-Scharf PhD², Haim Reuveni MD⁴, Ariel Tarasiuk PhD⁴

¹ Department of Medicine, Pulmonary Institute, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva, Israel ² Department of Pulmonary and Critical Care, University of Maryland, Baltimore, USA ³ Guilford Glazer School of Business and Management, Ben-Gurion University, Beer-Sheva, Israel ⁴ Sleep laboratory, Soroka University Medical Center and Faculty of Health Sciences Ben-Gurion University Beer-Sheva, Israel

ABSTRACT

Background: Chronic obstructive pulmonary disease patients may suffer from poor sleep and health related quality of life. We hypothesized that disturbed sleep is correlated with quality of life.

Methods: In 180 patients with chronic obstructive pulmonary disease (FEV₁ 47.6±15.2% predicted, 77.8% male, age 65.9±11.7 years), we administered general (Health Utilities Index3, and disease specific (St Georges Respiratory) questionnaires and an index of disturbed sleep (Pittsburgh Sleep Quality Index).

Results: Overall scores indicated poor general (Health Utilities Index3: .52±.38), disease specific (St. Georges: 57.0±21.3) quality of life, and poor sleep quality (Pittsburgh 11.0±5.4). Sleep time correlated with the number of respiratory and anxiety symptoms reported at night. On multivariate regression, the Pittsburgh Sleep Quality Index was an independent predictor of both the Health Utilities Index3 and the St. Georges scores, accounting for 3% and 5% respectively of the scores. In spite of being younger and with less smoking, women had significantly worse sleep quality and disease specific quality of life: Pittsburgh (13.3 vs. 10.3, p=.0016, respectively), St. Georges (67.0 vs 54.2, p=.0008, respectively).

Conclusions: Most patients with chronic obstructive pulmonary disease suffer disturbed sleep. Sleep quality was correlated with general and disease specific quality of life. Women had lower sleep quality and quality of life scores than men. Attention should be paid to assessing and addressing specific sleep disturbances when evaluating these patients.
The Association Between Headache and Obstructive Sleep Apnea

Weitzman D¹, Ifergane G², Mushkalo A³, Abu-Madigm M³, Greenberg-Dotan S⁴, Simon-Tuval T³, Tarasiuk A⁴, Maimon N³

¹Department of Public Health, Faculty of Health Sciences, Ben-Gurion University Beer-Sheva, Israel. ²Department of Neurology, Soroka University Medical Center and Faculty of Health Sciences Ben-Gurion University Beer-Sheva, Israel. ³Department of Medicine, Pulmonology Institute, Soroka University Medical Center and Faculty of Health Sciences Ben-Gurion University Beer-Sheva, Israel. ⁴Sleep laboratory, Department of Medicine, Soroka University Medical Center and Faculty of Health Sciences Ben-Gurion University Beer-Sheva, Israel. ⁵Guilford Glazer School of Business and Management, Ben-Gurion University, Beer-Sheva, Israel.

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Conflict of interest – We are here to disclose that we have no conflict of interest related to the subject of this paper.

ABSTRACT

Background: In the general population, OSA is common and its prevalence is approximately 4% to 9%. Although there is a known clinical relationship between headaches and sleep disturbances, the connection between headaches and sleep apnea syndrome is still controversial. Some recent reports have suggested that OSA may specifically predispose to headache while at least one study has failed to find such a link. Obstructive apneas are accompanied by recurrent hypoxia, arousals from sleep and repetitive surges in heart rate and blood pressure. All of these events may predispose patients with OSA to headache. We sought to determine the incidence of headaches and the correlation to other clinical, demographic and polysomnographic parameters in patients who were referred to our tertiary sleep laboratory.

Methods: A prospective cohort study conducted on data from questionnaires completed by patients aged 18 and over, who were evaluated for suspected sleep disturbances. We compared reported headaches among patients diagnosed with sleep apnea to subjects without sleep apnea.

Results: Out of 692 polysomnographies, OSA was diagnosed in 568 patients (82.1%). 27.3% (N = 189) of patients with OSA reported headaches compared with 32.3% of subjects with normal sleep laboratory (p-value = 0.172). Women and Bedouin ethnicity were associated with headache with a RR of 3.33 and 6.64 respectively. In addition, the relative risk of headaches in patients with significant desaturation (reduction of saturation below 90% over 50% of sleep time) compared to the other subjects were 2.09 and 2.31 at all groups and in subjects with sleep apnea syndrome, respectively. Co-morbidities such as heart failure and strokes were correlated positively with reports of headaches with RR of 1.84 and 3.94 respectively.

Conclusions: This study did not show significant association between sleep apnea syndrome and headaches. However we found significant correlation between nocturnal desaturation and reported headaches.
A single cell growth from a lung epithelial carcinoma cells
Molecular Characterization of Tumor Associated Neutrophils from NSCLC and Mesothelioma tumors

Zvi G. Fridlender¹,², Sunil Singhal², Veena Kapoor², Inbal Mishalian¹, Jing Sun², Wenhwai Horng³, Gil Fridlender¹, Steven M. Albelda².

¹ - Hadassah-Hebrew University Medical Center, Jerusalem, Israel, 2 - University of Pennsylvania, Philadelphia, PA, 3 – The Wistar Institute, Philadelphia, PA

Rationale: We previously identified and preliminarily characterized two phenotypes of tumor-associated neutrophils (TAN) in murine models of non-small cell lung cancer (NSCLC) and mesothelioma, dependent on the presence or absence of active TGF-b (Cancer Cell, 2009). In the current study, we further define the characteristics of these TAN using a microarray approach comparing naïve bone-marrow neutrophils (NN) to N1 (“anti-tumor”) and N2 (“pro-tumor”) TAN from mice bearing mesothelioma and NSCLC tumors.

Methods: Balb/C mice bearing large mesothelioma flank tumors were treated with SM16, a TGF-β-R1 kinase inhibitor (N1-TAN) or left untreated (N2-TAN). Neutrophils were isolated from tumors using microbeads (CD11b) and flow cytometry (Ly6G). NN were isolated from naïve mice. mRNA from each subgroup was arrayed on Illumina chips. Enrichment pathways were identified using Genomica software. Selected results were validated by RT-PCR in these tumors and in tumors originating from an NSCLC line.

Results: Hierarchical clustering and PCA analysis showed that the three types of cells were clearly separated. Differences between N1- and N2-TAN were less prominent than between them and NN. Many more genes were up-regulated than down-regulated in TAN compared to NN, including pathways related to immune responses (e.g. Toll-like receptors), cytokine pathways (e.g. IL1b and TNF), and a striking up-regulation of chemokines, including chemoattractants for T-cells (e.g. CXCL10), neutrophils (e.g. CXCL1), B-cells (CXCL13) and macrophages (e.g. CCL2). For several of these we found increased secretion to supernatant from TAN compared to NN.

Several pathways related to responses to stimuli were up-regulated in N1 versus N2 TAN, including the IL3 signaling pathway, IRF-1, and some important anti-oxidants. Up-regulated immune genes included TNF, Jak3, MapK14 and NFkB-1a, and several antigen-processing and presentation genes. Macrophage chemoattractants (CCL2, CCL6 and CXCL10), as well as CCL8 and CCL3 were upregulated in N1-TAN, whereas the T-regulatory cell chemoattractant CCL17, was the only up-regulated in N2-TAN.

In order to validate these results in humans, we are currently isolating and characterizing neutrophils from human NSCLC tumors.

Conclusions: Our data demonstrate major differences between naïve neutrophils and N1/N2-TAN in mesothelioma and NSCLC tumors, primarily in immune responses and chemotaxis. N1-TAN appear to make more macrophage chemoattractants and antigen processing and presentation genes. N2-TAN may attract Treg's with CCL17. The observation that differences between N1/N2-TAN are less prominent than between them and BMN, suggests that the change between N2 and N1 phenotypes is intra-tumoral and not d/t differential recruitment.
Chemotherapy Delivered After Viral Vector-Mediated Immunogene Therapy Augments Antitumor Efficacy via Multiple Immune-mediated Mechanisms – From Bench to Bedside

ZG Fridlender¹,², DH Sterman², S Singhal², J Sun², V Kapoor² and SM Albelda²

1. Inst. Of Pulmonology, Hadassah – Hebrew University Medical Center, Jerusalem, Israel.
2. Thoracic Oncology Research Laboratory, 1016B ARC, University of Pennsylvania, 3615 Civic Center Blvd., Philadelphia, PA 19104-6160

Introduction: The most widely studied approach to cancer immunotherapy is tumor vaccines, often necessitating multiple administrations of antigens. Unfortunately, this need for repeated delivery often limits the use of a novel, effective tumor immunotherapy approach - immunogene therapy using viral vectors - because of the rapid induction of neutralizing antibodies directed against the viral vector. This problem was demonstrated in a Phase I trial of repeated intrapleural adenoviral-mediated interferon-beta gene transfer for mesothelioma and metastatic pleural effusions, which we recently completed.

We hypothesized, therefore, that we could maximize therapeutic benefit by utilizing viral immunogene therapy to “prime” an initial strong antitumor immune response, with subsequent “boosts” provided by sequential courses of chemotherapy.

Methods: Three adenoviral (Ad)-based immunogene therapy regimens were administered to animals with bulky syngeneic malignant mesothelioma and lung cancer tumors followed by three weekly intraperitoneal administrations of a drug regimen commonly used to treat these tumors (Cisplatin/Gemcitabine).

Results: Immunogene therapy followed by chemotherapy resulted in markedly increased antitumor efficacy associated with increased numbers of antigen-specific, activated CD8+ T-cells systemically and within the tumors. Possible mechanisms included: (i) decreases in immunosuppressive cells such as myeloid-derived suppressor cells (MDSC), T-regulatory cells (T-regs), and B-cells; (ii) stimulation of memory cells by intratumoral antigen release leading to efficient cross-priming; (iii) alteration of the tumor microenvironment with production of “danger signals” and immunostimulatory cytokines.

Based on these results, we are conducting a clinical trial using intrapleural adenoviral-mediated interferon-alpha gene transfer followed by first or second-line chemotherapy in patients with malignant pleural mesothelioma.

Conclusions: Chemotherapy delivered after viral immunogene therapy augments antitumor efficacy. This is achieved via multiple immune-mediated mechanisms.

The same approach could be applied to other trials of viral immunogene therapy.
Mapping Air Pollution by Monitoring Inflammation Particle Burden in Human Airways

Aya Lavi1,2, Oded Puchter, PhD3, Isaac Omer, PhD3, Elizabeth Fireman PhD2,4

1The Porter School of Environmental Studies, Tel Aviv University; 2Lung and Allergy Institute, Tel Aviv Medical Center; 3Geography and Human Environment Department, Tel Aviv University; 4Epidemiology and Preventive Medicine Department, School of Public Health, Tel Aviv University

Rationale: Environmental measurements are an excellent means only for evaluating regulatory compliance. The models used to extrapolate body burden from these measurements are complex. Unless all possible routes of exposure (i.e., inhalation, dermal absorption, etc.) are taken into account, exposure to a toxicant can easily be underestimated. To address this problem, measurements of the internal dose of a toxicant can be used alone or in combination with environmental data for enhanced exposure assessment. Based on our previous studies, we hypothesized that the quantitative analysis of particles recovered by induced sputum (IS) can serve as a biological monitoring method in the periodic evaluations of air pollution in a given location.

Objective: To screen the extent of air pollution in the Gush Dan area by biological monitoring of human exposure by determining inflammation and size of particles in IS samples.

Methods: Pulmonary function testing (PFT) and IS analyses were done by conventional methods. Included were 88 adults living in that area who were referred for evaluation of respiratory symptoms between the periods February-July 2007 and June-December, 2009. Environmental data were retrieved from the Ministry for Environmental Protection and Israel Electric Corporation stations and assessed by interpolation of inverse distance weight by the geographical information system (GIS) for cumulative concentration of PM2.5 (µg/m³). Biological data were acquired by measuring particle size distribution (0-3 μ) in IS samples by means of laser technologies (Donner Tech, Israel) and Kriging Interpolation by GIS.

Results: None of the tested biological and functional parameters correlated with environmental monitoring, but they correlated significantly with biological monitoring. Small particles in IS (0-2 μ and 0-5 μ) correlated with % neutrophils (p=0.05 and p=0.02, respectively), and FEV1, FVC, and FEV1/FVC parameters correlated with eosinophilic inflammation (p=0.02, p=0.05 and p=0.004, respectively).

Conclusions: The information retrieved from the environmental stations does not adequately reflect inflammatory and functional abnormalities of individuals in that area who have respiratory symptoms. Biological monitoring should be added to environmental monitoring for comprehensive information on regulatory compliance and health sequelae.
Induced Sputum Analyses in Beryllium-Exposed Dental Technicians Reflect Hygiene and Oxidative Stress

Moshe Stark¹,²,³, Yehuda Lerman²,³, Arik Kapel, Asher Pardo Yehuda Swartz, Lee Newman⁵, Lisa Maier⁴, Elizabeth Fireman¹,³

¹The Institute of Pulmonary Diseases, National Laboratory Service for ILD, Tel-Aviv Sourasky Medical Center, ²Occupational Health Department Clalit Medical Services, ³Department of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine, Tel Aviv University, ⁴Division of Environmental and Occupational Health Sciences National Jewish Medical and Research Center, ⁵Environmental Occupational Health Department, Colorado School of Public Health and Department of Medicine, University of Colorado, Aurora, CO

Rationale: Chronic beryllium disease and beryllium sensitization are caused by occupational exposure to beryllium. The incidence of the disease continues to increase despite environmental controls.

Objective: To assess whether size and shape of induced sputum particulate matter and oxidative stress parameters can biologically monitor beryllium-exposed workers.

Methods: This cross-sectional study included 83 dental technicians. Induced sputum and beryllium lymphocyte proliferation tests were done by conventional methods. Particle size distribution and shape image analysis were done by laser and video technologies. Shape analysis was by aspect ratio, convexity, circularity, average concavity, and gray level. Heme oxygenase-1 gene expression was evaluated in induced sputum samples by quantitative PCR.

Results: A cut-off of 92% of particles that were <5 µ in induced sputum samples was correlated to the presence of a risk for a positive beryllium lymphocyte proliferation test (odds ratio of 3.4 [0.9-13]). Particle opacity (gray level) in induced sputum was associated with beryllium exposure (odds ratio 0.95 [0.91-0.98]) and it was higher in non-exposed compared to exposed workers. Exposure to fumes vs dust and the use of hood/personal masks vs no protection yielded differences in opacity as well. HO1 gene expression was associated with opacity (r = 0.25 P = 0.04) with high values in fume- vs dust-exposed workers.

Conclusions: We describe novel biological markers for screening workers exposed to hazardous dust. The opaqueness of particles in induced sputum is sensitive to the hygienic condition in the workplace and affects the oxidative stress molecular pathway.
CHEST IMAGING

Keynote Lecture – DUAL ENERGY CT
Dual Energy CT – from anatomic to functional imaging

Naama Bogot, MD
Cardiothoracic radiologist
Department of Radiology
Shaaree Zedek Medical Center and
Department of Radiology
University of Michigan Health System
Ann Arbor, Michigan

Dual Energy Computed Tomography is a novel technological development. CT is scanning is performed in two energies simultaneously, creating spectral separation of the X-rays. As different tissues have different attenuation of the X-ray beam, the spectral differentiation allows to look beyond the density of tissues, into the chemical properties of the materials scanned.

Dual Energy CT has a special role in thoracic imaging. Iodine has different attenuation properties in low and high x-ray energies, enabling formation of colored coded iodine distribution maps of the lung, which demonstrate the blood pool. These maps add information to that obtained by standard CT and provide functional data on the pulmonary parenchymal blood flow, beyond the anatomic description. Iodine distribution maps have been shown to correlate with the lung perfusion imaging obtained in nuclear scintigraphy.

For instance, it allows differentiation between occluding and non occluding clots of pulmonary emboli, identify patterns of the iodine distribution suggesting pulmonary hypertension or structural changes related to airway diseases. These aspects of the technique are already in routine clinical use.

Dual Energy CT has also some experimental use. Looking at the wash in and wash out phase of inhaled xenon gas provides dynamic ventilation maps, which may provide functional information in obstructive lung diseases.

Dual energy images are sensitive to iodine content of tissues enabling measurement of the iodine tissue levels, beyond the customary density measurements. Vascularity of
tissues can therefore be determined based on the dual energy scanning. Active research is done to outline the use of these novel techniques to differentiate between areas of atelectasis, infection or inflammation and lung tumors.

The lecture will review several technical aspects (i.e. how dual energy CT is performed) and associated radiation level as well as common artifacts seen with the iodine maps will be discussed.
CHEST INFECTIONS, TUBERCULOSIS & PLEURAL INFLAMMATION
High dose Isoniazid adjuvant therapy in MDR-XDR-TB: a preliminary study

Bendayan D MD, Litman K MD, Hendler A MD, Polansky V MD.

Pulmonary and Tuberculosis Department, Shmuel Harofe Hospital, Beer Yaakov, Israel. Affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Introduction: MDR-XDR TB has emerged in Israel following the immigration waves from the FSU and Ethiopia. It is a serious life threatening condition, refractory to therapy with a progression rate that reminds the prognosis of the disease before the antibiotic discovery. Treatment includes the second line anti tuberculosis drug combined with surgical resection in case of regimen failure.

Despite the fact that MDR-XDR TB is by definition resistant to at least Isoniazid (INH) and Rifampicin, some evidence suggests that continued use of INH at higher dose may be of value. The hypothesis is that high dose INH overcomes the potential cross resistance with Ethionamide and that the MIC of INH is usually below the steady state plasma concentration of high dose INH, therefore eliminates strains with low level of resistance.

Case description: 6 MDR XDR TB patients hospitalized in the Pulmonary and Tuberculosis department of Shmuel Harofe Hospital were selected to receive high dose isoniazid in addition to the second line anti tuberculosis drugs. The dose used was 16-20 mg/kg/day (and no more than 900 mg /day). All of these patients were chronic cases, previously treated from months to years, refractory to the antituberculous therapy, highly contagious with evidence of disease progression. Only patient with normal base line hepatic function test (included negative viral hepatitis serology) and negative HIV serology test were proposed to receive high dose adjuvant INH therapy.

The patients were mostly men (83%), young with a median age of 33 (range from 26 to 42 years), originated from the FSU (84%) or from Ethiopia (16%). All the patients were heavy smoker and did not present any other co morbidity. Bilateral cavitory infiltrates were the most usual radiological findings. Drug susceptibility tests reported a high resistance pattern not only to the first line drugs, but also to the second line drugs.

High dose INH therapy was considered successful if the sputum smear and culture converted to negative during 6 months of adjuvant therapy.

Results: During a period of 6 months, we found that 50% of the patients succeeded to convert their sputum culture and to become not contagious. In 83% of the patients, we observed a bacteriological improvement as the sputum examination become negative for Acid Fast Bacilli, but the culture is still positive for MTB.

Two patients needed surgical resection (one pneumonectomy and one lobectomy) following disease progression, unfortunately, they are still contagious.

INH was well tolerated without any gastro intestinal, or neurological side effect. Following INH administration, the radiological findings improved in 50% of the patients.

Conclusion:

Our results are encouraging, and support the safe benefit of high dose INH adjuvant therapy, however, the number of patients is small and further larger studies are needed to confirm these results.
Complications of influenza A/ H1N1. Four months experience at the medical intensive care unit (MICU) at Soroka University Medical Center (SUMC)

Avnon L, Munteanu D, Smoliakov A, Almog Y, Barski L.

Abstract

Worldwide considerable differences have been reported on the severity and fatality from the 2009 influenza A/ H1N1.

Aim: To report on patients with real-time PCR confirmed H1N1 disease that we cared for at MICU during September to December 2009 with an emphasis on complications experienced.

Patients: During the four months period twenty patients had rt-PCR confirmed H1N1 disease which constituted 20% of all patients admitted during the period. Seven patients were male and 13 women. Thirteen patients (65%) were of Bedouin background, six (30%) were Jewish and one was a Sudanese refugee. Their mean (SD) age was 36 (14) (range: 19-67) years. Five of 13 women were pregnant. Only one patient had no underlying conditions. None had been vaccinated, but all received oseltamir as soon as H1N1 had been suspected even one patient with hospital acquired infection.

Results: We experienced the following complications:

Viral pneumonia in 14 patients (67%) with refractory hypoxemia and ARDS; they underwent prolonged mechanical ventilation (MV) with nitric oxide (NO), prone position and muscle-relaxation. ECMO was unavailable. Three patients experienced bilateral barotraumas.

Concomitant bacterial infections on admission in five patients: UTI in three, bacteremia in two (Strep pneum, E.coli), staph aureus farunculosis of skin. Further more one patient suffered severe oral herpes simplex and was prescribed acyclovir.

Pregnancy related H1N1 influenza: in five of 13 women. There were three 2nd trimester pregnancy losses (at 21, 24 and 28 weeks) and two emergency cesarean sections both at 36 weeks of pregnancy, both babies were healthy and survived. Two of the five pregnant women died.

Thrombotic events were identified in five patients among the 14 patients with ARDS and MV. In four of the five patients the thrombotic event occurred in spite of prophylactic s/c unfractionated heparin. We saw extensive CVA in 19 years old woman who was pregnant on admission but aborted a few hours after admission, she survived; acute myocardial infarction in 28 years old pregnant woman that died without aborting at 24 weeks of pregnancy. Three patients had DVT, two in subclavian veins and one in femoral, all three were unrelated to central lines.

Mortality in MICU three patients died from intractable hypoxemic respiratory failure, two pregnant women on day 36 and 13 and one 51 years old woman with overweight (BMI: 29) on day 39. Late mortality after discharge from MICU occurred in three patients 22, 20 and 112 days after discharge: a 35 years old woman with immune liver cirrhosis, 40 year old man seven years after bone marrow transplantation from hospital acquired infection and a 49 years old man who was admitted 8 weeks after heart transplantation.

Conclusions: Our experience with influenza A/ H1N1 revealed a condition with very severe pneumonia (14/20), intractable hypoxemia, ARDS and considerable mortality (3/14) in a young population. Late mortality was related to back ground conditions and hospital acquired infection. The number of concomitant infections justifies use of broad-spectrum antibiotics in addition to oseltamivir. As reported pregnant women constitute a particular risk group with mortality. The propensity for thrombotic events is peculiar and important to consider.
The impact of fluoroquinolone resistance of Gram - negative bacteria in respiratory secretions on the outcome of lung transplant (non- Cystic Fibrosis) recipients

Michal Shteinberg ¹, Yael Raviv², Jihad Bishara³, Nili Stein⁴, Dror Rosengarten², Ilana Bakal ², Mordechai R Kramer ²

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Running Title: Quino lone resistance and lung transplantation outcome

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Abstract

Rationale: Bacterial airway colonization is frequent among lung transplant recipients. These patients are often treated with antibiotics, which may lead to selection of resistant bacteria. The purpose of this study was to assess whether antibiotic treatment causes acquisition of quinolone- resistant gram- negative bacteria (QR-GNB), and the effect of such colonization on mortality and on lung rejection.

Methods: We have retrospectively examined data from non- CF, non- Bronchiectases lung transplant recipients for antibiotic treatment, GNB in respiratory secretions, BOS and mortality.

Results: Of 126 patients included, 86 patients had QR-GNB, 22 had quinolone-sensitive bacteria (QS- GNB), and 17 had no growth. Median antibiotic exposure, defined as the fraction of days with antibiotic treatment, was 2.8% in patients without growth, 11.1% in patients with QS-GNB (p= 0.012), and 26% in patients with QR-GNB (p<0.0001). Age adjusted mortality hazard ratio was 9.2 (95% CI 1.272-78.9) for patients with QR-GNB compared with QS-GNB. Age adjusted hazard ratios for BOS was 3.7 (95% CI 1.33-10.3) for QR-GNB compared with QS-GNB.

Discussion: We found a positive correlation between antibiotic treatment and emergence of quinolone resistant GNB. Airway colonization with Quinolone resistant GNB was significantly associated with mortality and with BOS.

Conclusions: Further research is needed to determine whether a change in antibiotic subscription policy is required.
The use of C-reactive protein for the differential diagnosis of pleural effusion

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Key words: C-reactive protein, pleural effusion, lung transplantation

ABSTRACT

Background: Pleural effusion can occur as a complication of various diseases. Conventional methods are not always capable of establishing the cause of pleural effusion and alternative tests are need for accurate diagnosis. A variety of biological markers have been proposed to facilitate differential diagnosis among causes of pleural effusion, including pleural fluid concentration of adenosine deaminase, interferon–gamma, a variety of tumor markers and cytokines. However, the use of these measurements in clinical practice remains controversial. CRP is an acute-phase protein widely used as a marker of inflammation. Several studies have found that CRP in pleural fluid shows high sensitivity and specificity in discrimination malignant and inflammatory disorders.

The purpose of the study was to assess whether C-reactive protein is a sensitive marker for discrimination between different cause of pleural effusion in immunocompetent and lung transplantation recipient patient.

63 patients (35 males and 28 females) were enrolled in the study. According to preset diagnostic criteria, 25 patient’s effusions were classified as transudates (secondary to heart or liver disease), 24 - exudative pleural effusion caused by neoplastic disease, 11 patients were lung transplantation recipients with new pleural effusion of unknown reason and 3 patients were with parapneumonic effusion.

Pleural fluid samples were used to measure classical parameters (pH, protein, glucose and LDH) and the C-reactive protein. A comparison of serum and pleural effusion C-reactive protein level in this subgroups of patients was made.

Results: Pleural C-reactive protein level was significantly lower in the transudative group (0.57 mg/dl) than in neoplastic disease (2.83mg/dl) , lung transplantation group (1.04 mg/dl) and parapneumonic effusions (6.33 mg/dl) and P< 0.001, p=0.17, p=0.30, respectively. In lung transplantation recipient patients C-reactive protein level was significantly lower than in neoplastic disease effusion (p<0.05). We had found a correlation between the pleural and serum C-reactive protein.

Conclusion: The pleural CRP level provides useful information for the study of pleural exudates. It can be considered as diagnostic tool to differentiate pleural effusion in lung transplantation patients.
BRONCHOSCOPY & LUNG TRANSPLANTATION
Metallic stent placement for airway complications after lung transplantation – Long Term Follow Up

Nader Abdel Rahman, Oren Fruchter, Yael Raviv, Dror Rosengarten; Victoria Rusanov, Mordechai R Kramer

Pulmonary Institute Rabin Medical Center Beilinson Campus Petach Tikva

**Background:** Lung transplantation (LTx) is an effective treatment option for selected patients with a variety of end-stage lung diseases. Although LTx can significantly improve the quality of life and prolong survival, airway complications in particular at the anastomotic area may result in significant morbidity and limit long-term survival and require stent placement. The purpose of the current study is to analyze data collected at our center regarding the recognition and early treatment of airway complications with self expanding metallic stent (SEMS), and to investigate the influence of SEMS insertion on changes of the spirometric values before and after the procedure (FVC, FEV1), and on long term survival.

**Methods:** We retrospectively analyzed the medical records of all patients who underwent (LTx) in Rabin Medical Centre between August 2002 and December 2010. Patients with significant stenosis at the anastomotic area underwent insertions of SEMS with follow up bronchoscopy every three months.

**Results:** During the observation period, 302 lung transplants were performed. A total of 36 patients (11.9%) 20 males and 16 females had developed post LTx airway complication in a form of Stenosis and underwent SEMS placement. The stenosis developed between the day 14 of (LTx) and day 212.

8 patients (22%) underwent Bilateral (LTx), 4 of them had developed stenosis and underwent insertion of SEMS in both lungs, and 1 in one site only. Ten of the patients needed insertion of second SEMS at the same site, 2 patients needed a third stent to achieve desirable airway patency.

During the follow up period 16 patients (44%) died. Causes of death were infection and chronic graft rejection. One, three, and five years survival in patients that required SEMS were 80%, 75% and 61%, respectively. The corresponding survival rates in patients without stents were 81%, 76% and 65%, (P< 0.05).

**Conclusions:** SEMS are safe and effective tool in the management of airway complications in selected patients post-LTx with an immediate improvement in symptoms and flows in the majority of cases. However, the long term mortality is significantly higher in these patients compared with other LTx patients.
Propofol safety in bronchoscopy: Prospective randomized trial using Trancutaneous PCO2 monitoring

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The Pulmonary Division. Rabin Medical Center, Petach Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT

Background: Midazolam is commonly used for sedation during flexible bronchoscopy because of its wide therapeutic window. Recently, sedation with propofol has become popular, although it concern has been raised regarding its potential to induce respiratory depression. The aim of this study was to evaluate the safety of sedation under midazolam+alfentanil compared to propofol using continous trancutaneous carbon dioxide tension monitoring.

Methods: The study group included 115 patients undergoing bronchoscopy, prospectively randomized to receive sedation with either midazolam+alfentanil (n=59) or propofol (n=56).

Results: Intra-procedural carbon dioxide tension values were higher in the midazolam+alfentanil than the propofol group (maximum, 53.72 vs 49.49 mmHg; mean, 46.78 vs 43.78 mmHg), but the differences did not reach statistical significance (p= 0.149 and 0.193 respectively). Carbon dioxide tension values were higher in the midazolam+alfentanil than the propofol group at 5 and 10 minutes following procedure (51.7 vs 49.3 p= 0.026 and 50.8 vs 42.7 p<0.01 respectively), and more patients in the midazolam+alfentanil group needed oxygen supplementation or airway support.

Conclusions: Midazolam + alfentanil and propofol are equally safe for sedation during bronchoscopy. Sedation with propofol, using small boluses at short intervals, does not cause excessive respiratory drive depression.
Is routine chest radiography after transbronchial biopsy necessary?  
A Prospective Study of 109 Patients

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Joseph L MB ChB, Tennenhaus E RN, Izbicki G MD.

The Institute of Pulmonology, Shaare Zedek Medical Center, Jerusalem

**Rational:** Pneumothorax occurs in 1-6% of cases undergoing flexible bronchoscopy (FB) with transbronchial biopsy (TBB). Routine chest radiography (CXR) is the standard of care after TBB. Previous retrospective study suggested that in asymptomatic patients, routine CXR is not necessary (Chest 2006;129;1561-1564). The objective of this study was to determine prospectively if routine CXR after bronchoscopy with TBB is necessary.

**Methods:** The study group included patients which underwent FB with TBB and agreed not to have a routine CXR after the procedure. Additionally, clinical symptoms and information about the bronchoscopy were recorded in all patients. All patients were asked about symptoms suggestive of pneumothorax. If pneumothorax was suspected the patient underwent CXR. The patients were followed (phone conversation) after 24-48 hours to detect any signs of Pneumothorax or other complications.

**Results:** Until now one hundred and nine patients agreed to participate in the study. Forty six women and sixty three males. Mean age 60.7±17.8. We clinically suspected pneumothorax in ten patients and sent them for a CXR. Pneumothorax was confirmed radiologically in 3 patients (2.8%). The clinical follow up after 24-48 hours did not reveal other cases of Pneumothorax.

**Discussion:** Ninety percent of the patients had no CXR after bronchoscopy. The fact that CXR was not done did not change the outcome of the patients. In asymptomatic patients, significant pneumothorax is probably very rare so routine CXR is not necessary in this category of patients. Our findings might prevent unnecessary radiography in hundreds of thousands of patients every year. It might save time, money and unnecessary radiation.

**Conclusions:** We conclude that routine CXR after bronchoscopy with TBB is not needed in asymptomatic patients.
AIRWAY and PARENCHYMAL INFLAMMATION, FIBROSIS & SARCOIDOSIS
Airway Hyperresponsiveness and Remodeling in Asthma: Clues from the Mouse

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Background: Asthma is characterized by airway inflammation, remodeling and hyperresponsiveness (AHR). While present therapy for reducing inflammation is effective, there is no good treatment for remodeling or to reduce AHR. "Extra-domain A-fibronectin" (EDA-FN), an alternatively-spliced form of the extra-cellular matrix protein FN, plays a critical role in myofibroblast differentiation and tissue fibrosis.

Aim: To determine the effects of chronic allergen challenge on different parameters of airway remodeling, inflammation and airway hyperresponsiveness in EDA knockout (-/-) mice.

Methods: EDA -/- and wild type mice were sensitized and exposed to inhaled ovalbumin (OVA) or saline for 5 weeks and sacrificed 24 hours after the last inhalation. Airway hyperresponsiveness was determined using a Flexivent system to measure airway resistance in-vivo in response to methacholine. Peribronchial fibrosis (Trichrome staining and Sircoll assay), smooth muscle area (IHC), mucus-producing cell number (PAS staining) and bronchoalveolar cell counts were measured.

Results: OVA-treated WT mice have increased AHR and this is attenuated in EDA -/- mice. EDA -/- mice show selective attenuation of airway fibrosis together with impaired fibroblast activation and differentiation but with no change in airway smooth muscle area or in airway inflammation.

Conclusions: Fibroblast activation and airway fibrosis are necessary for the development of AHR. EDA-containing FN is essential for the development of OVA-induced airway fibrosis and AHR. Better understanding of remodeling will pave the way for development of new therapies for this unmet need in asthma.
“Autoimmunity” Fights Fibrosis; FasL-positive Immune Cells Dissipate Myofibroblasts with Low FLIP levels

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Hadassah – Hebrew University Medical Center, Jerusalem, Israel

Rationale: Immune cells in general, and those expressing the ligand of the Fas-death receptor (FasL) in particular, induce apoptosis in ‘unwanted’ cells bearing Fas-death receptor, as a mechanism of immune-surveillance. We have previously showed that fibrotic-lung myofibroblasts acquire an "immune-privilege-like" phenotype, using FasL to kill T-cells committed to kill them, thus allowing their accumulation and fibrosis (Wallach-Dayan et al., PNAS 2007). Methods- Pulmonary myofibroblasts and tissue sections were isolated from lungs of bleomycin treated mice (0.06 mU), at phases of evolution and resolution of fibrosis. Staining of Annexin v- marker of apoptosis, and cell counts, were assessed in myofibroblasts following coculture with gld FasL-deficient T cells or with wild-type T cells, with or without the addition of anti-FasL mAb. GFP+ Myofibroblasts cell survival/accumulation in the lungs was estimated in vivo using flow cytometry and histochemistry. This was performed following their intratracheal transplantation into allogeneic BALB/c vs. SCID mice and into syngeneic gld mice vs. gld C57BL/6 mice reconstituted with wild-type immune cells. Flice-Like-Inhibitory-Protein (FLIP) was determined by qPCR and Western blot and its role by transfection of myofibroblasts with FLIP cDNA expression vector.

Results: We show here, for the first time that resolution of lung fibrosis involves dissipation of myofibroblasts which, in allogeneic BALB/c but not SCID mice, lose their ability to escape immune-surveillance. In vitro studies reveal that apoptosis of fibroblasts from lungs resolving fibrosis can be induced by, wild-type (FasL-positive) CD4 T-cells, but neither by corresponding gld (FasL-deficient) cells, nor by wild-type CD4-T cells treated with anti-FasL mAb. Further, lung fibrosis is resolved in gld mice reconstituted with FasL-positive immune cells. During resolution, myofibroblasts downregulate FLIP levels which we show to be critical to regain their susceptibility to Fas/immune cell-induced apoptosis.

Discussion & Conclusion: This implies that the immune-system is empowered to execute immune-surveillance to fight fibrosis by diminution of FLIP and the "immune privilege-like" phenotype of fibrotic-lung myofibroblasts. Remarkably, in this context "autoimmunity" reduces the pathological effect rather than the opposite.
Everolimus - a new therapy for patients with progressive Lymphangioleiomyomatosis (LAM) our early experience in 5 patients

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Abstract

**Background:** Lymphangioleiomyomatosis (LAM) is a rare, cystic, lung disease. LAM affects women almost exclusively, occurs sporadically or with association to tuberous sclerosis complex (TSC). LAM and TSC are caused by mutations in either of the tuberous sclerosis genes, which control cell growth, survival, and motility through the mammalian target of Rapamycin (mTOR) signaling pathway. Sirolimus and Everolimus are both mTOR inhibitors. The safety profile of Everolimus is different from Sirolimus. Recently several studies have been published suggesting that Sirolimus might be considered as a therapeutic option in rapidly declining LAM. Simultaneously there is a study that is currently recruiting participants to determine effectiveness of Everolimus in patients with LAM.

**Patients and Methods:** Everolimus (mean level 5 ng/ml) was administered to 5 female patients (age 24-62) with progressive LAM. Serial pulmonary function tests, drug level in serum, visits at the clinic and periodic radiographic exams were performed.

**Results:** One patient had lung transplantation 7 years ago, and there was a recurrence of LAM in the donor allograft (chylous pleural effusion and cyst), an impressive improvement radiologically and clinically after initiation of treatment with Everolimus. 3 more patient had an improvement in lung function or clinically. One patient had rise in proteinuria which begun before treatment. The connection to treatment is in doubt.

**Conclusions:** Our data suggest that Everolimus might be an option for treatment in patients with progressive LAM in order to improve or at least stabilize their condition, in some cases as a bridge to transplantation.
**Oncostatin M in Bronchoalveolar Lavage Correlated with the Severity of Sarcoidosis**

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**Rationale:** Oncostatin M (OSM) is a multifunctional cytokine that belongs to the IL-6 subfamily and produced mainly by activated T cells, neutrophils, monocytes, and macrophages. Recent studies have shown that OSM might have a role in T cell–mediated inflammatory processes in which mast cells have also been found to be involved, including pulmonary fibrosis. We thus hypothesized that cell-to-cell contact with activated T cells might result in OSM release from mast cells. We therefore examine whether OSM cytokine is expressed by mast cells harvested in BAL correlate the severity of sarcoidosis.

**Patients and Methods:** Twelve patients with sarcoidosis who presented at the Pulmonary Department between November 2008 and May 2010 were eligible for the study. All patients underwent bronchoscopy for diagnosis with Transbronchial biopsies TBB and BAL. Serum was taken for ACE.

**Immunocytochemistry:** Paraffin-embedded sections of lung biopsies from patients with sarcoid granuloma were deparaffinized in xylene, dehydrated in ethanol, rinsed with PBS, immersed in EDTA and heated in a microwave oven. Samples were covered with blocker serum, and incubated with the primary antibody rabbit anti-human c-kit, CD117 for overnight at 4°C. Then, the slides were rinsed and incubated with biotinylated antibody, washed and covered with alkaline phosphatase streptavidin (Zymed), and developed with BCIP/NBT–chromogen (Chemicon). Slides were examined using a 40X objective under a BX41 microscope; images were taken using a DP70 digital camera and the image acquisition software DP Controller.

**Results:** Table 1 summarized the characteristics of the study population.

<table>
<thead>
<tr>
<th>Parameters</th>
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</tr>
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<tbody>
<tr>
<td>Age, years</td>
<td>45±13</td>
</tr>
<tr>
<td>Angiotensin converting enzyme</td>
<td>62±22</td>
</tr>
<tr>
<td>FEV1, liter</td>
<td>2.7±0.94</td>
</tr>
<tr>
<td>FEV1, %</td>
<td>87±25</td>
</tr>
<tr>
<td>FVC, liter</td>
<td>3.48±1.0</td>
</tr>
<tr>
<td>DLCO, %</td>
<td>73±11</td>
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**Correlations between lung function parameters and OSM cytokine findings:** Correlations were noted between FEV and FEV% with the OSM cytokine findings. FEV1 was correlated with the activated total left, average right and left active mast cell. FVC was correlated with the cell counts. FEV1/FVC was correlated both with activated right and left cell and % of activated to total cell (p=0.05, r=0.58; p=0.028, r=0.63, respectively).

**Conclusions:** OSM correlated with the severity of sarcoidosis. OSM have a role in T cell–mediated inflammatory processes in which mast cells have also been found to be involved, including pulmonary fibrosis.
PULMONARY HYPERTENSION and VENOUS THROMBOEMBOLISM

Dr Ernst von Romberg

Recognized pulmonary hypertension as a distinct entity (1891)
Über Sklerose der Lungenarterie
Sarcoidosis-associated pulmonary hypertension in Patients with Near-normal Lung Function Tests: Radiographic and Functional features

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Introduction: Pulmonary hypertension (PH) is a predictor of poor outcome in sarcoidosis. Early diagnosis of this complication may improve outcome. Previous studies found that DLCO <60% and oxygen desaturation below 90% have a high likelihood of PH. Little is known about the epidemiology of PH among patients with sarcoidosis and near normal lung function tests.

Patients and Methods: A retrospective analysis of 61 patients with sarcoidosis and near normal lung function tests (FVC > 70%, FEV1 >70% and DLCO >60%) who underwent high resolution computed tomography (HRCT) scan, 6 min walk test (6MWT) and echocardiogram was conducted. Demographic, pulmonary function and HRCT scan findings were analyzed and compared between patients with and without PH.

Results: Eighteen patients (29%) were found to have PH. 3(16.6%) had mild PH, 10 (55.5%) moderate PH and 5 (27%) severe PH. Patients with PH were more likely to have high ACE (p=0.038), lower 6MWD (p=0.009) and low saturation at exercise (p=0.0001) compared to those without PH. Comparison of HRCT pattern between patients with and without PH showed significant high frequencies of lymphadenopathy, ground glass appearance and fibrosis on HRCT (p=0.04, p=0.011 and p=0.0001, respectively).

Conclusion: PH is common in sarcoidosis patients with near normal lung function tests. Physiological and radiographical characteristics appeared to differentiate patients with PH from those without PH. Physicians should be aware to PH also in this subpopulation of sarcoidosis.
Out of proportion pulmonary hypertension and heart failure with preserved systolic function

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Rationale: A subset of patients with heart failure with preserved systolic function (HFPEF) will have a marked increase in the pulmonary pressures. To assess the hemodynamic characteristics of this subgroup of patients and the relation to metabolic syndrome, we retrospectively reviewed the charts of patients with HFPEF and out of proportion PH (HFPEF-PH), and compare their clinical and hemodynamic data to 20 patients with iPAH matched by age.

Methods: Out of proportion PH defined by right heart catheterization (RHC) as TPG > 12 mmHg. Clinical, echocardiographic and hemodynamic were collected and analyzed.

Results: Twenty consecutive patients with HFPEF and out of proportion PH and 20 patients with iPAH were included in the study. Their average age was similar, 71.0 ± 6.6 y and 70.3 ± 6.8 y respectively. Most of the HFPEF-PH patients were post menopausal females (16 out of 20, as opposed to only 6 out of 20 in the iPAH patients. HFPEF-PH patients were obese with higher BMI compare to iPAH patients (31.0 ± 6.8 vs 28.2 ± 3.2), had at least two features of the metabolic syndrome (hypertension, diabetes, hyperlipidemia) and atrial fibrillation. On RHC the TPG was significantly higher in the iPAH patients as well as the difference between the diastolic pulmonary artery pressure and the PCWP (40.5 ± 8.8 and 22.1 ± 7.8 vs 28.7 ± 5.8 and 6.2 ± 8.9, respectively.

Discussion: It seems that in the elderly patient with severe PH, the clinical phenotype of female gender, with one or more features of the metabolic syndrome and, chronic atrial fibrillation suggest the diagnosis of HFPEF - PH. We suggest that the current definition of out of proportion PH might be misleading since the increased in TPG is mainly due to the elevated systolic PAP and the difference between diastolic PAP and the PCWP is low, suggesting that the increased in TPG is not due to pulmonary vascular remodeling and increased PVR but depend on increased pulmonary vascular stiffness. Therefore the current definition should be updated and include increased difference between the diastolic PAP and PCWP.
The role of left atrial size in the assessment of pulmonary hypertension

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Keywords: Pulmonary Hypertension, Chronic Lung Disease, Congestive Heart Failure, Left atrial size, Right Heart Catheterization, Echocardiogram.

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Conflict of interest – We are here to disclose that we have no conflict of interest related to the subject of this abstract.

ABSTRACT

Background: The distinction between primary pulmonary hypertension and pulmonary hypertension that is secondary to left heart disease is a key point for therapeutic decision-making. The current gold standard is right heart catheterization (RHC) and capillary wedge pressure (CWP) measurement. Many patients, however, are unable to undergo such invasive procedure and non-invasive alternatives are needed as the therapy for these two conditions is entirely different. We suggest that increased left atrial size may be used as an indicator for increased CWP.

Goals: To determine whether there is a correlation between an enlarged left atrium, as measured by echocardiogram, and CWP ≥15mmHg, assessed by RHC.

Methods: Retrospective cohort study was performed at the Soroka University Medical Center. All patients who underwent RHC during a 13-year period between 1997 to 2009 were included. Patients were categorized as Group I (CWP≥15mmHg) and Group II (CWP<15mmHg) and then compared to left atrial size measurement per echocardiogram.

Results: 413 RHC were carried out during the period of interest and 395 were included. The mean PCWP was 12 ± 6 mmHg in Group I and 21 ± 7 mmHg in Group II (P = 0.001). The estimated LA size was 19.4 ± 4.9 cm2 in Group I and 39.9 ± 7.6 cm2 in Group II (P = 0.001). Cutoff LA size of above 55mm predicted high CWP. Significant correlations were found between uncorrected PCWP and LA size (R = 0.45, P = 0.005), corrected PCWP and LA size (R = 0.47, P = 0.003).

Conclusion: The presence of LA size ≥ 55mm on echocardiogram, ruled out the possibility of high CWP. Additionally, enlarged LA size was associated with an elevated PCWP. For patients undergoing PH evaluation, increased LA size could suggest left heart dysfunction as a possible cause of PH.
The Clinical Characteristics and Outcomes of Patients with Clinically Unexpected Pulmonary Embolism versus Patients with Clinically Suspected Pulmonary Embolism

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\textbf{Rationale:} The routine use of multidetector computed tomography scanners has led to an increased detection of unexpected pulmonary embolism (PE). The clinical relevance of these unexpected findings is unknown.

The purpose of this work was to compare the clinical characteristics and prognosis of patients with unexpected PE to patients with suspected PE.

\textbf{Methods:} We retrospectively reviewed the charts of patients diagnosed with PE at Carmel Medical Center between the years 2003-2007. Clinically unexpected PE was defined as PE found on CT scans performed for indications other than PE diagnosis. We have compared a group of patients with unexpected PE to those in whom PE was clinically suspected for differences in age, co-morbidities, thromboembolic risk factors, presenting complaints, physical examination, ECG, imaging and echocardiographic findings. We assessed the long term outcomes by using electronic patient records from "Sherutei Briut Clalit".

\textbf{Results:} 500 patients with a diagnosis of PE were included in our study. 408 had clinically suspected PE and 92 had unexpected PE. No difference was found between the two groups regarding age and sex distribution. Malignancy was more prevalent in patients with unexpected PE (39% vs. 23%, P< 0.0068). Unexpected PE patients had less tachypnea (37% vs. 57%, P=0.0005), dyspnea (47% vs. 87%, P<0.0001), chest pain (19% vs. 42%, P<0.0001) and hypoxemia (36% vs. 55%, P=0.0011), but a higher prevalence of concurrent pneumonia (16.3% vs. 9.1%, P=0.04). Mortality was significantly higher in patients with unexpected PE (70.3% vs. 53%, P= 0.0029).

\textbf{Discussion:} The main finding of our study is that patients with unexpected PE have a higher mortality despite a less severe clinical presentation, suggesting that unexpected PE may be a marker of higher morbidity.
Satirical cartoon by James Gilray, showing a Royal Institution lecture on Pneumatics, with Humphry Davy holding the bellows and Count Rumford looking on at the extreme right. Dr. Garnett is the lecturer holding the victim’s nose.
Pectus Excavatum: "The Little Chest Syndrome" or "The Little Lung Syndrome"?

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**Introduction:** Pectus Excavatum (PE) is a developmental anomaly of the thoracic cage. Conventionally, it is thought that this results in secondary compression of the thoracic organs, especially the lungs. If so, lung volumes and FRC are expected to be reduced. However, lung volume measurements demonstrate hyperinflation.

**Patients:** We studied 32 patients with PE, 27 had no correction and 5 were studied only after surgical correction of the chest wall.

**Methods:** Body-plethysmometry and mathematical modeling.

<table>
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<tr>
<th>Results</th>
<th>TLC (% of pred)</th>
<th>RV (% of pred)</th>
<th>VC (% of pred)</th>
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<tr>
<td>Without correction #27</td>
<td>92% ± 4%</td>
<td>155% ± 12%</td>
<td>73% ±5%</td>
</tr>
<tr>
<td>After correction #5</td>
<td>61% ±8%</td>
<td>124% ±20%</td>
<td>56% ±7%</td>
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**Discussion and Conclusion:**

Near normal TLC, increased RV and decreased VC, can be achieved only if the lungs are hyperinflated and not compressed. Hence, the lung is the primary organ affected in PE. This imbalance between morphological lung volumes and chest volume is either because of lung hypoplasia (The Little Lung Syndrome), or because of the excess volume of the chest, but not due to primary deformation of the chest. The negative intrapleural pressure in these patients during normal inhalation can reach 7-8cm of water. This negative pressure can increase 7-8 times during maximum inhalation, creating pressure of up to 50-70 kg that may lead to chest wall deformity. This explanation can account for the lack of improvement in lung function and exercise capacity after surgical correction of PE. Increasing the volume of the thorax by surgery may worsen the state of the lungs and hemodynamics.
What Limits Patients with Mild to Severe Cystic Fibrosis during Exercise?

Ronen Reuveny, Dublin City University, Ireland, Part of PhD Research

Background: The aim of this study was to determine the limiting factor that may affect exercise response during incremental maximal exercise in adults with mild, moderate and severe CF.

Methods: A total of 33 CF patients (22±3 yr) with different severities and 34 healthy controls (24±6 yr) performed an incremental maximal exercise test on a cycle ergometry. The FEV$_1$ % predicted was 86±12, 50±8, and 28±2.0 for patients in the mild (n = 18, f = 5), moderate (n = 9, f = 3), and severe (n = 6, f =1) CF categories, respectively.

Results: Peak Oxygen uptake (VO$_2$), anaerobic threshold (AT) and O$_2$ pulse were (a) higher in healthy controls than CF patients, (b) similar in patients with mild and moderate CF and (c) lower in severe than mild and moderate CF. There was a relation between V$_T$/max/VC and peakVO$_2$ corrected for lean body mass (r = 0.58 P< 0.01) and inverse relation between V$_E$/VCO$_2$ @AT and peak VO$_2$ (r = -0.44 p< 0.05).

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<tr>
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<th>Healthy</th>
<th>CF</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tr>
<td>VO$_2$ peak (ml/kg LBM/min)</td>
<td>52.2±8.9</td>
<td>39.1±6.7 †</td>
<td>37.8±8.7†</td>
<td>21.6±1.9‡</td>
<td></td>
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<tr>
<td>O$_2$ Pulse %predicted</td>
<td>108±32</td>
<td>90±13 †</td>
<td>84±15†</td>
<td>55±13†*</td>
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<tr>
<td>SpO$_2$ %</td>
<td>97.6±1.0</td>
<td>97±1.6</td>
<td>92.3±4.6†*</td>
<td>87±3.9‡</td>
<td></td>
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<tr>
<td>V$_E$/ MVV (%)</td>
<td>64.6±16.6</td>
<td>70.8±11.8</td>
<td>96.6±9†*</td>
<td>94.6±20.9‡</td>
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<tr>
<td>V$_T$/max/VC</td>
<td>50.0±9.8</td>
<td>48.1±8.7</td>
<td>48.6±7.5</td>
<td>35.3±6.8‡</td>
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<tr>
<td>V$_E$/VCO$_2$ @ AT</td>
<td>23.9±2.1</td>
<td>29±3.7†</td>
<td>31±4†</td>
<td>33±4†</td>
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<tr>
<td>P$_E$/TCO$_2$ (mmHg)</td>
<td>39.6±5.3</td>
<td>37.3±4.1</td>
<td>40.7±5.1</td>
<td>43.6±3</td>
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Values are mean ± SD; ‡ p <0.05 different from all the other groups; † p <0.05 vs. healthy; * Vs. mild <0.05;

Conclusion: Peak exercise capacity was lower in all CF groups. In patients with FEV$_1$ less than 30% predicted, exercise limitation is multifactorial, and may include, ventilatory mechanical limitation, abnormal gas exchange, and reduced cardiovascular response. Patients with moderate CF may be limited by ventilatory limitation, slight reduced gas exchange, and deconditioning. Patients with mild CF may be limited by deconditioning.
Determinants of Elevated Healthcare Utilization in COPD Patients

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Key words: Chronic Obstructive Pulmonary Disease, Quality of Life, Health Care Utilization, Hospitalizations.

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Conflict of interest – We are here to disclose that we have no conflict of interest related to the subject of this paper.

ABSTRACT

Background: Patients with Chronic obstructive pulmonary disease (COPD) impose a significant burden on health systems worldwide. Little is known about the determinants of elevated health care utilization among these patients. We sought to define the determinants of increased health care utilization in patients with COPD.

Methods: Cross-sectional retrospective study in the pulmonary clinic of the Soroka University Medical Center. Health care utilization indicators and presence of co-morbidities were obtained from the financial administrative databases of the Clalit Health care Services (CHS). Health related quality of life (HRQoL) indices were obtained using validated Hebrew translations of four-week recall questionnaires.

Results: One-hundred seventy-seven adults with COPD (age >35) were included. We defined a “most-costly” group consisting of the upper 25% (N=45) of the health care utilization costs per patient (median annualized cost: $7681.1, compared to $1728.6 for the rest). Compared with the rest of the patients, the “most costly” patients had greater co-morbidity burden as defined by higher age adjusted Charlson co-morbidity index (9 vs. 5, p<0.0001). Age and severity of airflow obstruction (FEV₁ and GOLD criteria) were not determinants of being in the “most costly” group. Multivariate analysis revealed that independent determinants of being in the “most costly” group included concomitant presence of myocardial infarct, congestive heart failure, peptic ulcer disease and diabetes. Perceived quality of life (general, COPD specific and sleep related) were not determinants of being in the “most costly” group.

Conclusions: Co-morbidity burden, not patients’ age and the extent of airflow obstruction, is an important determinant of cost of care for patients with COPD, the most important co-morbid conditions being heart disease, peptic ulcer disease and diabetes. Hence, there might be a need to design interventions tailored to these specific diagnoses.
Incidence of Hospitalizations among Severe COPD Patients Treated with Home Non-Invasive Ventilation

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Key words: Home Non-Invasive Ventilation – Home NIV, Chronic Obstructive Pulmonary Disease – COPD, Bi-level Positive Airway Ventilation - BPAP, Hospitalizations, COPD Exacerbations.

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Conflict of interest – We are here to disclose that we have no conflict of interest related to the subject of this abstract.

ABSTRACT

Background: Patients with COPD and frequent hospital admissions, impose a significant burden on health systems worldwide. Randomized controlled data exist supporting the use of acute non-invasive ventilation (NIV) in patients with COPD exacerbation. However the use of home NIV in chronic stable COPD remains controversial with conflicting reports of its efficacy and acceptability. Cumulative data of the recent years showed that home chronic NIV with BPAP therapy for severe COPD patients improve physiologic parameters, but very little was done to conclude whether this therapy has benefits in terms of hospitalizations and economic burden on health systems. We evaluated the incidence and total length of hospitalizations in the year before and the year after prescribing chronic home NIV with BPAP for selected group of COPD patients with more than 4 hospitalizations per year.

Design: Retrospective cohort study of patients with severe COPD who were prescribed chronic home NIV with BPAP.

Results: 65 patients were receiving BPAP therapy between Jan/1/2003 to Jan/1/2010. 22 patients were excluded (Incomplete data, another major intervention during the follow-up, documented incompliance). Out of 43 patients who were included, 28 (65%) were males and the mean age was 67.7 (SD ±10.3) years. There was a statistically significant reduction of 13 hospitalization days per year and in the number of hospitalization days due to COPD exacerbations (p<0.01). Non-statistically significant reduction was found in the following categories: ER admissions, number of hospitalizations, number of invasive ventilations procedures, hospitalization days in wards other than internal medicine wards, respiratory ICU or any other ICU.

Conclusions: Our findings demonstrate a significant reduction in hospitalization days after the first year of BPAP therapy in highly selected group of COPD patients with recurrent admissions. Such evidence is important in obtaining financial support for providing such a service.
Transcutaneous capnography measurement and BiPAP titration

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Pulmonary Institute, Rabin Medical Center, Beilinson Campus, Petah Tiqwa; affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Abstract

Background: Bi-level positive airway pressure (BPAP) titration is indicated for many patients with obstructive sleep apnea and hypoventilation. It can be done in a sleep lab overnight exam or in a day care facility under proper supervision.

In patients with carbon dioxide retention the BiPAP titration is accomplished by measurement of the arterial blood levels of carbon dioxide before and after the titration. This is an unpleasant procedure and requires at least two arterial blood punctures.

Aims of study: To review the data of BPAP titration using transcutaneous carbon dioxide tension (PcCO2) measurement.

Patients and methods: We retrospectively analyzed the medical records of 20 patients who underwent BiPAP titration at our facility from January 2009 until January 2010 using transcutaneous CO2 tension measurement during the titration. The patient's baseline and optimal PcCO2 levels were recorded as well as the gender, age and main disease. We also looked for the IPAP and EPAP settings suitable for the patient.

Results: The mean PcCO2 was 57mm Hg at baseline and 43mm Hg after BPAP titration. The mean PO2 rose from 85 mm Hg to 97mm Hg. The mean IPAP was 12 cm H2O and the mean EPAP was 5 cm H2O.

There were no significant differences between the baseline PCO2 and PO2 when we compared the arterial blood gases and the transcutaneous measurements. Three months after the titration 80% of the patients kept using the BiPAP device with high satisfaction.

Conclusions: BPAP titration by measurement of PcCO2 without arterial blood gas sampling is feasible and comfortable for both the patient and the medical staff.
Rob Roy Canoe on the Jordan River
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