COPD/Emphysema PubMed search results covering the period 26/10/2019 to 17/01/2020
Systematic reviews and clinical trials

Search strategy: (("pulmonary disease, chronic obstructive"[MeSH Terms] OR "emphysema"[MeSH Terms]) AND ((systematic[sb] OR Clinical Trial[ptyp]) AND English[lang]) AND ("2019/10/19"[CDAT] : "3000"[CDAT])) AND ((systematic[sb] OR Clinical Trial[ptyp]) AND English[lang]) AND ((systematic[sb] OR Clinical Trial[ptyp]) AND English[lang])

Abdallah, S. J., B. M. Smith, et al. (2018). **"Effect of Vaporized Cannabis on Exertional Breathlessness and Exercise Endurance in Advanced Chronic Obstructive Pulmonary Disease. A Randomized Controlled Trial."** Ann Am Thorac Soc **15**(10): 1146-1158.

RATIONALE: A series of studies conducted approximately 40 years ago demonstrated an acute bronchodilator effect of smoked cannabis in healthy adults and adults with asthma. However, the acute effects of vaporized cannabis on airway function in adults with advanced chronic obstructive pulmonary disease (COPD) remain unknown. OBJECTIVES: To test the hypothesis that inhaled vaporized cannabis would alleviate exertional breathlessness and improve exercise endurance by enhancing static and dynamic airway function in COPD. METHODS: In a randomized controlled trial of 16 adults with advanced COPD (forced expiratory volume in 1 second [FEV1], mean +/- SD: 36 +/- 11% predicted), we compared the acute effect of 35 mg of inhaled vaporized cannabis (18.2% Delta(9)-tetrahydrocannabinol, <0.1% cannabidiol) versus 35 mg of a placebo control cannabis (CTRL; 0.33% Delta(9)-tetrahydrocannabinol, <0.99% cannabidiol) on physiological and perceptual responses during cardiopulmonary cycle endurance exercise testing; spirometry and impulse oscillometry at rest; and cognitive function, psychoactivity, and mood. RESULTS: Compared with CTRL, cannabis had no effect on breathlessness intensity ratings during exercise at isotime (cannabis, 2.7 +/- 1.2 Borg units vs. CTRL, 2.6 +/- 1.3 Borg units); exercise endurance time (cannabis, 3.8 +/- 1.9 min vs. CTRL, 4.2 +/- 1.9 min); cardiac, metabolic, gas exchange, ventilatory, breathing pattern, and/or operating lung volume parameters at rest and during exercise; spirometry and impulse oscillometry-derived pulmonary function test parameters at rest; and cognitive function, psychoactivity, and mood. CONCLUSIONS: Single-dose inhalation of vaporized cannabis had no clinically meaningful positive or negative effect on airway function, exertional breathlessness, and exercise endurance in adults with advanced COPD. Clinical trial registered with www.clinicaltrials.gov (NCT03060993).

Alcazar, J., J. Losa-Reyna, et al. (2019). **"Effects of concurrent exercise training on muscle dysfunction and systemic oxidative stress in older people with COPD."** Scand J Med Sci Sports **29**(10): 1591-1603.

Oxidative stress is associated with disease severity and limb muscle dysfunction in COPD. Our main goal was to assess the effects of exercise training on systemic oxidative stress and limb muscle dysfunction in older people with COPD. Twenty-nine outpatients with COPD (66-90 years) were randomly assigned to a 12-week exercise training (ET; high-intensity interval training (HIIT) plus power training) or a control (CT; usual care) group. We evaluated mid-thigh muscle cross-sectional area (CSA; computed tomography); vastus lateralis (VL) muscle thickness, pennation angle, and fascicle length (ultrasonography); peak VO2 uptake (VO2peak) and work rate (Wpeak) (incremental cardiopulmonary exercise test); rate of force development (RFD); maximal muscle power (Pmax ; force-velocity testing); systemic oxidative stress (plasma protein carbonylation); and physical performance and quality of life. ET subjects experienced changes in mid-thigh muscle CSA (+4%), VL muscle thickness (+11%) and pennation angle (+19%), VO2peak (+14%), Wpeak (+37%), RFD (+32% to 65%), Pmax (+38% to 51%), sit-to-stand time (-24%), and self-reported health status (+20%) (all $P < 0.05$). No changes were noted in the CT group ($P > 0.05$). Protein carbonylation decreased among ET subjects (-27%; $P < 0.05$), but not in the CT group ($P > 0.05$). Changes in protein carbonylation were associated with changes in muscle size and pennation angle ($r = -0.44$ to -0.57), exercise capacity ($r = -0.46$), muscle strength ($r = -0.45$), and sit-to-stand performance ($r = 0.60$) (all $P < 0.05$). The combination of HIIT and power training improved systemic oxidative stress and limb muscle dysfunction in older people with COPD. Changes in oxidative stress were associated with exercise-induced structural and functional adaptations.

Blackstock, F. C., K. E. Webster, et al. (2018). **"Self-efficacy Predicts Success in an Exercise Training-Only Model of Pulmonary Rehabilitation for People With COPD."** J Cardiopulm Rehabil Prev **38**(5): 333-341.

PURPOSE: To determine whether people with chronic obstructive pulmonary disease (COPD) have characteristics that predict a clinically meaningful response to pulmonary rehabilitation (PR) that includes an education component compared with exercise training alone. METHODS: Participants were classified as responders or nonresponders to 2 models of PR; exercise training and education (ET + ED, n = 113) or exercise training alone (ET, n = 85). Responders were defined as those who achieved a clinically meaningful change in 6-min walk distance (6MWD) or any of the 4 domains of the Chronic Respiratory Questionnaire (CRQ). Baseline characteristics were compared between responders and nonresponders. The associations between baseline data and change in 6MWD and CRQ following PR were examined, and a binary logistic regression analysis was conducted for each model and primary outcome. RESULTS: There were no significant differences between the PR models in proportion of responders (ET + ED 92% vs ET 93%). Lower baseline CRQ scores predicted response in respective CRQ domains for fatigue, emotion, and mastery in the ET + ED group, and for dyspnea, fatigue, and mastery in the ET group. Higher baseline self-efficacy predicted 6MWD response and higher socioeconomic status predicted response in CRQ fatigue in the ET model only. There was no predictor of 6MWD response in the ET + ED group. CONCLUSIONS: Baseline characteristics did not reliably predict a clinically meaningful response to PR that included education. For exercise training alone, higher self-efficacy was a significant predictor for greater improvements in 6MWD, suggesting that those with higher confidence should be considered for this model.

Bohingamu Mudiyanselage, S., J. Stevens, et al. (2019). **"Personalised telehealth intervention for chronic disease management: A pilot randomised controlled trial."** J Telemed Telecare **25**(6): 343-352.

INTRODUCTION: The aim of this study was to assess the impact of home-based telehealth monitoring on health outcomes, quality of life and costs over 12 months for patients with diabetes and/or chronic obstructive pulmonary disease (COPD) who were identified as being at high risk of readmission to hospital. METHODS: This pilot study was a randomised controlled trial combined with an economic analysis to examine the outcomes of standard care versus home-based telehealth for people with diabetes and/or COPD who were at risk of hospital readmission within one year. The primary outcomes were (i) hospital admission and length of stay (LOS); and (ii) health-related quality of life (HRQOL); and the secondary outcomes were (i) health-related clinical outcomes; (ii) anxiety and depression scores; and (iii) health literacy. The costs of the intervention and hospitalisations were included. RESULTS: A total of 86 and 85 participants were randomised to the intervention and control groups respectively. The difference between groups in hospital LOS was -3.89 (95% confidence interval (CI): -9.40, 1.62) days, and for HRQOL, 0.09 (95% CI: 0.05, 0.14) in favour of the telehealth monitoring group. There was a saving of AUD$6553 (95% CI: -12145, -961) in the cost of hospitalisation over 12 months, which offset the increased cost of tele-monitoring. The intervention group showed an improvement in anxiety, depression and health literacy at 12 months, and in the diabetes group, a reduction in microalbuminuria. DISCUSSION: The telehealth monitoring intervention improved patient's health outcomes and quality of life at no additional cost.

Bourbeau, J., D. Granados, et al. (2019). **"Cost-effectiveness of the COPD Patient Management European Trial home-based disease management program."** Int J Chron Obstruct Pulmon Dis **14**: 645-657.

Purpose: Efficient management of COPD represents an international challenge. Effective management strategies within the means of limited health care budgets are urgently required. This analysis aimed to evaluate the cost-effectiveness of a home-based disease management (DM) intervention vs usual management (UM) in patients from the COPD Patient Management European Trial (COMET). Methods: Cost-effectiveness was evaluated in 319 intention-to-treat patients over 12 months in COMET. The analysis captured unplanned all-cause hospitalization days, mortality, and quality-adjusted life expectancy. Costs were evaluated from a National Health Service perspective for France, Germany, and Spain, and in a pooled analysis, and were expressed in 2015 Euros (EUR). Quality of life was assessed using the 15D health-related quality-of-life instrument and mapped to utility scores. Results: Home-based DM was associated with improved mortality and quality-adjusted life expectancy. DM and UM were associated with equivalent direct costs (DM reduced costs by EUR -37 per patient per year) in the pooled analysis. DM was associated with lower costs in France (EUR -806 per patient per year) and Spain (EUR -51 per patient per year), but higher costs in Germany (EUR 391 per patient per year). Evaluation of cost per death avoided and cost per quality-adjusted life year (QALY) gained showed that DM was dominant (more QALYs and cost saving) in France and Spain, and cost-effective in Germany vs UM. Nonparametric

bootstrapping analysis, assuming a willingness-to-pay threshold of EUR 20,000 per QALY gained, indicated that the probability of home-based DM being cost-effective vs UM was 87.7% in France, 81.5% in Spain, and 75.9% in Germany. Conclusion: Home-based DM improved clinical outcomes at equivalent cost vs UM in France and Spain, and in the pooled analysis. DM was cost-effective in Germany with an incremental cost-effectiveness ratio of EUR 2,541 per QALY gained. The COMET home-based DM intervention could represent an attractive alternative to UM for European health care payers.

Byrd, J. B., D. E. Newby, et al. (2018). **"Blood pressure, heart rate, and mortality in chronic obstructive pulmonary disease: the SUMMIT trial."** Eur Heart J **39**(33): 3128-3134.

Aims: To characterize the relationship between blood pressure (BP) or heart rate and mortality and morbidity in chronic obstructive pulmonary disease (COPD). Methods and results: We performed post hoc analysis of baseline BP or heart rate and all-cause mortality and cardiovascular events in the SUMMIT trial. SUMMIT was a randomized double-blind outcome trial of 16 485 participants (65 +/- 8 years, 75% male, and 47% active smokers) enrolled at 1368 sites in 43 countries. Participants with moderate COPD with or at risk for cardiovascular disease (CVD) were randomized to placebo, long-acting beta agonist, inhaled corticosteroid, or their combination. All-cause mortality increased in relation to high systolic [>/=140 mmHg; hazard ratio (HR) 1.27, 95% confidence interval (CI) 1.12-1.45] or diastolic (>/=90 mmHg; HR 1.35, 95% CI 1.14-1.59) BP and low systolic (<120 mmHg; HR 1.36, 95% CI 1.13-1.63) or diastolic (<80 mmHg; HR 1.15, 95% CI 1.00-1.32) BP. Higher heart rates (>/=80 per minute; HR 1.39, 95% CI 1.21-1.60) and pulse pressures (>/=80 mmHg; HR 1.39, 95% CI 1.07-1.80) were more linearly related to increases in all-cause mortality. The risks of cardiovascular events followed similar patterns to all-cause mortality. Similar findings were observed in subgroups of patients without established CVD. Conclusion: A 'U-shaped' relationship between BP and all-cause mortality and cardiovascular events exists in patients with COPD and heightened cardiovascular risk. A linear relationship exists between heart rate and all-cause mortality and cardiovascular events in this population. These findings extend the prognostic importance of BP to this growing group of patients and raise concerns that both high and low BP may pose health risks.

Chee, E. J. M., L. Prabhakaran, et al. (2019). **"Play and Learn with Patients-Designing and Evaluating a Serious Game to Enhance Nurses' Inhaler Teaching Techniques: A Randomized Controlled Trial."** Games Health J **8**(3): 187-194.

Objective: To describe the development and evaluation of a nurse-patient interactive serious game in improving nurses' self-efficacy and performances in teaching the correct inhaler technique. Materials and Methods: The technology, pedagogy, and content knowledge (TPACK) framework was applied to guide the development of the serious game. The learning effectiveness of the serious game was evaluated through a randomized controlled trial that involved 46 registered nurses. Participants in the experimental group were asked to teach the inhaler technique to a standardized patient using the serious game as a teaching tool, whereas participants in the control group were asked to provide their own usual teaching to a standardized patient without the serious game. The performances of both groups were assessed based on their feedback to a standardized patient who made several errors while demonstrating the inhaler technique. Self-efficacy levels of teaching the inhaler technique were examined before and after the intervention. Results: A significantly higher number of participants from the experimental group obtained perfect performance scores than those in the control group (65.21% vs. 21.74%, chi(2) (=) 15.18, P < 0.01). The posttest self-efficacy mean scores for the experimental group improved significantly (P < 0.001) after the intervention, and significantly higher (P < 0.05) compared to the posttest mean scores of the control group. Conclusion: The study provided evidence on the effectiveness of a serious game in improving the self-efficacy and immediate postintervention performances of nurses teaching the inhaler technique. This game provides a practical and accessible learning tool to help nurses ensure effective patient education.

Christenson, S. A., M. van den Berge, et al. (2019). **"An airway epithelial IL-17A response signature identifies a steroid-unresponsive COPD patient subgroup."** J Clin Invest **129**(1): 169-181.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a heterogeneous smoking-related disease characterized by airway obstruction and inflammation. This inflammation may persist even after smoking cessation and responds variably to corticosteroids. Personalizing treatment to biologically similar "molecular phenotypes" may improve therapeutic efficacy in COPD. IL-17A is involved in neutrophilic inflammation and corticosteroid resistance, and thus may be particularly important in a COPD molecular phenotype. METHODS: We generated a gene expression signature of IL-17A response in bronchial airway epithelial brushings from smokers with and without COPD (n = 238), and validated it using data from 2 randomized trials of IL-17 blockade in psoriasis. This IL-17 signature was related to clinical and pathologic characteristics in 2 additional human studies of COPD: (a) SPIROMICS (n = 47), which included former and current smokers with COPD, and (b) GLUCOLD (n = 79), in which COPD participants were randomized to placebo or corticosteroids. RESULTS: The IL-17 signature was associated with an inflammatory profile characteristic of an IL-17 response, including increased airway neutrophils and macrophages. In SPIROMICS the signature was associated with increased airway obstruction and functional small airways disease on quantitative chest CT. In GLUCOLD the signature was associated with decreased response to corticosteroids, irrespective of airway eosinophilic or type 2 inflammation. CONCLUSION: These data suggest that a gene signature of IL-17 airway epithelial response distinguishes a biologically, radiographically, and clinically distinct COPD subgroup that may benefit from personalized therapy. TRIAL REGISTRATION: ClinicalTrials.gov NCT01969344. FUNDING: Primary support from the NIH, grants K23HL123778, K12HL11999, U19AI077439, DK072517, U01HL137880, K24HL137013 and R01HL121774 and contracts HHSN268200900013C, HHSN268200900014C, HHSN268200900015C, HHSN268200900016C, HHSN268200900017C, HHSN268200900018C,

Cutrim, A. L. C., A. A. M. Duarte, et al. (2019). **"Inspiratory muscle training improves autonomic modulation and exercise tolerance in chronic obstructive pulmonary disease subjects: A randomized-controlled trial."** Respir Physiol Neurobiol **263**: 31-37.

OBJECTIVES: We aimed to evaluate the effect a regular inspiratory muscle training program on autonomic modulation measured by heart rate variability, exercise capacity and respiratory function in chronic obstructive pulmonary disease subjects (COPD). DESIGN: Single-center controlled study, with balanced randomization (1:1 for two arms). SETTING: A COPD reference hospital localized in Sao Luis, Brazil. PARTICIPANTS: 22 COPD subjects joined the study. INTERVENTIONS: Three times a week for four weeks inspiratory muscle training (IMT) at 30% of PImax. MAIN OUTCOME MEASURES: Pulmonary capacities and inspiratory pressure, total six-minute walk test and, cardiac autonomic modulation. RESULTS: The intervention group showed improvements in the cardiac autonomic modulation, with increased vagal modulation (total variability and HF [ms(2); adjusted $p < 0.05$]); increased expiratory and inspiratory capacities and, increased distance in the 6-min walk test. CONCLUSION: 12 weeks of IMT at 30% of the maximal inspiratory pressure increased cardiac autonomic modulation, expiratory and inspiratory and exercise capacity in COPD subjects.

de Souza, Y., K. M. da Silva, et al. (2018). **"Use of a Home-Based Manual as Part of a Pulmonary Rehabilitation Program."** Respir Care **63**(12): 1485-1491.

BACKGROUND: Pulmonary rehabilitation programs improve exercise capacity and quality of life in patients with COPD. Domiciliary strategies to maintain these benefits have been proposed. OBJECTIVE: This study aimed to determine whether a rehabilitation manual would facilitate the maintenance of the benefits acquired during out-patient pulmonary rehabilitation. METHODS: Fifty subjects with stable COPD were included (26 women and 24 men). All the subjects were evaluated during screening and after 12 wk of out-patient rehabilitation, and then were randomly divided into 2 groups, with one group that received the rehabilitation manual for home use (manual group) and the other group only received verbal recommendations (control group). At this point, the 2 groups were similar. After 12 wk at home, both groups were evaluated a third time. All evaluations included a 6-min walk test (6MWT), 6-min step test, COPD Assessment Test, and measurement of dyspnea by using the modified Medical Research Council dyspnea scale. RESULTS: When comparing the results of the 6MWT and 6-min step test done at out-patient discharge and after 12 wk at home, the manual group presented no differences (6MWT, 0 +/- 25 m; 6-min step test, 1 +/- 32 steps), whereas the control subjects lost part of the gain obtained during rehabilitation (6MWT -46 +/- 36 m; 6-min step test -39 +/- 33 steps). There was a significant difference between the groups ($P < .05$). When comparing the same time points, the change in the COPD Assessment Test score was -1 +/- 1 for the manual group and 1 +/- 2 for the control group ($P = .01$). For

the modified Medical Research Council dyspnea scale, the change in score was 0 +/- 1 for the manual group and 1 +/- 1 for the control group (P = .01). CONCLUSIONS: The use of a simple, well-illustrated manual facilitated the maintenance of the benefits acquired in out-patient pulmonary rehabilitation over a period of 3 months after study termination.

Fasoulas, A., C. Boutsioukis, et al. (2019). **"Subcutaneous emphysema in patients undergoing root canal treatment: a systematic review of the factors affecting its development and management."** Int Endod J **52**(11): 1586-1604.

BACKGROUND: Subcutaneous emphysema is an infrequent mishap during root canal treatment which, in rare cases, can lead to severe complications. AIM: To systematically review the literature on the factors affecting the development of subcutaneous emphysema during root canal treatment, and on its management. DATA SOURCES: An electronic search was conducted in EMBASE (1947-2018), LILACS (1982-2018), PubMed (1950-2018), SciELO (1997-2018), Scopus (1970-2018), Web of Science (1900-2018) and two grey literature databases. Moreover, all issues of nine journals and four endodontic textbooks were hand-searched. STUDY ELIGIBILITY CRITERIA, PARTICIPANTS, INTERVENTIONS: The retrieved studies were screened by two reviewers to select clinical studies, case reports or case series describing subcutaneous emphysema that developed during or immediately after root canal treatment in adult patients. STUDY APPRAISAL AND SYNTHESIS METHODS: Included studies were critically appraised according to a custom list of quality requirements. The extracted data were arranged in tables, and combined through a narrative synthesis. RESULTS: The search retrieved 99 unique articles. Thirty six case reports and 15 case series describing a total of 65 cases of subcutaneous emphysema were included in this review. The methodological quality was medium. Reported cases of emphysema more often involved females and maxillary teeth. Drying of the root canal system with air under pressure, inadvertent extrusion of hydrogen peroxide through the apical foramen, the air-water spray produced by handpieces or laser devices, and the use of ozone gas were the most commonly suspected causes. Its management involved prescription of antibiotics and NSAIDs/analgesics, local application of ice packs or compresses and hospitalization. The signs and symptoms resolved completely within 1-17 days. LIMITATIONS: Case reports and case series are a low level of evidence. CONCLUSIONS AND IMPLICATIONS OF KEY FINDINGS: Subcutaneous emphysema can develop during both nonsurgical and surgical root canal treatment. Pressurized air streams or air-water sprays should not be directed towards the root canals or areas with mucosal discontinuity. None of the management approaches were clearly related to expedited recovery. Guidelines should be developed in order to avoid unnecessary or potentially harmful interventions.

Fawzy, A., J. A. Anderson, et al. (2019). **"Association of platelet count with all-cause mortality and risk of cardiovascular and respiratory morbidity in stable COPD."** Respir Res **20**(1): 86.

BACKGROUND: Platelet count is a prognostic indicator in the general population and elderly. Thrombocytosis during acute exacerbation of COPD (AECOPD) has been associated with mortality; however, the relationship between platelet count and mortality in stable COPD is unknown. METHODS: We performed post hoc secondary analysis on a subsample of 1797 patients in the Study to Understand Mortality and Morbidity in COPD (SUMMIT) who had blood samples drawn at baseline. Participants were current or former smokers, 40-80 years old with moderate COPD and history or increased risk of cardiovascular (CV) disease. The primary outcome was on and post-treatment all-cause mortality. Secondary outcomes included first-on-treatment moderate/severe AECOPD and on-treatment CV composite event (CV death, myocardial infarction, stroke, unstable angina and transient ischemic attack). Multivariable Cox proportional hazards models were used to investigate study endpoint associations with platelet count quintile grouping, continuous platelet count utilizing two-term fractional polynomials, and categories of low, normal and high platelet count (< 150, >/=150 to < 300, >/=300 x 10(9)/L). RESULTS: Patients were followed for 2.3 +/- 0.9 years for vital status and 1.6 +/- 1.1 years for morbidity endpoints during which 105 (5.8%) died, 651 (36.2%) experienced AECOPD (159 with severe AECOPD) and 86 (4.8%) experienced a CV event. A U-shaped association between platelet count and all-cause mortality was observed. Compared to the third quintile group (Q3) of platelet count, risk of death was increased in the lowest quintile group (Q1; hazard ratio [HR]: 1.73; 95% confidence interval [CI]: 0.93-3.23) and highest quintile group (Q5; HR: 1.66; 95%CI: 0.89-3.10), though point estimates were imprecise. Using clinical cutoffs, compared with normal platelet counts (>/=150 to < 300 x 10(9)/L), risk of all-cause mortality was nominally increased among patients with thrombocytopenia (HR: 1.46; 95%CI: 0.81-2.64) and high platelet count (HR: 1.66; 95%CI: 0.96-2.86). Compared with Q3, CV events were nominally increased for Q5 (HR: 1.71; 95%CI: 0.83-3.49) and Q1 (HR: 1.41; 95%CI: 0.70, 2.85). There was no association between

platelet count and AECOPD. CONCLUSIONS: In stable COPD platelet count demonstrated a U-shaped association with increased risk of 3-year all-cause mortality, though a platelet count level above or below which risk of mortality was increased could not be definitively identified. TRIAL REGISTRATION: ClinicalTrials.gov NCT01313676 .

Furian, M., M. Lichtblau, et al. (2019). **"Effect of Dexamethasone on Nocturnal Oxygenation in Lowlanders With Chronic Obstructive Pulmonary Disease Traveling to 3100 Meters: A Randomized Clinical Trial."** JAMA Netw Open **2**(2): e190067.

Importance: During mountain travel, patients with chronic obstructive pulmonary disease (COPD) are at risk of experiencing severe hypoxemia, in particular, during sleep. Objective: To evaluate whether preventive dexamethasone treatment improves nocturnal oxygenation in lowlanders with COPD at 3100 m. Design, Setting, and Participants: A randomized, placebo-controlled, double-blind, parallel trial was performed from May 1 to August 31, 2015, in 118 patients with COPD (forced expiratory volume in the first second of expiration [FEV1] >50% predicted, pulse oximetry at 760 m >/=92%) who were living at altitudes below 800 m. The study was conducted at a university hospital (760 m) and high-altitude clinic (3100 m) in Tuja-Ashu, Kyrgyz Republic. Patients underwent baseline evaluation at 760 m, were taken by bus to the clinic at 3100 m, and remained at the clinic for 2 days and nights. Participants were randomized 1:1 to receive either dexamethasone, 4 mg, orally twice daily or placebo starting 24 hours before ascent and while staying at 3100 m. Data analysis was performed from September 1, 2015, to December 31, 2016. Interventions: Dexamethasone, 4 mg, orally twice daily (dexamethasone total daily dose, 8 mg) or placebo starting 24 hours before ascent and while staying at 3100 m. Main Outcomes and Measures: Difference in altitude-induced change in nocturnal mean oxygen saturation measured by pulse oximetry (Spo2) during night 1 at 3100 m between patients receiving dexamethasone and those receiving placebo was the primary outcome and was analyzed according to the intention-to-treat principle. Other outcomes were apnea/hypopnea index (AHI) (mean number of apneas/hypopneas per hour of time in bed), subjective sleep quality measured by a visual analog scale (range, 0 [extremely bad] to 100 [excellent]), and clinical evaluations. Results: Among the 118 patients included, 18 (15.3%) were women; the median (interquartile range [IQR]) age was 58 (52-63) years; and FEV1 was 91% predicted (IQR, 73%-103%). In 58 patients receiving placebo, median nocturnal Spo2 at 760 m was 92% (IQR, 91%-93%) and AHI was 20.5 events/h (IQR, 12.3-48.1); during night 1 at 3100 m, Spo2 was 84% (IQR, 83%-85%) and AHI was 39.4 events/h (IQR, 19.3-66.2) (P < .001 both comparisons vs 760 m). In 60 patients receiving dexamethasone, Spo2 at 760 m was 92% (IQR, 91%-93%) and AHI was 25.9 events/h (IQR, 16.3-37.1); during night 1 at 3100 m, Spo2 was 86% (IQR, 84%-88%) (P < .001 vs 760 m) and AHI was 24.7 events/h (IQR, 13.2-33.7) (P = .99 vs 760 m). Altitude-induced decreases in Spo2 during night 1 were mitigated by dexamethasone vs placebo by a mean of 3% (95% CI, 2%-3%), and increases in AHI were reduced by 18.7 events/h (95% CI, 12.0-25.3). Similar effects were observed during night 2. Subjective sleep quality was improved with dexamethasone during night 2 by 12% (95% CI, 0%-23%). Sixteen (27.6%) patients using dexamethasone had asymptomatic hyperglycemia. Conclusions and Relevance: In lowlanders in Central Asia with COPD traveling to a high altitude, preventive dexamethasone treatment improved nocturnal oxygen saturation, sleep apnea, and subjective sleep quality. Trial Registration: ClinicalTrials.gov Identifier: NCT02450994.

George, L., A. Wright, et al. (2019). **"Sputum Streptococcus pneumoniae is reduced in COPD following treatment with benralizumab."** Int J Chron Obstruct Pulmon Dis **14**: 1177-1185.

We hypothesized whether the reduction in eosinophilic airway inflammation in patients with chronic obstructive pulmonary disease (COPD) following treatment with benralizumab, a humanized, afucosylated, monoclonal antibody that binds to interleukin-5 receptor alpha, increases the airway bacterial load. Analysis of sputum samples of COPD patients participating in a Phase II trial of benralizumab indicated that sputum 16S rDNA load and Streptococcus pneumoniae were reduced following treatment with benralizumab. However, in vitro, eosinophils did not affect the killing of the common airway pathogens S. pneumoniae or Haemophilus influenzae. Thus, benralizumab may have an indirect effect upon airway bacterial load.

Hakim, A., Y. Khan, et al. (2019). **"Low-Dose Budesonide/Formoterol Counteracts Airway Inflammation and Improves Lung Function in Chronic Obstructive Pulmonary Disease."** Am J Respir Crit Care Med **199**(5): 662-664.

Hao, W., M. Li, et al. (2019). **"Inflammatory mediators in exhaled breath condensate and peripheral blood of healthy donors and stable COPD patients."** Immunopharmacol Immunotoxicol **41**(2): 224-230.
Objective: The aim of this work was to compare matrix metalloproteinase-9 and -12, tissue inhibitor of metalloproteinase-1 and -4, and neutrophil elastase in exhaled breath condensate (EBC) and peripheral blood of patients with COPD. Methods: Peripheral blood and EBC samples from COPD patients and healthy donors were collected. In serum and EBC, MMP-9, MMP-12, NE, TIMP-1, and TIMP-4 proteins were detected by ELISA. The mRNA expression levels of MMP-9, MMP-12, NE, TIMP-1, and TIMP-4 in peripheral blood mononuclear cells (PBMCs) were analyzed by qRT-PCR. Results: The protein levels of MMP-9 (p=.034) and MMP-12 (p=.041) in the EBC of COPD smokers were higher than those of COPD never-smokers. The concentrations of TIMP-1 (p=.072) and TIMP-4 (p=.084) in the EBC of COPD smokers were higher than those of COPD never-smokers; however, the difference was not statistically significant. MMP-9 (r=-0.78, p<.0001) and TIMP-1 (r=-0.71, p<.0001) levels in EBC were significantly negatively correlated with pulmonary function FEV1%pred. The protein levels of MMP-12 (r=-0.37, p=.034) and TIMP-4 (r=-0.34, p=.041) were also negatively correlated with FEV1%pred. The expression of MMP-9, MMP-12, NE, TIMP-1, and TIMP-4 in PBMCs and serum of COPD smokers were significantly higher than those of control never-smokers (p<.05). Conclusions: Exhaled MMP-9, MMP-12, TIMP-1, and TIMP-4 levels increased in stable COPD patients and were negatively correlated with FEV1%pred, which suggests the usefulness of their measurement in EBC for the monitoring of airway inflammation. However, to better assess their diagnostic or prognostic value, larger studies are necessary.

Huang, K., Y. Guo, et al. (2019). **"The efficacy of adding budesonide/formoterol to ipratropium plus theophylline in managing severe chronic obstructive pulmonary disease: an open-label, randomized study in China."** Ther Adv Respir Dis **13**: 1753466619853500.
BACKGROUND: Patients diagnosed with chronic obstructive pulmonary disease (COPD) in China are commonly prescribed ipratropium plus theophylline (I+T) therapy. Studies have shown that an inhaled corticosteroid (ICS)/long-acting beta(2)-agonist (LABA) combination is also efficacious in reducing symptoms and exacerbations. This study evaluated the efficacy and tolerability of adding budesonide/formoterol (BUD/FORM) to I+T in Chinese patients with severe COPD. METHODS: A randomized, parallel-group, open-label, multicenter phase IV study (Clinical Trials.gov identifier: NCT01415518) was conducted in China. Patients received either BUD/FORM (160/4.5 microg; two inhalations twice daily [bid] via Turbuhaler((R))) + I (20 microg per inhalation, two inhalations four times daily) + T (100 mg bid) or I+T alone for 12 weeks. The primary efficacy variable was change from baseline in predose forced expiratory volume in 1 s (FEV1). RESULTS: A total of 584 patients were randomized equally between treatment groups. At the end of the study, the BUD/FORM plus I+T group displayed significant improvements in predose FEV1 versus the I+T group (between-group difference 6.9%; 95% confidence interval [CI]: 4.3, 9.6; p < 0.0001). Forced vital capacity, inspiratory capacity, peak expiratory flow and health-related quality of life (HRQoL) scores were significantly improved (all p < 0.0001) and exacerbation frequency was reduced (43.5% reduction; rate ratio 0.565, 95% CI 0.325, 0.981; p = 0.0425) with BUD/FORM plus I+T versus I+T alone. CONCLUSION: Patients with severe COPD in China treated with BUD/FORM plus I+T showed significant improvements in lung function and HRQoL and a reduction in exacerbations compared with I+T alone. Both treatments were well tolerated and no safety concerns were noted. The reviews of this paper are available via the supplemental material section.

Janaudis-Ferreira, T. (2018). **"In chronic obstructive pulmonary disease, home-based maintenance telerehabilitation reduced the risk of exacerbations, hospitalisations and emergency visits [synopsis]."** J Physiother **64**(1): 56.

Kawachi, S. and K. Fujimoto (2019). **"Efficacy of tiotropium and olodaterol combination therapy on dynamic lung hyperinflation evaluated by hyperventilation in COPD: an open-label, comparative before and after treatment study."** Int J Chron Obstruct Pulmon Dis **14**: 1167-1176.

Background: Dynamic lung hyperinflation (DLH) following metronome-paced incremental hyperventilation (MPIH) was reported to be useful for assessment of pathophysiological impairment in patients with chronic obstructive pulmonary disease (COPD), and the effects of tiotropium and olodaterol on DLH following MPIH have not been reported. Methods: Treatment consisted of administration of tiotropium/olodaterol 5/5 mug inhalation solution (2.5/2.5 mug per actuation) using a soft-mist inhaler once a day. We compared outcomes before and after 8 weeks of treatment. The primary outcome was defined as a decrease in inspiratory capacity (IC) from rest by MPIH, which is an index of DLH. The secondary outcomes were COPD assessment test (CAT), forced expiratory volume in 1 s (FEV1), and 6-min walking distance (6MWD). In addition, we investigated whether there were correlations between changes with treatment in DLH and FEV1, 6MWD, and dyspnea. Results: Thirty-three of the 38 registered patients completed this study. Most of these 33 patients had mild to moderate COPD. Decreasing IC by MPIH was significantly reduced by treatment for 8 weeks, with a mean change of about -0.11 to -0.13 mL ($P < 0.05$). In addition, CAT score, FEV1, and 6MWD improved with treatment ($P < 0.05$). There were no significant correlations between changes in DLH, FEV1, 6MWD, or dyspnea with treatment. Conclusions: The results of this study showed that the combination of tiotropium and olodaterol is effective for improvement of DLH following hyperventilation.

Langer, D., C. Ciavaglia, et al. (2018). **"Inspiratory muscle training reduces diaphragm activation and dyspnea during exercise in COPD."** J Appl Physiol (1985) **125**(2): 381-392.

Among patients with chronic obstructive pulmonary disease (COPD), those with the lowest maximal inspiratory pressures experience greater breathing discomfort (dyspnea) during exercise. In such individuals, inspiratory muscle training (IMT) may be associated with improvement of dyspnea, but the mechanisms for this are poorly understood. Therefore, we aimed to identify physiological mechanisms of improvement in dyspnea and exercise endurance following inspiratory muscle training (IMT) in patients with COPD and low maximal inspiratory pressure (Pimax). The effects of 8 wk of controlled IMT on respiratory muscle function, dyspnea, respiratory mechanics, and diaphragm electromyography (EMGdi) during constant work rate cycle exercise were evaluated in patients with activity-related dyspnea (baseline dyspnea index <9). Subjects were randomized to either IMT or a sham training control group (n = 10 each). Twenty subjects (FEV1 = 47 +/- 19% predicted; Pimax = -59 +/- 14 cmH2O; cycle ergometer peak work rate = 47 +/- 21% predicted) completed the study; groups had comparable baseline lung function, respiratory muscle strength, activity-related dyspnea, and exercise capacity. IMT, compared with control, was associated with greater increases in inspiratory muscle strength and endurance, with attendant improvements in exertional dyspnea and exercise endurance time (all $P < 0.05$). After IMT, EMGdi expressed relative to its maximum (EMGdi/EMGdimax) decreased ($P < 0.05$) with no significant change in ventilation, tidal inspiratory pressures, breathing pattern, or operating lung volumes during exercise. In conclusion, IMT improved inspiratory muscle strength and endurance in mechanically compromised patients with COPD and low Pimax. The attendant reduction in EMGdi/EMGdimax helped explain the decrease in perceived respiratory discomfort despite sustained high ventilation and intrinsic mechanical loading over a longer exercise duration. NEW & NOTEWORTHY In patients with COPD and low maximal inspiratory pressures, inspiratory muscle training (IMT) may be associated with improvement of dyspnea, but the mechanisms for this are poorly understood. This study showed that 8 wk of home-based, partially supervised IMT improved respiratory muscle strength and endurance, dyspnea, and exercise endurance. Dyspnea relief occurred in conjunction with a reduced activation of the diaphragm relative to maximum in the absence of significant changes in ventilation, breathing pattern, and operating lung volumes.

Leaker, B. R., D. Singh, et al. (2019). **"Evaluation of systemic absorption and bronchodilator effect of glycopyrronium bromide delivered by nebulizer or a dry powder inhaler in subjects with chronic obstructive pulmonary disease."** Respir Res **20**(1): 132.

BACKGROUND: Effective bronchodilator therapy depends upon adequate drug deposition in the lung. COPD patients who are unable to administer medications efficiently with conventional inhalers may benefit from the use of a nebulizer device. The aim of this study was to evaluate the systemic bioavailability and bronchodilator response of glycopyrronium bromide (GLY) administered by a novel nebulizer (eFlow(R) closed system [CS] vibrating membrane nebulizer) or dry powder inhaler (DPI) in subjects with moderate-to-severe chronic obstructive pulmonary disease (COPD). METHODS: In this randomized, open-label, single-dose, five-way crossover study, subjects received a sequence of either 50 mug GLY delivered by eFlow CS nebulizer (GLY/eFlow) or 63 mug GLY delivered by DPI (GLY/DPI), with and without activated charcoal, followed by intravenous infusion of 50 mug GLY with a washout period of 7 days between doses. Endpoints included plasma pharmacokinetics, safety and efficacy. RESULTS: The mean (+/- SD) baseline predicted forced expiratory volume in 1 s (FEV1) of the 30 subjects who completed the study was 51 +/- 15%, with a FEV1/forced vital capacity ratio of 50 +/- 11%. Without charcoal, the absolute systemic bioavailability of GLY/eFlow and GLY/DPI were approximately 15 and 22%, respectively. Changes from baseline in FEV1 at 60 min post-dose, without administration of charcoal, were 0.180 L and 0.220 L for GLY/eFlow and GLY/DPI, respectively; FEV1 improvements were similar when charcoal was administered (0.220 L for both GLY/eFlow and GLY/DPI). There were no significant differences in spirometry between the two devices. Fewer subjects administered GLY/eFlow reported adverse events (n = 15) than GLY/DPI (n = 18). CONCLUSIONS: After single doses, GLY/DPI delivered numerically higher peak and steady state levels of drug than did GLY/eFlow. Nebulized GLY produced similar bronchodilation but lower systemic levels of drug than GLY/DPI. Slightly higher number of subjects reported adverse events with GLY/DPI than with GLY/eFlow. Nebulized GLY may offer an effective alternative to patients with COPD not adequately treated with other devices. TRIAL REGISTRATION: NCT02512302 (ClinicalTrials.gov). Registered 28 May 2015.

Lee, A. L., M. K. Beauchamp, et al. (2018). **"Clinical and Physiological Effects of Rollators in Individuals With Chronic Obstructive Pulmonary Disease: A SYSTEMATIC REVIEW."** J Cardiopulm Rehabil Prev **38**(6): 366-373.

PURPOSE: To determine the effects of using a rollator in people with chronic obstructive pulmonary disease (COPD). METHODS: Studies were systematically identified from literature searches of MEDLINE, CINAHL, PEDro, PubMed, EMBASE, and the Cochrane Library databases and the reference lists of included studies. Two reviewers independently selected randomized controlled or crossover studies examining the effects of rollator usage compared with no aid in individuals with COPD. Methodologic quality was assessed by 2 reviewers independently using the Cochrane Risk of Bias tool. Two reviewers also used a customized form to extract characteristics of and outcomes for subjects related to exercise capacity, symptoms, health-related quality of life (HRQOL), physiological, and gait parameters. Weighted mean differences (WMD) with 95% CI were calculated using a fixed-effects model. RESULTS: A total of 7 studies (126 participants) were included. Use of a rollator during a 6-Minute Walk Test (6MWT) improved distance walked (WMD = 13 m; 95% CI, 5-22) and lowered end-6MWT dyspnea rating (WMD = 0.97; 95% CI, 0.63-1.32). Longer-term use did not appear to impact exercise capacity or HRQOL, although this may be related to the frequency of use. CONCLUSIONS: When used in the short-term, rollators resulted in a small increase in 6MWT and a reduction in dyspnea. Details on patient adherence are required to accurately evaluate the longer-term effects of rollator usage.

Leite, M. R., E. M. C. Ramos, et al. (2018). **"Analysis of Autonomic Modulation in Response to a Session of Aerobic Exercise at Different Intensities in Patients With Moderate and Severe COPD."** Copd **15**(3): 245-253.

Despite the many benefits of performing physical exercise in patients with chronic obstructive pulmonary disease (COPD), information on the response of acute cardiac autonomic modulation in subjects with moderate and severe COPD during and after an aerobic exercise session at different intensities is unknown. The aim of this study was to evaluate the response of cardiac autonomic modulation in patients with moderate and severe COPD during and after an aerobic exercise session at different intensities. Twenty-seven patients with COPD, divided into: Moderate Group and Severe Group, underwent an aerobic exercise sessions with intensities equivalent to 60% and 90% of velocity corresponding to peak oxygen consumption. The heart rate variability (HRV) indices were analyzed in the time and frequency domains at the following times: at rest, during exercise, immediately after, and 5, 10, and 15 minutes after

exercise. In the comparison analysis between the two groups, no differences were observed in any of the HRV indices at different intensities applied. However, it was observed that the exercise caused autonomic changes when the groups were analyzed separately. Sessions of aerobic exercise influence the autonomic modulation in patients with COPD. However, COPD severity did not influence the autonomic nervous system response to exercise and recovery moments; and there was no difference between the exercise intensities.

Lewis, N., J. C. M. Gelinas, et al. (2019). **"Cerebrovascular function in patients with chronic obstructive pulmonary disease: the impact of exercise training."** Am J Physiol Heart Circ Physiol **316**(2): H380-h391.

This study examined cerebral blood flow (CBF) and its regulation before and after a short-term periodized aerobic exercise training intervention in patients with chronic obstructive pulmonary disease (COPD). Twenty-eight patients with COPD (forced expiratory volume in 1 s/forced vital capacity < 0.7 and <lower limit of normal) and 24 healthy control subjects participated in the study. Extracranial CBF (duplex ultrasound), middle cerebral artery velocity (MCAv; transcranial Doppler), cerebrovascular reactivity to hypocapnia and hypercapnia, and dynamic cerebral autoregulation (transfer function analysis) were quantified. These tests were repeated in both patients with COPD (n = 23) and control subjects (n = 20) after 8 wk of periodized upper and lower body aerobic exercise training (3 sessions/wk). At baseline, global extracranial CBF was comparable between the COPD and control groups (791 +/- 290 vs. 658 +/- 143 ml/min, P = 0.25); however, MCAv was lower in patients with COPD compared with control subjects (46 +/- 9 vs. 53 +/- 10 cm/s, P = 0.05). Although there were no group differences in dynamic cerebral autoregulation or the MCAv response to hypercapnia, patients with COPD had a lower MCAv response to hypocapnia compared with control subjects (-1.1 +/- 1.5 vs. -1.6 +/- 1.3 cm.s(-1).mmHg(-1), P = 0.02). After aerobic training, absolute peak O2 consumption increased in both groups, with a greater improvement in control subjects (1.7 +/- 0.4 vs. 4.1 +/- 0.2 ml.kg(-1).min(-1), respectively, P = 0.001). Despite these improvements in peak O2 consumption, there were no significant alterations in CBF or any measures of cerebrovascular function after exercise training in either group. In conclusion, patients with COPD have a blunted cerebrovascular response to hypocapnia, and 8 wk of aerobic exercise training did not alter cerebrovascular function despite significant improvements in cardiorespiratory fitness. NEW & NOTEWORTHY No study to date has investigated whether exercise training can alter resting cerebral blood flow (CBF) regulation in patients with chronic obstructive pulmonary disease (COPD). This study is the first to assess CBF regulation at rest, before, and after aerobic exercise training in patients with COPD and healthy control subjects. This study demonstrated that while exercise training improved aerobic fitness, it had little effect on CBF regulation in patients with COPD or control subjects.

Lichtblau, M., M. Furian, et al. (2019). **"Dexamethasone improves pulmonary hemodynamics in COPD-patients going to altitude: A randomized trial."** Int J Cardiol **283**: 159-164.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) may predispose to symptomatic pulmonary hypertension at high altitude. We investigated hemodynamic changes in lowlanders with COPD ascending rapidly to 3100m and evaluated whether preventive dexamethasone treatment would mitigate the altitude-induced increase in pulmonary artery pressure. METHODS: In this placebo-controlled, double-blind trial, non-hypercapnic COPD patients living <800m, were randomized to receive either dexamethasone (8mg/day) or placebo tablets one day before ascent from 760m and during a 3-day-stay at 3100m. Echocardiography was performed at 760m and after the first night at 3100m. The trans-tricuspid pressure gradient (RV/RA, main outcome), cardiac output (Q) by velocity-time integral of left ventricular outflow, indices of right and left heart function, blood gases and pulse-oximetry (SpO2) were compared between groups. RESULTS: 95 patients, 79 men, mean+/-SD age 57+/-8y FEV1 89+/-21% pred, SpO2 95+/-2% were included in the analysis. In 52 patients receiving dexamethasone, RV/RA, Q and SpO2 at 760 and 3100m were 19+/-5mmHg and 26+/-7mmHg, 4.9+/-0.7 and 5.7+/-1.1l/min, SpO2 95+/-2% and 90+/-3% (P<0.05 all changes). In 43 patients receiving placebo the corresponding values were 20+/-4mmHg and 31+/-9mmHg, 4.7+/-0.9l/min and 95+/-3% and 89+/-3% (P<0.05 all changes) between group differences of altitude-induced changes were (mean, 95% CI): RV/RA -4.8 (-7.7 to -1.8) mmHg, Q 0.13 (-0.3 to 0.6) l/min and SpO2 1 (-1 to 2) %. CONCLUSIONS: In lowlanders with COPD travelling to 3100m preventive dexamethasone treatment mitigates the altitude-induced rise in RV/RA potentially along with a reduced pulmonary vascular resistance and improved oxygenation.

Liu, N., Y. Li, et al. (2019). **"Effects of exercise-induced dyspnoea on the aspiration rate among patients with acute exacerbation of chronic obstructive pulmonary disease."** Clin Respir J **13**(7): 446-452.

PURPOSE: To use radionuclide imaging to investigate silent aspiration among patients recovering from an acute exacerbation of chronic obstructive pulmonary disease (AECOPD). We also evaluated the effects of exercise-induced dyspnoea on silent aspiration in COPD patients. PATIENTS AND METHODS: Recovering AECOPD patients admitted to the First Affiliated Hospital of Guangzhou Medical University between December 2013 and December 2015 were selected for the radionuclide aspiration test along with healthy volunteers of similar age. Aspiration-negative AECOPD patients were randomized into two subgroups. Patients in group A performed symptom-limited incremental cycle exercise test. Patients in group B were resting on the exercise bicycles. Aspiration-negative healthy volunteers performed symptom-limited incremental cycle exercise test (group C). Three groups performed a radionuclide aspiration test 30 min after exercise. RESULTS: The silent aspiration rates among recovering AECOPD patients and healthy volunteers were 44.19% (57/129) and 0 (0/18) (P = 0.00). The aspiration rates in groups A and B were 33.33% (10/30) and 23.33% (7/30), (P = 0.39) and groups A and C were 33.33% (10/30) and 0% (0/12), (P = 0.04). CONCLUSION: Recovering AECOPD patients had significantly higher silent aspiration rates than healthy volunteers of similar age. The evidence is not strong enough to support the patients with exercise-induced dyspnoea-increased aspiration rate.

Mehta, R., E. Pefani, et al. (2018). **"Population Pharmacokinetic Analysis of Fluticasone Furoate/Umeclidinium/Vilanterol via a Single Inhaler in Patients with COPD."** J Clin Pharmacol **58**(11): 1461-1467.

A population pharmacokinetic analysis was conducted from a subset of samples obtained from the Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy trial to characterize the pharmacokinetics of fluticasone furoate, umeclidinium, and vilanterol in patients with symptomatic COPD following treatment with fluticason furoate-umeclidinium-vilanterol combined in a single inhaler. This was a randomized, double-blind, double-dummy study comparing 24 weeks of once-daily triple therapy (fluticason furoate-umeclidinium-vilanterol, 100 mug/62.5 mug/25 mug; Ellipta inhaler) with twice-daily dual therapy (budesonide/formoterol 400 mug/12 mug; Turbuhaler). The analyses were conducted in a subset of 74 patients who received fluticason furoate-umeclidinium-vilanterol and provided serial or sparse samples. Monte Carlo simulations and a model-based estimation approach both indicated that systemic drug concentrations of fluticasone furoate, umeclidinium, and vilanterol after administration of fluticason furoate-umeclidinium-vilanterol triple combination therapy from a single inhaler were within the ranges observed following administration of these drugs as monotherapy (fluticasone furoate, umeclidinium, and vilanterol) or as dual-combination therapy (fluticasone furoate/vilanterol or umeclidinium/vilanterol).

Mountain, J. E., P. Santer, et al. (2018). **"Potential for noninvasive assessment of lung inhomogeneity using highly precise, highly time-resolved measurements of gas exchange."** J Appl Physiol (1985) **124**(3): 615-631.

Inhomogeneity in the lung impairs gas exchange and can be an early marker of lung disease. We hypothesized that highly precise measurements of gas exchange contain sufficient information to quantify many aspects of the inhomogeneity noninvasively. Our aim was to explore whether one parameterization of lung inhomogeneity could both fit such data and provide reliable parameter estimates. A mathematical model of gas exchange in an inhomogeneous lung was developed, containing inhomogeneity parameters for compliance, vascular conductance, and dead space, all relative to lung volume. Inputs were respiratory flow, cardiac output, and the inspiratory and pulmonary arterial gas compositions. Outputs were expiratory and pulmonary venous gas compositions. All values were specified every 10 ms. Some parameters were set to physiologically plausible values. To estimate the remaining unknown parameters and inputs, the model was embedded within a nonlinear estimation routine to minimize the deviations between model and data for CO2, O2, and N2 flows during expiration. Three groups, each of six individuals, were studied: young (20-30 yr); old (70-80 yr); and patients with mild to moderate chronic obstructive pulmonary disease (COPD). Each participant undertook a 15-min measurement protocol six times. For all parameters reflecting inhomogeneity, highly significant differences were found between the three participant groups (P < 0.001, ANOVA). Intraclass correlation coefficients were 0.96, 0.99, and 0.94 for the parameters reflecting inhomogeneity in deadspace, compliance, and vascular conductance, respectively. We conclude that, for the particular participants selected, highly repeatable estimates for parameters reflecting inhomogeneity could be obtained from noninvasive measurements of respiratory gas exchange. NEW & NOTEWORTHY This study describes a new method, based on highly precise

measures of gas exchange, that quantifies three distributions that are intrinsic to the lung. These distributions represent three fundamentally different types of inhomogeneity that together give rise to ventilation-perfusion mismatch and result in impaired gas exchange. The measurement technique has potentially broad clinical applicability because it is simple for both patient and operator, it does not involve ionizing radiation, and it is completely noninvasive.

Nelsen, L. M., L. A. Lee, et al. (2019). **"Reliability, validity and responsiveness of E-RS:COPD in patients with spirometric asthma-COPD overlap."** Respir Res **20**(1): 107.

BACKGROUND: The Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease (E-RS:COPD) is a patient-reported diary that assesses respiratory symptoms in stable COPD. METHODS: This post hoc analysis of a randomized, double-blind, parallel-arm trial (GSK ID: 200699; NCT02164539) assessed the structure, reliability, validity and responsiveness of the E-RS, and a separate wheeze item, for use in patients with a primary diagnosis of asthma or COPD, but with spirometric characteristics of both (fixed airflow obstruction and reversibility to salbutamol; a subset of patients referred to as spirometric asthma-COPD overlap [ACO]; N = 338). RESULTS: Factor analysis demonstrated that E-RS included Cough and Sputum, Chest Symptoms, and Breathlessness domains, with a Total score suitable for quantifying overall respiratory symptoms (comparative fit index: 0.9), consistent with the structure shown in COPD. The wheeze item did not fit the model. Total and domain scores were internally consistent (Cronbach's alpha: 0.7-0.9) and reproducible (intra-class correlations > 0.7). Moderate correlations between RS-Total and RS-Breathlessness scores were observed with St George's Respiratory Questionnaire (SGRQ) Total and Activity domain scores at baseline (r = 0.43 and r = 0.48, respectively). E-RS scores were sensitive to change when a patient global impression of change and SGRQ change scores were used to define responders, with changes of >/= - 1.4 in RS-Total score interpreted as clinically meaningful. CONCLUSIONS: E-RS:COPD scores were reliable, valid and responsive in this sample, suggesting the measure may be suitable for evaluating the severity of respiratory symptoms and the effects of treatment in patients with asthma and COPD that exhibit spirometric characteristics of both fixed airflow obstruction and reversibility. Further study of this instrument and wheeze in new samples of patients with ACO is warranted.

Osman, K. L., J. M. C. Jefferies, et al. (2018). **"Patients with Chronic Obstructive Pulmonary Disease harbour a variation of Haemophilus species."** Sci Rep **8**(1): 14734.

H. haemolyticus is often misidentified as NTHi due to their close phylogenetic relationship. Differentiating between the two is important for correct identification and appropriate treatment of infective organism and to ensure any role of H. haemolyticus in disease is not being overlooked. Speciation however is not completely reliable by culture and PCR methods due to the loss of haemolysis by H. haemolyticus and the heterogeneity of NTHi. Haemophilus isolates from COPD as part of the AERIS study (ClinicalTrials - NCT01360398) were speciated by analysing sequence data for the presence of molecular markers. Further investigation into the genomic relationship was carried out using average nucleotide identity and phylogeny of allelic and genome alignments. Only 6.3% were identified as H. haemolyticus. Multiple in silico methods were able to distinguish H. haemolyticus from NTHi. However, no single gene target was found to be 100% accurate. A group of omp2 negative NTHi were observed to be phylogenetically divergent from H. haemolyticus and remaining NTHi. The presence of an atypical group from a geographically and disease limited set of isolates supports the theory that the heterogeneity of NTHi may provide a genetic continuum between NTHi and H. haemolyticus.

Phillips, D. B., C. D. Steinback, et al. (2018). **"The carotid chemoreceptor contributes to the elevated arterial stiffness and vasoconstrictor outflow in chronic obstructive pulmonary disease."** J Physiol **596**(15): 3233-3244.

KEY POINTS: The reason(s) for the increased central arterial stiffness in chronic obstructive pulmonary disease (COPD) are not well understood. In this study, we inhibited the carotid chemoreceptor with both low-dose dopamine and hyperoxia, and observed a decrease in central arterial stiffness and muscle sympathetic nervous activity in COPD patients, while no change was observed in age- and risk-matched controls. Carotid chemoreceptor inhibition increased vascular conductance, secondary to reduced arterial blood pressure in COPD patients. Findings from the current study suggest that elevated carotid chemoreceptor activity may contribute to the increased arterial stiffness typically observed in COPD patients. ABSTRACT: Chronic obstructive pulmonary disease (COPD) patients have increased central arterial stiffness and muscle sympathetic nervous activity (MSNA), both of which contribute to cardiovascular (CV) dysfunction and increased CV risk. Previous work suggests that COPD patients have

elevated carotid chemoreceptor (CC) activity/sensitivity, which may contribute to the elevated MSNA and arterial stiffness. Accordingly, the effect of CC inhibition on central arterial stiffness, MSNA and CV function at rest in COPD patients was examined in a randomized placebo-controlled study. Thirteen mild-moderate COPD patients (forced expired volume in 1 s (FEV1) predicted +/- SD: 83 +/- 18%) and 13 age- and risk-matched controls completed resting CV function measurements with either i.v. saline or i.v. dopamine (2 mug kg(-1) min(-1)) while breathing normoxic or hyperoxic air (100% O2). On a separate day, a subset of COPD patients and controls completed MSNA measurements while breathing normoxic or hyperoxic air. Arterial stiffness was determined by pulse-wave velocity (PWV) and MSNA was measured by microneurography. Brachial blood flow was determined using Doppler ultrasound, cardiac output was estimated by impedance cardiography, and vascular conductance was calculated as flow/mean arterial pressure (MAP). CC inhibition with dopamine decreased central and peripheral PWV, and MAP ($P < 0.05$) while increasing vascular conductance in COPD. No change in CV function was observed with dopamine in controls. CC inhibition with hyperoxia decreased peripheral PWV and MSNA ($P < 0.05$) in COPD, while no change was observed in controls. CC inhibition decreased PWV and MSNA, and improved vascular conductance in COPD, suggesting that tonic CC activity is elevated at rest and contributes to the elevated arterial stiffness in COPD.

Plaza, V., J. Giner, et al. (2018). **"Errors in the Use of Inhalers by Health Care Professionals: A Systematic Review."** J Allergy Clin Immunol Pract **6**(3): 987-995.

BACKGROUND: Inefficient inhaler technique (IT) compromises the optimal delivery of medication. However, the IT knowledge of health care professionals (HCPs) has received scant attention. OBJECTIVE: The objective of this study was to perform a systematic review of published reports assessing the IT proficiency of HCPs in using pressurized metered dose (pMDI) and dry powder (DPI) inhalers. METHODS: Studies published between 1975 and 2014 that directly assessed the IT skills of HCPs were selected according to predefined selection criteria. RESULTS: Data were extracted from 55 studies involving 6,304 HCPs who performed 9,996 tests to demonstrate their IT proficiency. Overall, the IT was considered correct in 15.5% of cases (95% confidence interval [CI], 12-19.3), decreasing over time from 20.5% (95% CI, 14.9-26.8) from the early period (defined as 1975-1995) to 10.8% (95% CI, 7.3-14.8) during the late period (1996-2014). The most common errors in the use of pMDIs were as follows: not breathing out completely before inhalation (75%; 95% CI, 56-90), lack of coordination (64%; 95% CI, 29-92), and postinhalation breath-hold (63%; 95% CI, 52-72). The most common errors using DPI were deficient preparation (89%; 95% CI, 82-95), not breathing out completely before inhalation (79%; 95% CI, 68-87), and no breath-hold (76%; 95% CI, 67-84). CONCLUSIONS: HCPs demonstrated inadequate knowledge of the proper use of inhalers. The poor understanding of the correct use of these devices may prevent these professionals from being able to adequately assess and teach proper inhalation techniques to their patients.

Polkey, M. I., J. Praestgaard, et al. (2019). **"Activin Type II Receptor Blockade for Treatment of Muscle Depletion in Chronic Obstructive Pulmonary Disease. A Randomized Trial."** Am J Respir Crit Care Med **199**(3): 313-320.

RATIONALE: Bimagrumab is a fully human monoclonal antibody that blocks the activin type II receptors, preventing the activity of myostatin and other negative skeletal muscle regulators. OBJECTIVES: To assess the effects of bimagrumab on skeletal muscle mass and function in patients with chronic obstructive pulmonary disease (COPD) and reduced skeletal muscle mass. METHODS: Sixty-seven patients with COPD (mean FEV1, 1.05 L [41.6% predicted]; aged 40-80 yr; body mass index < 20 kg/m(2) or appendicular skeletal muscle mass index </= 7.25 [men] and </= 5.67 [women] kg/m(2)), received two doses of either bimagrumab 30 mg/kg intravenously (n = 33) or placebo (n = 34) (Weeks 0 and 8) over 24 weeks. MEASUREMENTS AND MAIN RESULTS: We assessed changes in thigh muscle volume (cubic centimeters) as the primary endpoint along with 6-minute-walk distance (meters), safety, and tolerability. Fifty-five (82.1%) patients completed the study. Thigh muscle volume increased by Week 4 and remained increased at Week 24 in bimagrumab-treated patients, whereas no changes were observed with placebo (Week 4: +5.9% [SD, 3.4%] vs. 0.0% [3.3%], $P < 0.001$; Week 8: +7.0% [3.7%] vs. -0.7% [2.8%], $P < 0.001$; Week 16: +7.8% [5.1%] vs. -0.9% [4.5%], $P < 0.001$; Week 24: +5.0% [4.9%] vs. -1.3% [4.3%], $P < 0.001$). Over 24 weeks, 6-minute-walk distance did not increase significantly in either group. Adverse events in the bimagrumab group included muscle-related symptoms, diarrhea, and acne, most of which were mild in severity. CONCLUSIONS: Blocking the action of negative muscle regulators through the activin type II receptors with bimagrumab treatment safely increased skeletal muscle mass

but did not improve functional capacity in patients with COPD and low muscle mass. Clinical trial registered with www.clinicaltrials.gov (NCT01669174).

Reeves, E. P., D. M. Dunlea, et al. (2019). **"Circulating Truncated Alpha-1 Antitrypsin Glycoprotein in Patient Plasma Retains Anti-Inflammatory Capacity."** J Immunol **202**(8): 2240-2253.

Alpha-1 antitrypsin (AAT) is an acute phase protein that possesses immune-regulatory and anti-inflammatory functions independent of antiprotease activity. AAT deficiency (AATD) is associated with early-onset emphysema and chronic obstructive pulmonary disease. Of interest are the AATD nonsense mutations (termed null or Q0), the majority of which arise from premature termination codons in the mRNA coding region. We have recently demonstrated that plasma from an AATD patient homozygous for the Null Bolton allele (Q0bolton) contains AAT protein of truncated size. Although the potential to alleviate the phenotypic consequences of AATD by increasing levels of truncated protein holds therapeutic promise, protein functionality is key. The goal of this study was to evaluate the structural features and anti-inflammatory capacity of Q0bolton-AAT. A low-abundance, truncated AAT protein was confirmed in plasma of a Q0bolton-AATD patient and was secreted by patient-derived induced pluripotent stem cell-hepatic cells. Functional assays confirmed the ability of purified Q0bolton-AAT protein to bind neutrophil elastase and to inhibit protease activity. Q0bolton-AAT bound IL-8 and leukotriene B4, comparable to healthy control M-AAT, and significantly decreased leukotriene B4-induced neutrophil adhesion ($p = 0.04$). Through a mechanism involving increased mRNA stability ($p = 0.007$), ataluren treatment of HEK-293 significantly increased Q0bolton-AAT mRNA expression ($p = 0.03$) and Q0bolton-AAT truncated protein secretion ($p = 0.04$). Results support the rationale for treatment with pharmacological agents that augment levels of functional Q0bolton-AAT protein, thus offering a potential therapeutic option for AATD patients with rare mutations of similar theratype.

Reychler, G., W. Poncin, et al. (2019). **"Efficacy of yoga, tai chi and qi gong on the main symptoms of chronic obstructive pulmonary disease: A systematic review."** Respir Med Res **75**: 13-25.

INTRODUCTION: The aim of this systematic review was to summarize the effects of yoga, qi gong or tai chi in COPD patients. METHODS: Studies evaluating effects of the selected complementary therapies on lung function, dyspnea, quality of life or functional exercise capacity in COPD patients were identified and reviewed from three databases. RESULTS: Eighteen studies were included. Six studies evaluated the effects of yoga and the others focused on tai chi or qi gong separately or combined. The duration of the programs ranged from 6 weeks to 6 months and the frequency from 2 to 7 times a week. Each session reached 30 to 90 minutes. Benefits were observed on lung function and functional exercise capacity but benefit was clearly stated neither on quality of life nor on dyspnea. CONCLUSION: This systematic review

Rodrigues, F. M., H. Demeyer, et al. (2019). **"Health status deterioration in subjects with mild to moderate airflow obstruction, a six years observational study."** Respir Res **20**(1): 93.

BACKGROUND: Patients with COPD need to cope with a disabling disease, which leads to health status impairment. AIM: To investigate the long term change of health status in subjects with mild to moderate airflow obstruction and to compare this to subjects without airflow obstruction, with and without a smoking history. Second, to investigate the factors potentially associated to rapid health status decline in our total cohort. METHODS: Two hundred and one subjects were included. Generic [Short form 36 health survey (SF36) and EuroQol - 5 dimensions (EQ-5D)] and disease specific [Clinical COPD questionnaire (CCQ) and COPD Assessment Test (CAT)] health status questionnaires were regularly repeated over a six years period. Other functional outcomes comprised measures of lung function, physical fitness, physical activity and emotional state. RESULTS: On average, health status decline did not differ between groups with the exception of the EQ-5D index, which deteriorated faster in subjects with airflow obstruction compared to the never smoking control group [- 0.018(0.008) versus 0.00006(0.003), $p = 0.03$]. Subjects presenting at least one exacerbation had faster rate of deterioration measured with CAT [0.91(0.21) versus - 0.26(0.25), $p < 0.01$]. Characteristics of the fast declining group were older age, worse lung function, physical fitness, physical activity and disease specific baseline health status. Subjects with airflow obstruction had a 2.5 (95% CI 1.36-4.71) higher risk of presenting fast overall health status decline. Fast overall decline was associated with the presence of acute exacerbation(s) (44% of the subjects with exacerbation(s) versus 17% of subjects without exacerbation, $p = 0.03$). Changes in fat free mass, functional exercise capacity and in symptoms of anxiety and depression correlated weakly to changes in health status measured with all questionnaires. CONCLUSION: Subjects with mild airflow obstruction present a significant deterioration of health status, which is generally not much faster compared to smoking and never smoking controls. Subjects with fast decline in overall health status are

older and more likely to have airflow obstruction, acute respiratory exacerbation(s), reduced physical fitness, physical activity and impaired COPD specific health status at baseline. TRIAL REGISTRATION: NCT01314807 - retrospectively registered on March 2011.

Roth, M., L. Fang, et al. (2019). **"Pelargonium sidoides radix extract EPs 7630 reduces rhinovirus infection through modulation of viral binding proteins on human bronchial epithelial cells."** PLoS One **14**(2): e0210702.

Bronchial epithelial cells are the first target cell for rhinovirus infection. The course of viral infections in patients with acute bronchitis, asthma and COPD can be improved by oral application of Pelargonium sidoides radix extract; however, the mechanism is not well understood. This study investigated the in vitro effect of Pelargonium sidoides radix extract (EPs 7630) on the expression of virus binding cell membrane and host defence supporting proteins on primary human bronchial epithelial cells (hBEC). Cells were isolated from patients with severe asthma (n = 6), moderate COPD (n = 6) and non-diseased controls (n = 6). Protein expression was determined by Western-blot and immunofluorescence. Rhinovirus infection was determined by immunofluorescence as well as by polymerase chain reaction. Cell survival was determined by manual cell count after live/death immunofluorescence staining. All parameters were determined over a period of 3 days. The results show that EPs 7630 concentration-dependently and significantly increased hBEC survival after rhinovirus infection. This effect was paralleled by decreased expression of the inducible co-stimulator (ICOS), its ligand ICOSL and cell surface calreticulin (C1qR). In contrast, EPs 7630 up-regulated the expression of the host defence supporting proteins beta-defensin-1 and SOCS-1, both in rhinovirus infected and un-infected hBEC. The expression of other virus interacting cell membrane proteins such as MyD88, TRL2/4 or ICAM-1 was not altered by EPs 7630. The results indicate that EPs 7630 may reduce rhinovirus infection of human primary BEC by down-regulating cell membrane docking proteins and up-regulating host defence proteins.

Sakornsakolpat, P., M. McCormack, et al. (2019). **"Genome-Wide Association Analysis of Single-Breath DlCO."** Am J Respir Cell Mol Biol **60**(5): 523-531.

DlCO is a widely used pulmonary function test in clinical practice and a particularly useful measure for assessing patients with chronic obstructive pulmonary disease (COPD). We hypothesized that elucidating genetic determinants of DlCO could lead to better understanding of the genetic architecture of COPD. We estimated the heritability of DlCO using common genetic variants and performed genome-wide association analyses in four cohorts enriched for subjects with COPD (COPDGene [Genetic Epidemiology of COPD], NETT [National Emphysema Treatment Trial], GenKOLS [Genetics of Chronic Obstructive Lung Disease study], and TESRA [Treatment of Emphysema With a Gamma-Selective Retinoid Agonist study]) using a combined European ancestry white dataset and a COPDGene African American dataset. We assessed our genome-wide significant and suggestive associations for DlCO in previously reported genome-wide association studies of COPD and related traits. We also characterized associations of known COPD-associated variants and DlCO. We estimated the SNP-based heritability of DlCO in the European ancestry white population to be 22% (P = 0.0004). We identified three genome-wide significant associations with DlCO: variants near TGFB2, CHRNA3, and PDE11A loci (P < 5 x 10(-8)). In addition, 12 loci were suggestively associated with DlCO in European ancestry white (P < 1 x 10(-5) in the combined analysis and P < 0.05 in both COPDGene and GenKOLS), including variants near NEGR1, CADM2, PCDH7, RETREG1, DACT2, NRG1, ANKRD18A, KRT86, NTN4, ARHGAP28, INSR, and PCBP3. Some DlCO-associated variants were also associated with COPD, emphysema, and/or spirometric values. Among 25 previously reported COPD loci, TGFB2, CHRNA3/CHRNA5, FAM13A, DSP, and CYP2A6 were associated with DlCO (P < 0.001). We identified several genetic loci that were significantly associated with DlCO and characterized effects of known COPD-associated loci on DlCO. These results could lead to better understanding of the heterogeneous nature of COPD.

Schwarz, E. I., T. D. Latshang, et al. (2019). **"Blood pressure response to exposure to moderate altitude in patients with COPD."** Int J Chron Obstruct Pulmon Dis **14**: 659-666.

Purpose: Patients with COPD might be particularly susceptible to hypoxia-induced autonomic dysregulation. Decreased baroreflex sensitivity (BRS) and increased blood pressure (BP) variability (BPV) are markers of impaired cardiovascular autonomic regulation and there is evidence for an association between decreased BRS/increased BPV and high cardiovascular risk. The aim of this study was to evaluate the effect of short-term exposure to moderate altitude on BP and measures of cardiovascular autonomic regulation in COPD patients. Materials and methods: Continuous morning beat-to-beat BP was noninvasively measured with a Finometer((R)) device for 10 minutes at low altitude (490 m, Zurich,

Switzerland) and for 2 days at moderate altitude (2,590 m, Davos Jakobshorn, Switzerland) - the order of altitude exposure was randomized. Outcomes of interest were mean SBP and DBP, BPV expressed as the coefficient of variation (CV), and spontaneous BRS. Changes between low altitude and day 1 and day 2 at moderate altitude were assessed by ANOVA for repeated measurements with Fisher's exact test analysis. Results: Thirty-seven patients with moderate to severe COPD (mean+/-SD age 64+/-6 years, FEV1 60%+/-17%) were included. Morning SBP increased by +10.8 mmHg (95% CI: 4.7-17.0, P=0.001) and morning DBP by +5.0 mmHg (95% CI: 0.8-9.3, P=0.02) in response to altitude exposure. BRS significantly decreased (P=0.03), whereas BPV significantly and progressively increased (P<0.001) upon exposure to altitude. Conclusion: Exposure of COPD patients to moderate altitude is associated with a clinically relevant increase in BP, which seems to be related to autonomic dysregulation. Clinical trial registration: ClinicalTrials.gov (NCT01875133).

Sethi, S., E. Kerwin, et al. (2019). **"AMPLIFY: a randomized, Phase III study evaluating the efficacy and safety of aclidinium/formoterol vs monocomponents and tiotropium in patients with moderate-to-very severe symptomatic COPD."** Int J Chron Obstruct Pulmon Dis **14**: 667-682.

Background: AMPLIFY assessed the efficacy and safety of aclidinium bromide/formoterol fumarate (AB/FF) vs its monocomponents and tiotropium (TIO) in patients with moderate-to-very severe symptomatic COPD (NCT02796677). Methods: In this 24-week, Phase III, double-dummy, active-controlled study, symptomatic patients (COPD Assessment Test score >/=10) were randomized to twice-daily AB/FF 400/12 microg, AB 400 microg, or FF 12 microg, or once-daily TIO 18 microg. Co-primary endpoints were change from baseline at week 24 in 1-hour morning post-dose FEV1 (AB/FF vs AB) and in pre-dose (trough) FEV1 (AB/FF vs FF). Non-inferiority of AB vs TIO in pre-dose FEV1 was also an objective. Normalized area under the curve (AUC)0-3/3 h FEV1 and nighttime and early morning symptoms were also assessed. A subgroup participated in a 24-hour serial spirometry sub-study. Results: A total of 1,594 patients were randomized; 566 entered the sub-study. At week 24, 1-hour post-dose FEV1 significantly improved with AB/FF vs AB, FF, and TIO (84, 84, and 92 mL; all P<0.0001). AB/FF significantly improved trough FEV1 vs FF (55 mL, P<0.001) and AB was non-inferior to TIO. AB/FF significantly improved AUC0-3/3 h FEV1 vs all comparators (P<0.0001) and provided significant improvements in early morning symptoms vs TIO. The 24-hour spirometry demonstrated significantly greater improvements with AB/FF in AUC12-24/12 h vs all comparators, and in AUC0-24/24 h vs FF or TIO at week 24. Conclusion: In patients with moderate-to-very severe symptomatic COPD, twice-daily AB/FF significantly improved lung function vs monocomponents and TIO, and early morning symptom control vs TIO.

Sun, X. J. and Z. Y. He (2019). **"Macrolides for treatment of chronic obstructive pulmonary disease."** Chin Med J (Engl) **132**(11): 1261-1263.

Takeuchi, K., K. Matsumoto, et al. (2018). **"Periodontal status and lung function decline in the community: the Hisayama study."** Sci Rep **8**(1): 13354.

This study aimed to determine whether periodontal status is related to a decline in lung function in a general Japanese population. We followed a total of 1,650 community-dwelling individuals (>/=40 years) without chronic obstructive pulmonary disease, with at least one teeth, for 3 years. Periodontal status was assessed at baseline by clinical attachment loss (CAL) and probing pocket depth (PPD) at two sites for each tooth, and the mean values were calculated for each subject. Lung function was measured at baseline and follow-up using spirometry, and longitudinal decline in forced expiratory volume in one second (FEV1) was calculated. Multivariate Poisson regression with robust error variance was used to estimate risk ratio (RR). After adjusting for potential confounders including smoking status, there was a tendency for the adjusted RR of developing rapid lung function decline (>/=160 mL/3years, the highest quartile of the distribution of FEV1 declines) to increase as mean CAL levels increased (P trend = 0.039). Likewise, a positive association was observed between mean PPD levels and RR of developing rapid lung function decline (P trend = 0.047). Our findings suggest deterioration of periodontal status could be a risk factor for rapid lung function decline in the general Japanese population.

Veil-Picard, M., T. Soumagne, et al. (2019). **"Is atopy a risk indicator of chronic obstructive pulmonary disease in dairy farmers?"** Respir Res **20**(1): 124.

Allergic mechanisms related to environmental and occupational exposure have been suggested to contribute to the development of chronic obstructive pulmonary disease (COPD). OBJECTIVES: To investigate the relationships between atopy markers, persistent airflow limitation (PAL) and occupational exposure in dairy farmers. METHODS: Clinical and biological (total IgE and 21 allergen specific IgE) markers of atopy were assessed in 101 dairy farmers with PAL (DF-PAL), 85 non-farmers with PAL (NF-PAL) (both groups were prospectively included from a screening program performed between 2011 and 2015), and matched controls, i.e. 98 farmers without PAL (DF-controls) and 89 non-farming subjects without PAL (NF-controls). Occupational exposure in farmers was estimated using a validated questionnaire. RESULTS: Prevalence of allergy history was significantly higher in DF-PAL and in NF-PAL than in controls. Polysensitization, and sensitization to seasonal and food allergens were more frequent in DF-PAL than in DF-controls, respectively: 13.8% vs 1% (adjusted odds ratio (aOR): 17.5 (2.2-134), 11.9% vs 3.1% (aOR: 4.4 (1.2-7.2) and 16.8% vs 4.1% (aOR: 5.2 (1.7-7.2)). The prevalence of atopy markers was similar between NF-PAL patients and NF-controls. CONCLUSIONS: PAL in farmers is associated with a high rate of markers of atopy, supporting atopy as a risk indicator. Clinical trial registered with ClinicalTrials.gov (NCT02540408).

Vogel-Claussen, J., C. O. Schonfeld, et al. (2019). **"Effect of Indacaterol/Glycopyrronium on Pulmonary Perfusion and Ventilation in Hyperinflated Patients with Chronic Obstructive Pulmonary Disease (CLAIM). A Double-Blind, Randomized, Crossover Trial."** Am J Respir Crit Care Med **199**(9): 1086-1096.

Rationale: In the CLAIM study, dual bronchodilation with indacaterol/glycopyrronium (IND/GLY) significantly reduced hyperinflation, which translated into improved cardiac function, measured by left ventricular end-diastolic volume and cardiac output. Pulmonary microvascular blood flow (PMBF) is reduced in chronic obstructive pulmonary disease (COPD); however, the effect of reduced lung hyperinflation on PMBF remains unknown. Objectives: To determine the effect of lung deflation with IND/GLY on PMBF and regional pulmonary ventilation using magnetic resonance imaging (MRI) in hyperinflated patients with COPD. Methods: In this double-blind, randomized, two-period crossover study, gadolinium-enhanced MRI and phase-resolved functional lung MRI were used to measure PMBF and regional ventilation, respectively, in patients with COPD receiving IND/GLY versus placebo. Measurements and Main Results: Sixty-two patients were randomized to receive once-daily IND/GLY (110/50 mug) for 14 days, followed by 14 days of placebo, or vice versa. Treatment periods were separated by a 14-day washout. Sixty patients were included in the per-protocol analysis. MRI measurements showed significant improvements in total PMBF ($P = 0.006$) and regional PMBF (P values for individual lobes were between 0.004 and 0.022) in response to IND/GLY versus placebo. Regional ventilation was also significantly improved with IND/GLY, as evidenced by a 12.4% increase versus placebo ($P = 0.011$), a 14.3% relative decrease in ventilation defect percentage of nonventilated/hypoventilated lung tissue (cutoff was defined as 0.075 regional ventilation; $P = 0.0002$), and a 15.7% reduction in the coefficient of variation of regional ventilation compared with placebo ($P < 0.0001$). Conclusions: Pharmacologic intervention with IND/GLY improves pulmonary microvascular blood flow and regional ventilation in patients with COPD with hyperinflation. Clinical trial registered with www.clinicaltrials.gov (NCT02442206).

Wu, J. J., H. R. Xu, et al. (2019). **"The characteristics of the frequent exacerbators with chronic bronchitis phenotype and the asthma-chronic obstructive pulmonary disease overlap syndrome phenotype in chronic obstructive pulmonary disease patients: A meta-analysis and system review."** Medicine (Baltimore) **98**(46): e17996.

To investigate the difference of clinical characteristics between chronic obstructive pulmonary disease (COPD) patients with the frequent exacerbators with chronic bronchitis (FE-CB) phenotype and those with the asthma-COPD overlap syndrome (ACO) phenotype.We searched CNKI, Wan Fang, Chongqing VIP, China Biology Medicine disc, PubMed, Cochrane Library, and EMBASE databases for studies published as of April 30, 2019. All studies that investigated COPD patients with the FE-CB and ACO phenotypes and which qualified the inclusion criteria were included. Cross-sectional/prevalence study quality recommendations were used to measure methodological quality. RevMan5.3 software was used for meta-analysis.Ten studies (combined n = 4568) qualified the inclusion criteria. The FE-CB phenotype of COPD was associated with significantly lower forced vital capacity percent predicted (mean difference [MD] -9.05, 95% confidence interval [CI] [-12.00, -6.10], $P < .001$, $I = 66\%$), forced expiratory volume in 1

second (FEV1) (MD -407.18, 95% CI [-438.63, -375.72], P < .001, I = 33%), forced expiratory volume in 1 second percent predicted (MD -9.71, 95% CI [-12.79, -6.63], P < .001, I = 87%), FEV1/forced vital capacity (MD -5.4, 95% CI [-6.49, -4.30], P < .001, I = 0%), and body mass index (BMI) (MD -0.81, 95% CI [-1.18, -0.45], P < .001, I = 44%) as compared to the ACO phenotype. However, FE-CB phenotype was associated with higher quantity of cigarettes smoked (pack-years) (MD 6.45, 95% CI [1.82, 11.09], P < .001, I = 73%), COPD assessment test score (CAT) (MD 4.04, 95% CI [3.46, 4.61], P < .001, I = 0%), mMRC score (MD 0.54, 95% CI [0.46, 0.62], P < .001, I = 34%), exacerbations in previous year (1.34, 95% CI [0.98, 1.71], P < .001, I = 68%), and BMI, obstruction, dyspnea, exacerbations (BODEx) (MD 1.59, 95% CI [1.00, 2.18], P < .001, I = 86%) as compared to the ACO phenotype.Compared with the ACO phenotype, COPD patients with the FE-CB phenotype had poorer pulmonary function, lower BMI, and higher CAT score, quantity of cigarettes smoked (pack-years), exacerbations in previous year, mMRC score, and BODEx.This study is an analysis of published literature, which belongs to the second study. Therefore, this study does not require the approval of the ethics committee. The findings will be disseminated through a peer-reviewed journal publication or conference presentation.

Yekefallah, L., M. A. Zohal, et al. (2019). **"Comparing the effects of upper limb and breathing exercises on six-minute walking distance among patients with chronic obstructive pulmonary disease: a three-group randomized controlled clinical trial."** Adv Respir Med **87**(2): 77-82.

INTRODUCTION: Physical exercise can improve patient outcomes and reduce hospitalization and mortality rates among subjects with chronic obstructive pulmonary disease. This study aimed to compare the effects of upper limb and breathing exercises on six-minute walking distance among these patients. MATERIAL AND METHODS: This three-group randomized controlled clinical trial was conducted in 2017-2018 in Velayat hospital, Qazvin, Iran. Seventy-five patients were purposively selected from the outpatient lung clinic of the hospital and randomly allocated to either the 25-patient groups of upper limb exercise, breathing exercise, or control. The patients in the first group were performing upper limb exercises thrice weekly for one month in the study setting. Their counterparts in the second group were doing pursed-lip and diaphragmatic breathing exercises four times daily for one month at their homes. However, the patients in the control group received no exercise intervention. Six-minute walk test was performed by each participant both before and after the study intervention. The SPSS for Windows program (v. 23.0) was used to analyze the data via the Chi-square test, the paired-sample t test, and the one-way analysis of variance. RESULTS: Before the intervention, the groups did not significantly differ from each other respecting six-minute walking distance. During the study, walking distance in the control group did not change significantly, while it remarkably increased in both the upper limb exercise and the breathing exercise groups ($p < 0.05$). After the intervention, walking distance in the upper limb exercise group was significantly greater than the breathing exercise group ($p < 0.05$) and the control group ($p < 0.05$); however, the difference between the breathing exercise and the control groups was not statistically significant ($p > 0.05$). CONCLUSION: Upper limb exercise is more effective than breathing exercise in increasing walking distance among patients with chronic obstructive pulmonary disease. Therefore, upper limb exercise can be used as a safe, simple, and inexpensive rehabilitation technique for these patients.

Yildiz, P., M. Bayraktaroglu, et al. (2019). **"Bronchodilator Efficacy of a Single-Dose 12/400-microg Formoterol/Budesonide Combination as a Dry Powder for Inhalation Delivered by Discair((R)) in Adult Patients with Moderate-to-Severe Stable COPD: Open-Label, Single-Arm, Phase IV Trial."** Clin Drug Investig **39**(10): 991-1001.

BACKGROUND AND OBJECTIVES: A patient-friendly and easy-to-use multi-dose dry powder inhaler, Discair((R)), has been recently developed. The objective of this study was to evaluate the bronchodilator efficacy of a single-dose 12/400-microg formoterol plus budesonide combination as a dry powder for inhalation delivered by Discair((R)) in adult patients with moderate-to-severe, stable, chronic obstructive pulmonary disease. METHODS: A total of 33 male patients with moderate-to-severe, chronic obstructive pulmonary disease were included in this single-arm, open-label, phase IV trial. The primary efficacy parameters were the average maximum change in forced expiratory volume in 1 s (FEV1, in L) and time to maximum FEV1 response. Absolute and percent change from baseline in FEV1 and forced vital capacity, maximum change and time to peak forced vital capacity response were also evaluated. RESULTS: The mean post-bronchodilator FEV1 maximum value was significantly higher than the pre-bronchodilator baseline FEV1 value [1.66 (standard deviation 0.43) vs. 1.32 (standard deviation 0.35), $p < 0.001$], with an absolute change of 0.34 (standard deviation 0.18) and a percent change of 26.0 (standard deviation 0.14) from baseline to maximum response. The average time to peak FEV1 response was 3.94 h (standard deviation

2.75), while the standardized area under the response-time curve from 0 to 12 h for FEV1 was 2.72 (standard deviation 1.84). The FEV1 and forced vital capacity values recorded at each time point during the 12-h post-bronchodilator period were also significantly higher than the baseline values ($p < 0.001$ for each). CONCLUSIONS: Our findings revealed significant changes from baseline in post-bronchodilator peak and average FEV1 and forced vital capacity responses, indicating bronchodilator efficacy of a single-dose 12/400 microg formoterol plus budesonide dry powder formulation delivered by Discair((R)) in patients with chronic obstructive pulmonary disease. TRIAL REGISTRATION: ClinicalTrials.gov Identifier NCT03028701.

Zhu, R., X. Xie, et al. (2019). **"The T helper type 17/regulatory T cell imbalance was associated with Ras-GTPase overexpression in patients with pulmonary hypertension associated with chronic obstructive pulmonary disease."** Immunology **157**(4): 304-311.

Pulmonary hypertension (PH) is a common but dangerous complication in chronic obstructive pulmonary disease (COPD). We hypothesized that dysregulation in the T helper type 17 (Th17) compartment could contribute to the development of COPD-associated PH (COPD-PH). To investigate this hypothesis, patients with COPD-PH and age- and sex-matched healthy controls were recruited, and their circulating CD4(+) T cells were activated using anti-CD3/CD28 antibodies. The frequency of interleukin-17 (IL-17) - secreting cells was significantly higher in COPD-PH patients than in healthy controls. The secretion of IL-17 was significantly higher from COPD-PH CD4(+) T cells than from control CD4(+) T cells, whereas the secretion of interferon-gamma and IL-4 was not significantly different. The expression of transforming growth factor-beta, on the other hand, was significantly higher in healthy controls than in COPD-PH patients. Activated CD4(+) T cells from COPD-PH patients also presented significantly lower forkhead box P3 (FOXP3) and higher retinoic acid receptor-related orphan C2 (RORC2) expression than CD4(+) T cells from healthy controls. In both controls and patients, a negative correlation between RORC2 and FOXP3 was found, ex vivo and after CD3/CD28 activation. The serum IL-6 level was slightly higher in COPD-PH patients than in controls, but the IL-6 transcription by monocytes was comparable in COPD-PH patients and controls. Interestingly, CD4(+) T cells from COPD-PH patients presented significantly higher levels of Kirsten rat sarcoma viral oncogene homolog and neuroblastoma RAS viral oncogene homolog than CD4(+) T cells from healthy controls. Inhibiting Ras-GTPases using farnesylthiosalicylic acid significantly reduced the ratio of RORC2/FOXP3 expression in CD4(+) T cells. Overall, we demonstrated that an imbalance of Th17/regulatory T cells was a hallmark of COPD-PH.

COPD/Emphysema PubMed search results covering the period 26/10/19 to 17/01/2020 Systematic reviews and clinical trials – In Process

(COPD[Title] OR Emphysema[Title] OR Chronic Obstructive Pulmonary Disease[Title] OR Chronic Bronchitis[Title]) AND (inprocess[sb] OR Publisher[sb]) AND ("meta-analysis"[All Fields] OR "meta-analyses"[All Fields] OR "randomised"[All] OR "random"[All Fields]) AND English[lang]

Ahrman, E., O. Hallgren, et al. (2018). **"Quantitative proteomic characterization of the lung extracellular matrix in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis."** J Proteomics **189**: 23-33.

Remodeling of the extracellular matrix (ECM) is a common feature in lung diseases such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). Here, we applied a sequential tissue extraction strategy to describe disease-specific remodeling of human lung tissue in disease, using end-stages of COPD and IPF. Our strategy was based on quantitative comparison of the disease proteomes, with specific focus on the matrisome, using data-independent acquisition and targeted data analysis (SWATH-MS). Our work provides an in-depth proteomic characterization of human lung tissue during impaired tissue remodeling. In addition, we show important quantitative and qualitative effects of the solubility of matrisome proteins. COPD was characterized by a disease-specific increase in ECM regulators, metalloproteinase inhibitor 3 (TIMP3) and matrix metalloproteinase 28 (MMP-28), whereas for IPF, impairment in cell adhesion proteins, such as collagen VI and laminins, was most prominent. For both diseases, we identified increased levels of proteins involved in the regulation of endopeptidase activity, with several proteins belonging to the serpin family. The established human lung quantitative proteome inventory and the construction of a tissue-specific protein assay library provides a resource for future quantitative proteomic analyses of human lung tissues. SIGNIFICANCE: We present a sequential

tissue extraction strategy to determine changes in extractability of matrisome proteins in end-stage COPD and IPF compared to healthy control tissue. Extensive quantitative analysis of the proteome changes of the disease states revealed altered solubility of matrisome proteins involved in ECM regulators and cell-ECM communication. The results highlight disease-specific remodeling mechanisms associated with COPD and IPF.

Ambrocio-Ortiz, E., G. Perez-Rubio, et al. (2018). **"Influence of proinflammatory cytokine gene polymorphisms on the risk of COPD and the levels of plasma protein."** Cytokine **111**: 364-370.

INTRODUCTION: Chronic obstructive pulmonary disease (COPD) is a complex and multifactorial disease involving systemic inflammation. Although certain genetic components have been implicated in the development and progression of this disease, few studies have examined the participation of polymorphisms in proinflammatory genes and the extent to which polymorphisms are related to plasma levels of cytokines involved in the inflammatory process. METHODS: Of the 1125 smokers participating in the study, 438 had COPD, and 687 did not. We determined the genotype of 5 SNPs distributed in the genes: IL6, CXL8, CSF2, CCL1 and IL1B. The plasma protein expression of these genes was also evaluated and categorized according to genotype and the severity of COPD (GOLD grade). RESULTS: An analysis using the codominant model showed an association between rs1818879 in IL6 and susceptibility to COPD (GA OR=1.1, AA OR=1.77; p<0.01), as well as an association between rs25882 in CSF2 and a greater severity of the disease (TC OR=1.84, CC OR=3.62; p<0.01). No association was found between the presence of certain alleles in the SNPs and the plasma levels of the corresponding proteins. CONCLUSIONS: There are genetic polymorphisms related to susceptibility to COPD (rs1818879/A in IL6), as well as to the risk of greater severity of the disease (rs25882/T in CSF2). The presence of the alleles of interest did not significantly affect plasma levels of the codified proteins.

Baarnes, C. B., B. H. Thuesen, et al. (2019). **"Determinants of airflow limitation in Danish adults - findings from the Health2006 cohort."** Int J Chron Obstruct Pulmon Dis **14**: 713-718.

Background and aim: Airflow limitation may be found in patients with both asthma and COPD and is often associated with more symptoms and poorer outcome. We aimed to identify factors associated with airflow limitation in a well-characterized, population-based sample of adults. Methods: From the Health2006 cohort, we selected participants aged >/=35 years at enrolment (n=2,959). Airflow limitation was defined as FEV1/FVC < lower limit of normal. Participants with (cases) and without (controls) airflow limitation were compared with regard to self-reported symptoms, medical history, atopy, lung function and exhaled nitric oxide. Between-group differences were analyzed using Chi-square and Mann-Whitney U tests, and effect size was estimated by logistic regression (reported as OR and 95% CI). Results: We identified 313 cases, majority of which were female, reported poor overall health, physically inactivity and experienced respiratory symptoms within the previous year. The presence of airflow limitation was associated with BMI (OR 3.1 for overweight, P<0.001, CI 1.97-4.78), age (OR 2.3, P<0.001 for age 55+, CI 1.7-3.2), tobacco exposure (OR 1.6, P=0.01, CI 1.1-2.32, and OR 1.76, P=0.019, CI 1.2-2.3 for former and current smokers, respectively), sex (OR 1.6 for being female, P=0.002, CI 1.2-2.2), presence of specific IgE to common aeroallergen(s) (OR 1.4, P=0.041, CI 1.2-2.0), and ever being diagnosed with asthma (OR 1.6, P=0.003, CI 1.3-2.0). Conclusion: Apart from tobacco exposure and age, the presence of airflow limitation was associated with being overweight, female, sensitized to common aeroallergens or ever having a diagnosis of asthma.

Ballmer, T., T. Helle, et al. (2019). **"Test-retest and inter-rater reliability of the Danish version of the management of everday technology assessment for use with older adults with and without COPD."** Scand J Occup Ther **26**(6): 463-474.

BACKGROUND: The trend towards telemedicine increasingly requires clients to manage everyday technology (ET) to access and use health services. The Management of Everday Technology Assessment (META) is an observation-based instrument developed to evaluate the ability to manage ET. AIM: To examine test-retest (TRR) and inter-rater reliability (IRR) of the Danish translation of the META for older adults with and without COPD. METHOD AND MATERIALS: 47 older adults with COPD (n = 23) and without (n = 24) were recruited. IRR was examined by four raters paired across 30 participants. TRR was examined for 21 participants by the same rater administering the META twice within four weeks. A rank-based method for paired ordinal data was used to calculate percentage agreement (PA) and measures of systematic disagreement and individual variability. Mann Whitney U tests were used to compare PA to health status (presence/absence of COPD). RESULTS: Inter-rater PA was acceptable across 10 of 11 items and test-retest PA across 8 of 11 items. Systematic disagreement was present for one item in TRR. No significant

differences in PA were found regarding health status. CONCLUSION: The Danish META generates reliable scores for this sample. However, conclusive statements cannot be made for all items.

Barberan-Garcia, A., P. A. Munoz, et al. (2019). **"Training-induced changes on quadriceps muscle oxygenation measured by near-infrared spectroscopy in healthy subjects and in chronic obstructive pulmonary disease patients."** Clin Physiol Funct Imaging **39**(4): 284-290.

AIM: We hypothesize that training-induced changes in muscle oxygen saturation (StO2) assessed by near-infrared spectroscopy (NIRS) during constant work rate cycling exercise (CWRE) may be a useful marker of the effects of training at 'vastus medialis' of the quadriceps in patients with chronic obstructive pulmonary disease (COPD). METHODS: Incremental exercise [peak oxygen uptake (VO2)] and CWRE at 70% pretraining peak VO2 , before and after 8-w training, were done in 10 healthy age-matched subjects (H) [80% men, 65(11) years, FEV1 105(14)%] and 16 COPD patients [94% men, 70(5) years, FEV1 46(11) %] encompassing the entire spectrum of disease severity, recruited in the outpatient clinics. NIRS was used to assess StO2 in the 'vastus medialis' of the left quadriceps. RESULTS: Pretraining CWRE decreased StO2 (P<0.05) and generated marked StO2 rebound (P<0.001) after unloading in the two groups. After training, VO2 peak increased in H [253(204) ml min(-1)] (P<0.01) and in COPD [180(183) ml.min(-1)] (P = 0.01) and blood lactate fell [-4.4 (2.7) and -1.6(2.3) mmol.m(-1)] (P<0.05 each). Training generated a further fall in StO2 during CWRE [-10(12)% and -10(10)%, P<0.05] and increased StO2 rebound after unloading [8(7)% and 5(9)%, P<0.05] in both groups. CONCLUSION: Endurance training further decreased StO2 during CWRE, similarly in both groups, likely due to training-induced enhancement of muscle O2 transfer and utilization. Training-induced StO2 fall during CWRE may be useful individual marker for non-invasive assessment of enhanced muscle aerobic post-training function.

Bon, J., Y. Zhang, et al. (2018). **"Radiographic Emphysema, Circulating Bone Biomarkers, and Progressive Bone Mineral Density Loss in Smokers."** Ann Am Thorac Soc **15**(5): 615-621.

RATIONALE: Osteoporosis is common in individuals with chronic obstructive pulmonary disease. Lung-specific factors, including radiographic emphysema, independently associate with low bone mineral density in cross-sectional smoking cohorts. However, factors associated with progressive bone loss in smokers are understudied and largely unknown. OBJECTIVES: To determine the relationship between radiographic emphysema, circulating bone metabolism markers, and pulmonary function and accelerated bone mineral density loss in smokers. METHODS: Two hundred and forty male and female current and former smokers, 40 years of age or older, underwent baseline and 2-year assessments of pulmonary function, computed tomography-assessed emphysema, dual X-ray absorptiometry-measured bone mineral density, and circulating bone metabolism biomarker levels (type I collagen C-telopeptide [CTX], amino-terminal propeptide of type I procollagen [P1NP]). The association of radiographic emphysema, bone metabolism biomarker levels, and pulmonary function with accelerated hip bone mineral density loss, defined by the 75th percentile of annual hip bone mineral density decline, was determined by logistic regression modeling with adjustment for age, sex, inhaled and intermittent steroid use, active smoking, body mass index, and the presence of baseline low hip bone mineral density. RESULTS: Of those participants with accelerated hip bone mineral density loss, 22% had moderate or severe visually assessed emphysema compared with 7.2% of smokers without accelerated bone mineral density decline. Moderate to severe visually assessed emphysema (odds ratio, 2.84; 95% confidence interval, 1.01-7.98 compared with trace/mild or no visually assessed emphysema) and the 75th percentile of CTX levels (odds ratio, 2.38; 95% confidence interval, 1.20-4.72 compared with CTX levels below the 75th percentile), a marker of bone resorption, were associated with accelerated hip bone mineral density decline after adjustment for covariates and the presence of baseline low hip bone mineral density. FEV1% predicted was not associated with accelerated bone mineral density decline after adjustment for covariates. Multivariate modeling showed moderate to severe visually assessed emphysema, and the 75th percentiles of CTX were independently associated with accelerated hip bone mineral density decline after adjustment for covariates. CONCLUSIONS: Emphysema and elevated markers of bone resorption are independently associated with progressive bone mineral density loss in smokers. These clinical markers may guide targeted bone mineral density screening and monitoring in smokers at highest risk.

Bonnevie, T., F. E. Gravier, et al. (2019). **"People undertaking pulmonary rehabilitation are willing and able to provide accurate data via a remote pulse oximetry system: a multicentre observational study."** J Physiother **65**(1): 28-36.

QUESTIONS: Can people referred to pulmonary rehabilitation easily learn to use a system for remote transmission of oximetry data? Do they consider remote transmission of oximetry data to be satisfactory? Are the transmitted data valid compared with locally stored data? DESIGN: Multicentre, prospective, observational study. PARTICIPANTS: One hundred and five adults with chronic respiratory disease who were referred to pulmonary rehabilitation. INTERVENTION: At an initial session, participants were taught to record and transmit their oximetry data to a remote server. At subsequent testing session(s), participants were requested to independently activate and use the oximetry monitoring system for a period of exercise on a cycle ergometer, until autonomy with the system was demonstrated. A subgroup of five participants undertook five 45-minute training sessions to generate a dataset to assess whether the transmitted data were valid compared with the locally stored data. OUTCOME MEASURES: Outcome measures included the number of sessions needed to become autonomous, participant satisfaction with the system, and measures of the validity of the transmitted data. RESULTS: Participants became autonomous quickly: 86% at the first testing session and 100% within three testing sessions. At least 98% of participants agreed that the system was easy to use and they would be willing to use it throughout pulmonary rehabilitation. The system transmitted usable data from 98% (95% CI 96 to 100) of sessions and introduced minimal artefact. Mean absolute differences were 0.365 beats/minute for heart rate and 0.133% for oxyhaemoglobin saturation. For heart rate, exact agreement was 72% (SD 9) and similar agreement (within 3 beats/minute) was 99% (SD 1). For oxyhaemoglobin saturation, exact agreement was 87% (SD 3) and similar agreement (within 3%) was 100% (SD 0). CONCLUSION: The telemonitoring system used in this study was sufficiently valid and acceptable for use in at-home pulmonary rehabilitation by people with chronic respiratory disease. STUDY REGISTRATION: ClinicalTrials.gov NCT03295474 and NCT03004716 (subgroup study).

Brigham, E. P., L. M. Steffen, et al. (2018). **"Diet Pattern and Respiratory Morbidity in the Atherosclerosis Risk in Communities Study."** Ann Am Thorac Soc **15**(6): 675-682.

RATIONALE: Dietary intake is a potential risk factor for respiratory morbidity in adult populations. Few studies capture the effect of dietary patterns, representative of the combination of nutrients consumed, on self-reported respiratory morbidity in combination with objective measures of lung function. OBJECTIVES: To evaluate patterns of dietary intake in relation to respiratory morbidity and objective measures of lung function in a U.S. POPULATION: METHODS: The ARIC (Atherosclerosis Risk in Communities) study investigators enrolled 15,792 participants from four U.S. communities between 1987 and 1989 and collected data using a validated food frequency questionnaire to assess diet. Principal component analysis was applied, and patterns representative of "Western" and "Prudent" diets emerged. We investigated cross-sectional associations between dietary patterns and pulmonary assessments that included asthma and chronic obstructive pulmonary disease (COPD) diagnosis, respiratory symptoms, and lung function. Multivariable Poisson regression models included quintiles of dietary patterns and potential confounders. Interaction of dietary patterns with obesity, sex, and smoking status was assessed in relation to all outcomes. RESULTS: Higher scores in the "Western" dietary pattern (quintile 5 vs. quintile 1) were associated with higher prevalence of COPD (prevalence ratio [PR], 1.62; 95% confidence ratio [CI], 1.33-1.97), wheeze (PR, 1.37; 95% CI, 1.11-1.69), cough (PR, 1.32; 95% CI, 1.32-1.59), and phlegm (PR, 1.27; 95% CI, 1.05-1.54) and lower percent predicted forced expiratory volume in 1 second (FEV1), percent predicted forced vital capacity (FVC), and FEV1/FVC ratio. Higher scores in the "Prudent" dietary pattern (quintile 5 vs. quintile 1) were associated with lower prevalence of COPD (PR, 0.82; 95% CI, 0.70-0.95) and cough (PR, 0.77; 95% CI, 0.67-0.89) and higher percent predicted FEV1 and FEV1/FVC ratio. The prevalence of asthma was not related to dietary intake. CONCLUSIONS: A "Western" dietary pattern was associated with respiratory symptoms, lower lung function, and COPD in ARIC participants.

Bui, D. S., H. E. Walters, et al. (2018). **"Childhood Respiratory Risk Factor Profiles and Middle-Age Lung Function: A Prospective Cohort Study from the First to Sixth Decade."** Ann Am Thorac Soc **15**(9): 1057-1066.

RATIONALE: Childhood risk factors for long-term lung health often coexist and their specific patterns may affect subsequent lung function differently. OBJECTIVES: To identify childhood risk factor profiles and their influence on lung function and chronic obstructive pulmonary disease (COPD) in middle age, and potential pathways. METHODS: Profiles of 11 childhood respiratory risk factors, documented at age 7, were identified in 8,352 participants from the Tasmanian Longitudinal Health Study using latent class analysis. We investigated associations between risk profiles and post-bronchodilator lung function and COPD at age 53, mediation by childhood lung function and adult asthma, and interaction with personal smoking. RESULTS: Six risk profiles were identified: 1) unexposed or least exposed (49%); 2) parental smoking (21.5%); 3) allergy (10%); 4) frequent asthma, bronchitis (8.7%); 5) infrequent asthma, bronchitis (8.3%); and 6) frequent asthma, bronchitis, allergy (2.6%). Profile 6 was most strongly associated with lower forced expiratory volume in 1 second (FEV1) (-261; 95% confidence interval, -373 to -148 ml); lower FEV1/forced vital capacity (FVC) (-3.4; -4.8 to -1.9%) and increased COPD risk (odds ratio, 4.9; 2.1 to 11.0) at age 53. The effect of profile 6 on COPD was largely mediated by adult active asthma (62.5%) and reduced childhood lung function (26.5%). Profiles 2 and 4 had smaller adverse effects than profile 6. Notably, the effects of profiles 2 and 6 were synergistically stronger for smokers. CONCLUSIONS: Profiles of childhood respiratory risk factors predict middle-age lung function levels and COPD risk. Specifically, children with frequent asthma attacks and allergies, especially if they also become adult smokers, are the most vulnerable group. Targeting active asthma in adulthood (i.e., a dominant mediator) and smoking (i.e., an effect modifier) may block causal pathways and lessen the effect of such established early-life exposures.

Burkes, R. M., J. Astemborski, et al. (2019). **"Plasma cathelicidin and longitudinal lung function in current and former smokers."** PLoS One **14**(2): e0212628.

INTRODUCTION: Cathelicidin (also known as LL-37 in humans) is an antimicrobial peptide secreted by epithelial and immune cells and regulated by vitamin D. The immunological roles of cathelicidin make it a putative biomarker to identify individuals at risk for reduced lung function. The objective of this study is to determine potential independent associations between low plasma cathelicidin and longitudinal lung function in current or former smokers without COPD. METHODS: In a nested analysis of 308 participants from an observational cohort study, plasma cathelicidin and serum 25-hydroxy-vitamin D measurements were obtained at baseline, years three and five. The independent association between lowest quartile cathelicidin (<35 ng/ml) and forced-expiratory-volume-in-1-second (FEV1) at baseline, six and 18 months from each cathelicidin measurement was assessed with generalized estimating equations after adjusting for age, sex, race, smoking status and intensity. The long-term stability of cathelicidin and relationship with vitamin D was evaluated. RESULTS: The cohort was 91% African-American, mean age 48.6 years, 32% female, and 81% current smokers. Participants with low cathelicidin were more likely to be female and have lower FEV1. Low cathelicidin was not independently associated with baseline FEV1. There was an independent association between low cathelicidin and reduced FEV1 at six months [-72 ml (95% CI, -140 to -8ml); p = 0.027] and 18 months [-103 ml (95% CI, -180 to -27 ml); p = 0.007]. Cathelicidin was stable over time and not correlated with vitamin D level. CONCLUSION: In current and former smokers with preserved lung function, low cathelicidin is associated with sustained lung function reductions at six and 18 months, suggesting that cathelicidin may be an informative biomarker to predict persistent lung function disparities among at-risk individuals.

Cantor, J. O. and G. M. Turino (2019). **"COPD Pathogenesis: Finding the Common in the Complex."** Chest **155**(2): 266-271.

Developing an effective treatment for COPD, and especially pulmonary emphysema, will require an understanding of how fundamental changes at the molecular level affect the macroscopic structure of the lung. Currently, there is no accepted model that encompasses the biochemical and mechanical processes responsible for pulmonary airspace enlargement. We propose that pulmonary emphysematous changes may be more accurately described as an emergent phenomenon, involving alterations at the molecular level that eventually reach a critical structural threshold where uneven mechanical forces produce alveolar wall rupture, accompanied by advanced clinical signs of COPD. The coupling of emergent morphologic changes with biomarkers to detect the process, and counteract it therapeutically, represents a practical approach to the disease.

Celli, B. R., M. Navaie, et al. (2019). **"Medication management patterns among Medicare beneficiaries with chronic obstructive pulmonary disease who initiate nebulized arformoterol treatment."** Int J Chron Obstruct Pulmon Dis **14**: 1019-1031.

Purpose: Global evidence-based treatment strategies for chronic obstructive pulmonary disease (COPD) recommend using long-acting bronchodilators (LABDs) as maintenance therapy. However, COPD patients are often undertreated. We examined COPD treatment patterns among Medicare beneficiaries who initiated arformoterol tartrate, a nebulized long-acting beta2 agonist (LABA), and identified the predictors of initiation. Methods: Using a 100% sample of Medicare administrative data, we identified beneficiaries with a COPD diagnosis (ICD-9 490-492.xx, 494.xx, 496.xx) between 2010 and 2014 who had >/=1 year of continuous enrollment in Parts A, B, and D, and >/=2 COPD-related outpatient visits within 30 days or >/=1 hospitalization(s). After applying inclusion/exclusion criteria, three cohorts were identified: (1) study group beneficiaries who received nebulized arformoterol (n=11,886), (2) a subset of the study group with no LABD use 90 days prior to initiating arformoterol (n=5,542), and (3) control group beneficiaries with no nebulized LABA use (n=220,429). Logistic regression was used to evaluate predictors of arformoterol initiation. Odds ratios (ORs), 95% confidence intervals (CIs), and p values were computed. Results: Among arformoterol users, 47% (n=5,542) had received no LABDs 90 days prior to initiating arformoterol. These beneficiaries were being treated with a nebulized (50%) or inhaled (37%) short-acting bronchodilator or a systemic corticosteroid (46%), and many received antibiotics (37%). Compared to controls, beneficiaries who initiated arformoterol were significantly more likely to have had an exacerbation, a COPD-related hospitalization, and a pulmonologist or respiratory therapist visit prior to initiation (all p<0.05). Beneficiaries with moderate/severe psychiatric comorbidity or dual-eligible status were significantly less likely to initiate arformoterol, as compared to controls (all p<0.05). Conclusion: Medicare beneficiaries who initiated nebulized arformoterol therapy had more exacerbations and hospitalizations than controls 90 days prior to initiation. Findings revealed inadequate use of maintenance medications, suggesting a lack of compliance with evidence-based treatment guidelines.

Chen, K. Y., S. M. Wu, et al. (2019). **"Effect of annual influenza vaccination on reducing lung cancer in patients with chronic obstructive pulmonary disease from a population-based cohort study."** Medicine (Baltimore) **98**(47): e18035.

Chronic obstructive pulmonary disease (COPD) patients are at a higher risk of development of lung cancer. Frequent exacerbations of COPD trigger the disease course to chronic inflammation which likely plays a role in the pathogenesis of lung cancer. Previous studies showed influenza virus infection is one of important causes for exacerbations of COPD. Therefore, the aim of this study was to know whether influenza vaccination could reduce the incidence of lung cancer in patients with COPD.This cohort study enrolled patients (>/=55 years old) with a recorded diagnosis of COPD between January 1, 2000 and December 31, 2012 by using the Taiwan Health Insurance Database. A propensity score was calculated to reduce vaccine therapy selection bias. Cox proportional hazard regressions were used to investigate the association between the influenza vaccination and lung cancer incidence after adjusting for known confounding factors. Besides, we categorized the patients into 4 groups according to vaccination status (unvaccinated, total number of vaccinations: 1, 2-3, >/=4) to evaluate the dose-dependent effect on reducing lung cancer occurrence of lung cancer in COPD patients.Our study comprised of 28,752 eligible individuals from the COPD cohort database. Among them, 51% (14,630) received influenza vaccination; the rest (49%) of the COPD patients did not receive influenza vaccination. We observed that COPD patients receiving influenza vaccination had a lower risk of lung cancer (adjusted HR = 0.40, 95% CI (0.35-0.45), P < .001). We also founded comparable protective effect in both sexes and all age groups (55-64, 65-74, >/=75) regardless of influenza seasonality. Furthermore, dose-dependent protective effect could be seen after stratifying patients according to the total number vaccinations, the adjusted HRs for lung cancer risk were 0.48 (0.40-0.54) and 0.24 (0.20-0.29) for patients who received 2 to 3 and >/=4 vaccinations during the follow-up period.This population-based cohort study demonstrated that annual influenza vaccination administration could reduce incidence of lung cancer in COPD patients.

Choi, J., J. Y. Oh, et al. (2019). **"The association between blood eosinophil percent and bacterial infection in acute exacerbation of chronic obstructive pulmonary disease."** Int J Chron Obstruct Pulmon Dis **14**: 953-959.

Introduction: The use of antibiotics is based on the clinician's experience and judgment, and antibiotics may often be overused in the treatment of acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Eosinophils have been studied as biomarkers of bacterial infection and prognostic factors in chronic obstructive pulmonary disease and AECOPD. Thus, the purpose of this study was to determine whether eosinophils could be used to determine bacterial infection in AECOPD events. Methods: We retrospectively analyzed the medical records of patients admitted to Korea University Guro Hospital for AECOPD between January 2011 and May 2017. Data pertaining to baseline characteristics, results of previous pulmonary function tests, treatment information during the admission period, and history of pulmonary treatment were collected before admission. Results: A total of 736 AECOPD events were eligible for inclusion and were divided into two groups based on the eosinophil count: those involving eosinophil counts of less than 2% (546 events) and those involving counts of 2% or more (190 events). In univariate analysis, the only bacterial pathogen identification events and bacterial-viral pathogen co-identification events were significantly more frequent in the group with eosinophil counts of less than 2% (P=0.010 and P=0.001, respectively). In logistic regression analysis, the rates of only bacterial pathogen identification [odds ratios =1.744; 95% confidence interval, 1.107-2.749; P=0.017] and bacterial-viral pathogen co-identification [odds ratios=2.075; 95% confidence interval, 1.081-3.984; P=0.028] were higher in the group with eosinophil count less than 2%. Conclusion: In conclusion, eosinophil counts of less than 2% are potential indicators of a bacterial infection in AECOPD events. Eosinophils could thus serve as a reference for the use of antibiotics in AECOPD treatment.

Clark, V. C., G. Marek, et al. (2018). **"Clinical and histologic features of adults with alpha-1 antitrypsin deficiency in a non-cirrhotic cohort."** J Hepatol **69**(6): 1357-1364.

BACKGROUND & AIMS: Alpha-1 antitrypsin deficiency (AATD) is an uncommonly recognized cause of liver disease in adults, with descriptions of its natural history limited to case series and patient-reported data from disease registries. Liver pathology is limited to selected patients or unavailable. Therefore, we aimed to determine the prevalence and severity of liver fibrosis in an adult AATD population who were not known to have cirrhosis, while defining risk factors for fibrosis and testing non-invasive markers of disease. METHODS: A total of 94 adults with classic genotype 'PI*ZZ' AATD were recruited from North America and prospectively enrolled in the study. Liver aminotransferases and markers of synthetic function, transient elastography, and liver biopsy were performed. RESULTS: The prevalence of clinically significant liver fibrosis (F>/=2) was 35.1%. Alanine aminotransferase, aspartate aminotransferase and gamma-glutamyltransferase values were higher in the F>/=2 group. Metabolic syndrome was associated with the presence of clinically significant fibrosis (OR 14.2; 95% CI 3.7-55; p <0.001). Additionally, the presence of accumulated abnormal AAT in hepatocytes, portal inflammation, and hepatocellular degeneration were associated with clinically significant fibrosis. The accuracy of transient elastography to detect F>/=2 fibrosis was fair, with an AUC of 0.70 (95% CI 0.58-0.82). CONCLUSIONS: Over one-third of asymptomatic and lung affected adults with 'PI*ZZ' AATD have significant underlying liver fibrosis. Liver biopsies demonstrated variable amounts of accumulated Z AAT. The risk of liver fibrosis increases in the presence of metabolic syndrome, accumulation of AAT in hepatocytes, and portal inflammation on baseline biopsy. The results support the hypothesis that liver disease in this genetic condition may be related to a "toxic gain of function" from accumulation of AAT in hepatocytes. LAY SUMMARY: Individuals diagnosed with classic alpha-1 antitrypsin deficiency (ZZ) are at risk of liver injury and scarring, because of the accumulation of abnormal alpha-1 antitrypsin in the liver. A liver biopsy in ZZ individuals can demonstrate the accumulation of alpha-1 antitrypsin within the liver and identify if any associated liver scarring is present. Indviduals with large amounts of alpha-1 antitrypsin on biopsy may be at risk of liver injury and fibrosis. Additional common medical conditions of diabetes, obesity, high cholesterol, and hypertension (known as metabolic syndrome) are associated with a greater degree of liver injury. CLINICAL TRIAL NUMBER: clinicaltrials.gov NCT01810458.

Cruz, T., A. Lopez-Giraldo, et al. (2019). **"Multi-level immune response network in mild-moderate Chronic Obstructive Pulmonary Disease (COPD)."** Respir Res **20**(1): 152.

BACKGROUND: Chronic Obstructive Pulmonary Disease (COPD) is associated with an abnormal pulmonary and systemic immune response to tobacco smoking. Yet, how do immune cells relate within and between these two biological compartments, how the pulmonary infiltrate influences the lung transcriptome, and what is the role of active smoking vs. presence of disease is unclear. METHODS: To investigate these questions, we simultaneously collected lung tissue and blood from 65 individuals stratified by smoking habit and presence of the disease. The immune cell composition of both tissues was assessed by flow cytometry, whole lung transcriptome was determined with Affymetrix arrays, and we used Weighted Gene Co-expression Network Analysis (WGCNA) to integrate results. RESULTS: Main results showed that: (1) current smoking and the presence of COPD were both independently associated with a reduction in the proportion of lung T cells and an increase of macrophages, specifically those expressing CD80 + CD163+; (2) changes in the proportion of infiltrating macrophages, smoking status or the level of airflow limitation were associated to different WGCNA modules, which were enriched in iron ion transport, extracellular matrix and cilium organization gene ontologies; and, (3) circulating white blood cells counts were correlated with lung macrophages and T cells. CONCLUSIONS: Mild-moderated COPD lung immune infiltrate is associated with the active smoking status and presence of disease; is associated with changes in whole lung tissue transcriptome and marginally reflected in blood.

Ding, G. Z. and W. S. Li (2018). **"The expressions and significance of APN, D-D, IL-17 and hs-CRP in patients with acute exacerbation of chronic obstructive pulmonary disease."** Eur Rev Med Pharmacol Sci **22**(19): 6463-6468.

OBJECTIVE: Inflammatory reactions and imbalance of oxidant/antioxidant and protease/anti-protease are the major causes of chronic obstructive pulmonary disease. Based on the information mentioned, the expressions and significance of adiponectin (APN), D-dimer (DD), Interleukin (IL)-17, and high-sensitivity CRP (hs-CRP) in patients with acute exacerbation of chronic obstructive pulmonary disease were investigated in this study. PATIENTS AND METHODS: A total of 70 patients with chronic obstructive pulmonary disease were enrolled and divided into stable group (group A, 28 cases) and acute exacerbation group (group B, 42 cases). Thirty-five healthy volunteers were included in the control group (group C, 35 cases). The levels of serum APN, IL- 17, D-D, and hs-CRP were tested and compared RESULTS: Levels of APN from Group B were significantly lower than that of Group A or Group C, while levels of APN of Group A were also significantly lower than that of Group C, ($p < 0.05$). Levels of IL-17, D-D, and Hs-CRP of group b were significantly increased compared to that of Group A or Group C, and levels of IL-17, D-D, and Hs-CRP of Group A were significantly elevated compared to that of Group C ($p < 0.05$). A negative statistical correlation was found between APN and IL-17, D-D, and Hs-CRP ($p < 0.05$). CONCLUSIONS: Levels of APN were downregulated in patients with acute exacerbation of chronic obstructive pulmonary disease. The expression levels of APN, IL-17, D-D, and Hs-CRP were closely correlated with clinical stages and can be used as parameters for the evaluation of the severity of chronic obstructive pulmonary disease.

Ding, Z., R. Stehlik, et al. (2019). **"Chronic pulmonary disease is associated with pain spreading and restless legs syndrome in middle-aged women-a population-based study."** Sleep Breath **23**(1): 135-142.

INTRODUCTION: Recent studies suggest an increased prevalence of chronic pain conditions and restless legs syndrome (RLS) in patients with chronic pulmonary disease (CPD). We analyzed the prevalence and risk factors for pain and RLS in a population-based sample of females with comorbid CPD. METHOD: Questionnaire-based data from 2745 women aged 18-64 years were analyzed regarding comorbid CPD status (severe bronchitis, emphysema, asthma). Pain status was assessed according to symptoms reflecting severity (Visual Analogue Scale, VAS rating 0-10) and duration and spreading (limited spread or widespread) of pain. A diagnosis of RLS was defined by four validated diagnostic criteria. Anthropometrics and co-morbidities were assessed as covariates in univariate and multivariate analyses. RESULTS: Widespread pain was overrepresented in women with CPD (44.6 vs. 24.6%, $p < 0.001$). The odds ratio for widespread pain in women with CPD was 1.6 (95% confidence interval (CI) 1.2-2.2, $p < 0.001$) in the fully adjusted model. Severe pain (VAS rating >/= 7) was more prevalent in females with known CPD (28.8 vs. 15.4%, $p < 0.001$, odd ratio 1.4 (95% CI 1.0-1.9, $p = 0.029$)). The prevalence of RLS was 37.4 and 23.8% in subjects with or without CPD, respectively ($p < 0.001$). In multivariate analysis, CPD was associated with a 30% risk increase for RLS (odds ratio 1.3 (95% CI 1.0-1.7, $p = 0.04$)). CONCLUSION: This population-based study identified CPD as an independent risk factor for severe and

widespread pain as well as for RLS. Further research addressing pathophysiological mechanisms linking CPD and chronic pain conditions/RLS is warranted.

Dorsch, J. J. and E. M. Wickwire (2019). **"OSA/COPD Overlap: Convergence on a Theme?"** J Clin Sleep Med **15**(1): 9-10.

Dziankowska-Zaborszczyk, E., M. Bryla, et al. (2019). **"Standard expected years of life lost (SEYLL) due to chronic obstructive pulmonary disease (COPD) in Poland from 1999 to 2014."** PLoS One **14**(3): e0213581.

PURPOSE: The aim of the study is to analyze the standard expected years of life lost (SEYLL) due to chronic obstructive pulmonary disease (COPD) in Poland from 1999 to 2014 by sex and place of residence. METHODS: The number of deaths due to chronic obstructive pulmonary disease (J40 -J44 and J47 according to ICD-10) over the period 1999 to 2014 was analyzed based on data obtained from the Central Statistical Office in Poland. Standard expected years of life lost due to chronic obstructive pulmonary disease were calculated by sex and place of residence according to the living population (SEYLLp) and the number of deaths caused by the disease (SEYLLd). Changes in the calculated measures were evaluated using joinpoint models. The annual percentage change (APC) and the average annual percentage change (AAPC) were also calculated. RESULTS: The study revealed that COPD contributed to 1.8% of the total number of deaths which occurred between 1999 and 2014. The greatest decrease in the analyzed measures was observed among males from rural areas ($p<0.05$) (SEYLL: AAPC = -1.6; 95%CI: -3.0;-0.2; SEYLLp: AAPC = -2.0; 95%CI: -3.4;-0.6; SEYLLd: AAPC = -1.1; 95%CI: -1.2;-0.9). A statistically significant increase in the SEYLL and SEYLLp indices was observed among female city dwellers (SEYLL: AAPC = 2.4; 95%CI:0.7;4.0 and SEYLLp: AAPC = 2.4; 95%CI: 0.8;4.1). CONCLUSIONS: All studied measures were higher in the male group than in the female group, regardless of the place of residence. A male who died of COPD in Poland in 2014 potentially lost 14.9 years of life, whereas a female lost 14.2 years.

Ebner, L., R. S. Virgincar, et al. (2019). **"Multireader Determination of Clinically Significant Obstruction Using Hyperpolarized (129)Xe-Ventilation MRI."** AJR Am J Roentgenol **212**(4): 758-765.

OBJECTIVE: The objective of our study was to identify the magnitude and distribution of ventilation defect scores (VDSs) derived from hyperpolarized (HP) (129)Xe-MRI associated with clinically relevant airway obstruction. MATERIALS AND METHODS: From 2012 to 2015, 76 subjects underwent HP (129)Xe-MRI (48 healthy volunteers [mean age +/- SD, 54 +/- 17 years]; 20 patients with asthma [mean age, 44 +/- 20 years]; eight patients with chronic obstructive pulmonary disease [mean age, 67 +/- 5 years]). All subjects underwent spirometry 1 day before MRI to establish the presence of airway obstruction (forced expiratory volume in 1 second-to-forced vital capacity ratio [FEV1/FVC] < 70%). Five blinded readers assessed the degree of ventilation impairment and assigned a VDS (range, 0-100%). Interreader agreement was assessed using the Fleiss kappa statistic. Using FEV1/FVC as the reference standard, the optimum VDS threshold for the detection of airway obstruction was estimated using ROC curve analysis with 10-fold cross-validation. RESULTS: Compared with the VDSs in healthy subjects, VDSs in patients with airway obstruction were significantly higher ($p < 0.0001$) and significantly correlated with disease severity ($r = 0.66$, $p < 0.0001$). Ventilation defects in subjects with airway obstruction did not show a location-specific pattern ($p = 0.158$); however, defects in healthy control subjects were more prevalent in the upper lungs ($p = 0.014$). ROC curve analysis yielded an optimal threshold of 12.4% +/- 6.1% (mean +/- SD) for clinically significant VDS. Interreader agreement for (129)Xe-MRI was substantial (kappa = 0.71). CONCLUSION: This multireader study of a diverse cohort of patients and control subjects suggests a (129)Xe-ventilation MRI VDS of 12.4% or greater represents clinically significant obstruction.

Fawzy, A., N. Putcha, et al. (2019). **"Aspirin Use and Respiratory Morbidity in COPD: A Propensity Score-Matched Analysis in Subpopulations and Intermediate Outcome Measures in COPD Study."** Chest **155**(3): 519-527.

BACKGROUND: Aspirin use in COPD has been associated with reduced all-cause mortality in meta-regression analysis with few equivocal studies. However, the effect of aspirin on COPD morbidity is unknown. METHODS: Self-reported daily aspirin use was obtained at baseline from SPIROMICS participants with COPD (FEV1/FVC < 70%). Acute exacerbations of COPD (AECOPD) were prospectively ascertained through quarterly structured telephone questionnaires up to 3 years and categorized as moderate (symptoms treated with antibiotics or oral corticosteroids) or severe (requiring ED visit or hospitalization). Aspirin users were matched one-to-one with nonusers, based on propensity score. The

association of aspirin use with total, moderate, and severe AECOPD was investigated using zero-inflated negative binomial models. Linear or logistic regression was used to investigate the association with baseline respiratory symptoms, quality of life, and exercise tolerance. RESULTS: Among 1,698 participants, 45% reported daily aspirin use at baseline. Propensity score matching resulted in 503 participant pairs. Aspirin users had a lower incidence rate of total AECOPD (adjusted incidence rate ratio [IRR], 0.78; 95% CI, 0.65-0.94), with similar effect for moderate but not severe AECOPD (IRR, 0.86; 95% CI, 0.63-1.18). Aspirin use was associated with lower total St. George's Respiratory Questionnaire score (beta, -2.2; 95% CI, -4.1 to -0.4), reduced odds of moderate-severe dyspnea (modified Medical Research Council questionnaire score >/= 2; adjusted odds ratio, 0.69; 95% CI, 0.51-0.93), and COPD Assessment Test score (beta, -1.1; 95% CI, -1.9 to -0.2) but not 6-min walk distance (beta, 0.7 m; 95% CI, -14.3 to 15.6). CONCLUSIONS: Daily aspirin use is associated with reduced rate of COPD exacerbations, less dyspnea, and better quality of life. Randomized clinical trials of aspirin use in COPD are warranted to account for unmeasured and residual confounding. TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT01969344; URL: www.clinicaltrials.gov.

Finucane, K. E. and B. Singh (2018). **"Role of bronchodilation and pattern of breathing in increasing tidal expiratory flow with progressive induced hypercapnia in chronic obstructive pulmonary disease."** J Appl Physiol (1985) **124**(1): 91-98.

Hypercapnia (HC) in vitro relaxes airway smooth muscle; in vivo, it increases respiratory effort, tidal expiratory flows (Vexp), and, by decreasing inspiratory duration (Ti), increases elastic recoil pressure (Pel) via lung viscoelasticity; however, its effect on airway resistance is uncertain. We examined the contributions of bronchodilation, Ti, and expiratory effort to increasing Vexp with progressive HC in 10 subjects with chronic obstructive pulmonary disease (COPD): mean forced expiratory volume in 1 s (FEV1) 53% predicted. Lung volumes (Vl), Vexp, esophageal pressure (Pes), Ti, and end-tidal Pco2 ([Formula: see text]) were measured during six tidal breaths followed by an inspiratory capacity (IC), breathing air, and at three levels of HC. Vexp and V with submaximal forced vital capacities breathing air (VsFVC) were compared. Pulmonary resistance (Rl) was measured from the Pes-V relationship. Vexp and Pes at end-expiratory lung volume (EELV) + 0.3 tidal volume [V(0.3Vt) and Pes(0.3Vt), respectively], Ti, and Rl correlated with [Formula: see text] ($P < 0.001$ for all) and were independent of tiotropium. [Formula: see text], Ti, and Pes(0.3Vt) predicted the increasing V(0.3Vt)/VsFVC(0.3Vt) [multiple regression analysis (MRA): P = 0.001, 0.004, and 0.025, respectively]. At [Formula: see text] >/= 50 Torr, V(0.3Vt)/VsFVC(0.3Vt) exceeded unity in 30 of 36 measurements and was predicted by [Formula: see text] and Pes(0.3Vt) (MRA: P = 0.02 and 0.025, respectively). Rl decreased at [Formula: see text] 45 Torr ($P < 0.05$) and did not change with further HC. IC and Vl(0.3Vt) did not change with HC. We conclude that in COPD HC increases Vexp due to bronchodilation, increased Pel secondary to decreasing Ti, and increased expiratory effort, all promoting lung emptying and a stable EELV. NEW & NOTEWORTHY The response of airways to intrapulmonary hypercapnia (HC) is uncertain. In chronic obstructive pulmonary disease (COPD), progressive HC increases tidal expiratory flows by inducing bronchodilation and via an increased rate of inspiration and lung viscoelasticity, a probable increase in lung elastic recoil pressure, both changes increasing expiratory flows, promoting lung emptying and a stable end-expiratory volume. Bronchodilation with HC occurred despite optimal standard bronchodilator therapy, suggesting that in COPD further bronchodilation is possible.

Fiorelli, A., C. Poggi, et al. (2019). **"Visual analysis versus quantitative CT analysis of interlobar fissure integrity in selecting emphysematous patients for endobronchial valve treatment."** Interact Cardiovasc Thorac Surg **28**(5): 751-759.

OBJECTIVES: The aim of this study is to compare the accuracy of the standard visual scoring of computed tomography (CT) scans with a cloud-based quantitative CT analysis that uses the StratX software, to measure collateral ventilation and, thus, predict lobar atelectasis after valve treatment. METHODS: This is a retrospective, multicentre study of patients who had previously undergone valve treatment for severe heterogeneous emphysema and whose required fissure integrity >/=90% had been qualitatively scored by visual assessment of CT scans. For this study, all preprocedural CT scans were retrospectively analysed using the StratX software to provide quantitative scores of fissure integrity. The diagnostic accuracies of the visual and quantitative scores for predicting a target lobe volume reduction (TLVR) of >/=350 ml were calculated and statistically compared, as this level of volume reduction can be achieved only with sound fissure integrity. The clinical outcome of TLVR was also evaluated according to the minimal clinically important difference criteria. RESULTS: Eighty-three patients were included in the analysis. Of them, 65 of 83 (78%) patients presented with TLVR >/=350 ml. Visual scoring correctly identified the

absence of collateral ventilation in 65 of 83 (78%) cases but failed in 18 of 83 (22%) cases. Of these 18 patients, quantitative analysis showed that 16 of 18 (89%) patients did not present completeness of the fissure. The diagnostic accuracy of the quantitative analysis was better than that of the visual analysis (96.4% vs 78.3%; P = 0.0003). Only patients having TLVR >/=350 ml met or exceeded the minimal clinically important difference criteria. CONCLUSIONS: The quantitative analysis using the StratX software contributed a more objective and efficient evaluation of collateral ventilation that would have improved the selection of emphysematous patients for endobronchial valve treatment in the study population.

Gavazzi, A., A. Aimo, et al. (2019). **"The importance of breathing not properly: Chronic obstructive pulmonary disease as a risk factor for rehospitalization in heart failure."** Int J Cardiol **290**: 127-128.

Giannico, O. V., I. Ambrosino, et al. (2019). **"Educational level, marital status and sex as social gender discharge determinants in chronic obstructive pulmonary disease exacerbations: a time-to-event analysis."** Monaldi Arch Chest Dis **89**(2)The aim of this study is to evaluate, in patients hospitalized for COPD exacerbation, how educational level, marital status and sex (social gender indicators) affect the prognosis (main effects) and how interact with each other in affecting prognosis (effect modification). Data for all patients discharged with a principal diagnosis of COPD with exacerbation (ICD-9 491.21) by Apulian facilities between 2013 and 2017 were retrieved from the National Hospital Discharge Register Database. A multivariable multi-stratified frailty cox proportional-hazard regression with interaction terms was fitted in order to assess the effect of sex, educational level and marital status on the time-to-event for home discharge through the estimation of hazard ratios. Adjusting for several hospitalization characteristics and for healthcare facilities, low educational level (<8 years of schooling) seems to be a risk factor in both sexes and in all marital status categories (HR 0.92, 95%CI 0.87-0.97, p=0.0020). Female sex seems to be a risk factor only in married patients (HR 0.83, 95%CI 0.78-0.88, p<0.0001). Marital status different from married seems to be a risk factor only in male patients, in particular single patients (HR 0.82, 95%CI 0.74-0.92, p=0.0009), separated or divorced patients (HR 0.71, 95%CI 0.58-0.86, p=0.0005) and widowed patients (HR 0.87, 95%CI 0.80-0.95, p=0.0018). Differently from findings about protective effect of education, the evidence of different effects of sex among civil statuses and of different effect of civil status among sexes is supposed to be a proxy for social gender health and healthcare inequalities.

Gifford, J. R., J. D. Trinity, et al. (2018). **"Altered skeletal muscle mitochondrial phenotype in COPD: disease vs. disuse."** J Appl Physiol (1985) **124**(4): 1045-1053.

Patients with chronic obstructive pulmonary disease (COPD) exhibit an altered skeletal muscle mitochondrial phenotype, which often includes reduced mitochondrial density, altered respiratory function, and elevated oxidative stress. As this phenotype may be explained by the sedentary lifestyle that commonly accompanies this disease, the aim of this study was to determine whether such alterations are still evident when patients with COPD are compared to control subjects matched for objectively measured physical activity (PA; accelerometry). Indexes of mitochondrial density [citrate synthase (CS) activity], respiratory function (respirometry in permeabilized fibers), and muscle oxidative stress [4-hydroxynonenal (4-HNE) content] were assessed in muscle fibers biopsied from the vastus lateralis of nine patients with COPD and nine PA-matched control subjects (CON). Despite performing similar levels of PA (CON: 18 +/- 3, COPD: 20 +/- 7 daily minutes moderate-to-vigorous PA; CON: 4,596 +/- 683, COPD: 4,219 +/- 763 steps per day, P > 0.70), patients with COPD still exhibited several alterations in their mitochondrial phenotype, including attenuated skeletal muscle mitochondrial density (CS activity; CON 70.6 +/- 3.8, COPD 52.7 +/- 6.5 U/mg, P < 0.05), altered mitochondrial respiration [e.g., ratio of complex I-driven state 3 to complex II-driven state 3 (CI/CII); CON: 1.20 +/- 0.11, COPD: 0.90 +/- 0.05, P < 0.05), and oxidative stress (4-HNE; CON: 1.35 +/- 0.19, COPD: 2.26 +/- 0.25 relative to beta-actin, P < 0.05). Furthermore, CS activity (r = 0.55), CI/CII (r = 0.60), and 4-HNE (r = 0.49) were all correlated with pulmonary function, assessed as forced expiratory volume in 1 s (P < 0.05), but not PA (P > 0.05). In conclusion, the altered mitochondrial phenotype in COPD is present even in the absence of differing levels of PA and appears to be related to the disease itself. NEW & NOTEWORTHY Chronic obstructive pulmonary disease (COPD) is associated with debilitating alterations in the function of skeletal muscle mitochondria. By comparing the mitochondrial phenotype of patients with COPD to that of healthy control subjects who perform the same amount of physical activity each day, this study provides evidence that many aspects of the dysfunctional mitochondrial phenotype observed in COPD are not merely due to reduced physical activity but are likely related to the disease itself.

Graziadio, S., R. A. O'Leary, et al. (2019). **"Can mid-regional pro-adrenomedullin (MR-proADM) increase the prognostic accuracy of NEWS in predicting deterioration in patients admitted to hospital with mild to moderately severe illness? A prospective single-centre observational study."** BMJ Open **8**(11): e020337.

OBJECTIVE: To assess the value added to the National Early Warning Score (NEWS) by mid-regional pro-adrenomedullin (MR-proADM) blood level in predicting deterioration in mild to moderately ill people. DESIGN: Prospective observational study. SETTING: The Medical Admissions Suite of the Royal Victoria Infirmary, Newcastle. PARTICIPANTS: 300 adults with NEWS between 2 and 5 on admission. Exclusion criteria included receiving palliative care, or admitted for social reasons or self-harming. Patients were enrolled between September and December 2015, and followed up for 30 days after discharge. OUTCOME MEASURE: The primary outcome measure was the proportion of patients who, within 72 hours, had an acuity increase, defined as any combination of an increase of at least 2 in the NEWS; transfer to a higher-dependency bed or monitored area; death; or for those discharged from hospital, readmission for medical reasons. RESULTS: NEWS and MR-proADM together predicted acuity increase more accurately than NEWS alone, increasing the area under the curve (AUC) to 0.61 (95% CI 0.54 to 0.69) from 0.55 (95% CI 0.48 to 0.62). When the confounding effects of presence of chronic obstructive pulmonary disease or heart failure and interaction with MR-proADM were included, the prognostic accuracy further increased the AUC to 0.69 (95% CI 0.63 to 0.76). CONCLUSIONS: MR-proADM is potentially a clinically useful biomarker for deterioration in patients admitted to hospital with a mild to moderately severe acute illness, that is, with NEWS between 2 and 5. As a growing number of National Health Service hospitals are routinely recording the NEWS on their clinical information systems, further research should assess the practicality and use of developing a decision aid based on admission NEWS, MR-proADM level, and possibly other clinical data and other biomarkers that could further improve prognostic accuracy.

Guillaud, O., J. Dumortier, et al. (2019). **"Assessment of liver fibrosis by transient elastography (Fibroscan((R))) in patients with A1AT deficiency."** Clin Res Hepatol Gastroenterol **43**(1): 77-81.

BACKGROUND: Alpha-1-antitrypsin deficiency (A1ATD) is a common genetic condition which predisposes to emphysema and liver disorders. It is estimated that 10-15% of homozygous individuals for the Z allele (PiZZ) may develop liver fibrosis. The optimal modalities to detect liver disease in PiZZ adult patients need to be defined. The aim of this prospective study was to perform a systematic non-invasive evaluation of the liver fibrosis by elastometry using Fibroscan((R)) in a cohort of A1ATD patients with emphysema. METHODS: Patients followed in our respiratory unit were enrolled in this prospective study and underwent on the same day a physical examination, a biochemical profiling, an abdominal ultrasound (US) and a Fibroscan((R)). RESULTS: Twenty-nine PiZZ adults (19 male) were included. Median age was 50.4 yrs (21.5-67.2). Median serum A1AT level was 0.20 g/L (0.15-0.33). Liver Function Tests (LFT) were not normal in 2 patients and US was abnormal in 6 patients. Two patients had both abdnormal LFT and US. Fibroscan((R)) was technically feasible in 28/29 (97%) patients. Median liver stiffness was 4.5 kPa (2.8-32.8), and was > 7.2 kPa in 5/28 (18%) and > 14 kPa in 2/28 (7%) patients. Liver stiffness was increased in 2/2 (100%) patients with abnormal LFT and US, in 1/4 (25%) with abnormal LFT or US and in 2/22 (10%) patients with normal LFT and US. CONCLUSIONS: Fibroscan((R)) is an easy and repeatable tool which can be used in PiZZ patients to screen for the presence of significant liver fibrosis and to identify patients at higher risk to develop liver complications in the future and who may benefit from a closer surveillance.

Gupta, V., N. Redkar, et al. (2019). **"A Study of Clinical Profile and Outcome of Acute Heart Failure in Elderly Patients."** J Assoc Physicians India **67**(11): 55-58.

Introduction: The significant increase of life expectancies over the last few decades, has lead to a major change in the morbidity and mortality profile of elders. Heart Failure (HF) is predominantly a disorder of the elderly with rates increasing exponentially with time. Material and Methods: The Observational and prospective study was conducted in a tertiary care teaching hospital. The study included all patients >60 years of age diagnosed as acute heart failure as per Boston Criteria. Patients with chronic obstructive pulmonary disease were excluded. Patients were followed till either discharge or death. Results: Total 56 patients were enrolled for the study. Male and female formed 53.57% and 46.43% of study population respectively. Based on Ejection fraction on 2D Echocardiography Diastolic HF (EF >40%) was seen in 30 patients (53.57%) while systolic dysfunction was seen in 26 patients (46.43%). As per Boston score criteria, maximum patient 33 (66.07) fell into range of 8-12 while remaining had score range 5-7. None

of the patients were in lesser score range of 1-4. Out of 56 patients 44 (78.57%) were discharged 12 (21.43%) patients expired.

Gurbeta, L., A. Badnjevic, et al. (2018). **"A telehealth system for automated diagnosis of asthma and chronical obstructive pulmonary disease."** J Am Med Inform Assoc **25**(9): 1213-1217.

This paper presents the development and real-time testing of an automated expert diagnostic telehealth system for the diagnosis of 2 respiratory diseases, asthma and Chronic Obstructive Pulmonary Disease (COPD). The system utilizes Android, Java, MATLAB, and PHP technologies and consists of a spirometer, mobile application, and expert diagnostic system. To evaluate the effectiveness of the system, a prospective study was carried out in 3 remote primary healthcare institutions, and one hospital in Bosnia and Herzegovina healthcare system. During 6 months, 780 patients were assessed and diagnosed with an accuracy of 97.32%. The presented approach is simple to use and offers specialized consultations for patients in remote, rural, and isolated communities, as well as old and less physically mobile patients. While improving the quality of care delivered to patients, it was also found to be very beneficial in terms of healthcare.

Hensel, M., M. S. Strunden, et al. (2019). **"Prehospital non-invasive ventilation in acute respiratory failure is justified even if the distance to hospital is short."** Am J Emerg Med **37**(4): 651-656.

AIMS: Evaluation of the efficacy of prehospital non-invasive ventilation (NIV) in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) and cardiogenic pulmonary edema (CPE). MATERIAL AND METHODS: Consecutive patients who were prehospitally treated by Emergency Physicians using NIV were prospectively included. A step-by-step approach escalating NIV-application from continuous positive airway pressure (CPAP) to continuous positive airway pressure supplemented by pressure support (CPAP-ASB) and finally bilevel inspiratory positive airway pressure (BIPAP) was used. Patients were divided into two groups according to the prehospital NIV-treatment-time (NIV-group 1: </=15min, NIV-group 2: >15min). In addition, a historic control group undergoing standard care was created. Endpoints were heart rate, peripheral oxygen saturation, breathing rate, systolic blood pressure, and a dyspnea score. RESULTS: A total of 99 patients were analyzed (NIV-group 1: n=41, NIV-group 2: n=58). The control group consisted of 30 patients. The majority of NIV-patients (90%) received CPAP-ASB, while CPAP without ASB was conducted in 8% and BIPAP-ventilation in 2% of all cases. Technical application of NIV lasted 6.1+/-3.8min. NIV-treatment-time was as follows: NIV-group 1: 13.1+/-3.2min, NIV-group 2: 22.8+/-5.9min. Differences between baseline- and hospital admission values of all endpoints showed significantly better improvement in NIV-groups compared to the control group ($p<0.001$). The stabilizing effect of NIV in terms of vital parameters was comparable between both NIV-groups, independent of the duration of treatment (n.s.). CONCLUSION: Prehospital NIV-treatment should be performed in patients with COPD-exacerbation and CPE, even if the distance between emergency scene and hospital is short.

Heraud, N., F. Alexandre, et al. (2018). **"Impact of Chronic Obstructive Pulmonary Disease on Cognitive and Motor Performances in Dual-Task Walking."** Copd **15**(3): 277-282.

When two tasks are performed simultaneously, they compete for attentional resources, resulting in a performance decrement in one or both tasks. Patients with attention disorders have a reduced ability to perform several tasks simultaneously (e.g., talking while walking), which increases the fall risk and frailty. This study assessed the cognitive and motor performances of patients with COPD and healthy controls within a dual-task walking paradigm. A subobjective was to assess the impact of a pulmonary rehabilitation program on the dual-task performances in COPD. Twenty-five patients with COPD and 20 controls performed a cognitive task (subtraction) and a 15-m walking test separately (single-task; ST) and jointly (dual-task; DT). In addition, a subsample of 10 patients performed the same evaluations 5 weeks later after a pulmonary rehabilitation program following current recommendations. Cognitive and gait performances in ST showed no differences between patients with COPD and controls (all $p > 0.05$). However, COPD patients exhibited a greater increase in gait variability than controls in DT (4.07 +/- 1.46% vs. 2.17 +/- 0.7%, $p < 0.001$). The pulmonary rehabilitation program had no effect on the dual-task impairment for the subsample of patients ($p = 0.87$). This study provides evidence of insufficient attentional resources to successfully deal with DT in patients with COPD, and this was expressed through an exaggerated increase in gait variability in DT walking. Given the high risk of falls and disability associated with altered gait variability, dual-task training interventions should be considered in pulmonary rehabilitation programs.

Herrera-Rivero, M., R. Zhang, et al. (2018). **"Circulating microRNAs are associated with Pulmonary Hypertension and Development of Chronic Lung Disease in Congenital Diaphragmatic Hernia."** Sci Rep **8**(1): 10735.

Pulmonary hypertension (PH) contributes to high mortality in congenital diaphragmatic hernia (CDH). A better understanding of the regulatory mechanisms underlying the pathology in CDH might allow the identification of prognostic biomarkers and potential therapeutic targets. We report the results from an expression profiling of circulating microRNAs (miRNAs) in direct post-pulmonary blood flow of 18 CDH newborns. Seven miRNAs differentially expressed in children that either died or developed chronic lung disease (CLD) up to 28 days after birth, compared to those who survived without developing CLD during this period, were identified. Target gene and pathway analyses indicate that these miRNAs functions include regulation of the cell cycle, inflammation and morphogenesis, by targeting molecules responsive to growth factors, cytokines and cellular stressors. Furthermore, we identified hub molecules by constructing a protein-protein interaction network of shared targets, and ranked the relative importance of the identified miRNAs. Our results suggest that dysregulations in miRNAs let-7b-5p, -7c-5p, miR-1307-3p, -185-3p, -8084, -331-3p and -210-3p may be detrimental for the development and function of the lungs and pulmonary vasculature, compromise cardiac function and contribute to the development of CLD in CDH. Further investigation of the biomarker and therapeutic potential of these circulating miRNAs is encouraged.

Hiller, A. M., E. Piitulainen, et al. (2019). **"Decline in FEV1 and hospitalized exacerbations in individuals with severe alpha-1 antitrypsin deficiency."** Int J Chron Obstruct Pulmon Dis **14**: 1075-1083.

Background and aim: The value of the forced expiratory volume in one second (FEV1) is useful in the diagnosis and prognosis of chronic obstructive pulmonary disease (COPD). Previous studies on lung function in individuals with severe alpha-1 antitrypsin deficiency (AATD) have shown a variable annual decline in FEV1 (FEV1). The aim of this study was to analyze FEV1 and to identify risk factors for FEV1 in individuals with severe AATD. Material and methods: Data on smoking habits, symptoms, results of lung function tests and exacerbations were obtained from the Swedish AATD Register and the Swedish National Patient Register (SNPR). The FEV1 was analyzed by random-effects modeling and adjusted for age and FEV1 at baseline. Results: One hundred and four (9%) current smokers, 539 (48%) ex-smokers and 489 (43%) never-smokers were included in the study and followed-up from 1991 to 2016. A total of 584 (52%) individuals with severe AATD had COPD at inclusion. The median (IQR) annual severe exacerbation rate was 0.66 (1.4). The adjusted mean FEV1 was significantly higher in the current smokers compared with the ex-smokers and never-smokers (70 [95% CI 56-83] vs 42 [95% CI 36-48] and 32 [95% CI 25-38) mL.yr(-1)], in the middle-aged individuals compared with the young individuals (48 [95% CI 41-55] vs 32 [95% CI 18-45] mL.yr(-1)), in the individuals with respiratory symptoms at inclusion compared with the asymptomatic individuals (46 [95% CI 40-52] vs 30 [95% CI 22-38]mL.yr(-1)), and in the individuals with frequent exacerbations compared with those with infrequent exacerbations (57 [95% CI 47-68] vs 27 [95% CI 17-37] mL.yr(-1)). Conclusion: Active smoking, age, respiratory symptoms at baseline and repeated severe exacerbations of COPD are factors associated with an accelerated decline of lung function in individuals with severe AATD.

Hlapcic, I., A. Somborac-Bacura, et al. (2020). **"Platelet indices in stable chronic obstructive pulmonary disease - association with inflammatory markers, comorbidities and therapy."** Biochem Med (Zagreb) **30**(1): 010701.

Introduction: Chronic obstructive pulmonary disease (COPD) is a complex inflammatory condition that can affect haemostasis. This study aimed to determine differences in platelet-related parameters between controls and COPD subjects. The hypothesis was that platelet indices are disturbed in COPD patients, and this would be accompanied by increased C-reactive protein (CRP), fibrinogen (Fbg) and white blood cells (WBC). Therefore, platelet count (Plt), platelet-related parameters - mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (Pct), their ratios (MPV/Plt, MPV/Pct, PDW/Plt, PDW/Pct), platelet to lymphocyte ratio (PLR), Plt index as well as CRP, Fbg and WBC were assessed. Materials and methods: Study included 109 patients with stable COPD and 95 control subjects, recruited at Clinical Department for Lung Diseases Jordanovac, University Hospital Centre Zagreb (Zagreb, Croatia). Complete blood count was performed on Sysmex XN-1000, CRP on Cobas c501, and Fbg on BCS XP analyser. Data were analysed with MedCalc statistical software. Results: Platelet ($P = 0.007$) and PLR ($P = 0.006$) were increased, while other platelet indices were decreased in COPD patients compared to controls. Combined model that included PLR, PDW and WBC showed great diagnostic performances, and correctly classified 75% of cases with an AUC of 0.845 (0.788 - 0.892), $P < 0.001$. Comorbidities

(cardiovascular or metabolic diseases) had no effect on investigated parameters, while inhaled corticosteroids/long-acting beta2-agonists (ICS/LABA) therapy increased MPV and PDW values in COPD patients. Conclusion: Platelet indices were altered in COPD patients and they could be valuable as diagnostic markers of COPD development, especially if combined with already known inflammatory markers.

Horwood, C. R., D. Mansour, et al. (2019). **"Long-Term Results After Lung Volume Reduction Surgery: A Single Institution's Experience."** Ann Thorac Surg **107**(4): 1068-1073.

BACKGROUND: The National Emphysema Treatment Trial (NETT) showed a clear survival and quality of life benefit for patients selected for lung volume reduction surgery (LVRS). However, long-term outcomes after LVRS are still lacking. The aim of this study was to evaluate overall mortality and functional durability in this single-institution cohort of patients undergoing LVRS. METHODS: A single-institution registry identified all patients who had undergone LVRS from January 2006 through August 2017. Records were retrospectively reviewed, and data were collected to include pulmonary functions test values, he University of California, San Diego shortness of breath questionnaire and complication and mortality rate. RESULTS: LVRS was performed in 135 patients with a 2.2% 90-day mortality rate (n = 3). Estimated 1-, 2- and 5-year survival was 0.94 (95% confidence interval [CI], 0.88 to 0.97), 0.91 (95% CI, 0.83 to 0.95), and 0.71 (95% CI, 0.57 to 0.81), respectively. Mean improvement in forced expiratory volume in 1 second% predicted from preoperative baseline at 1 and 2 years was 5.3 (95% CI, 3.1 to 7.4) and 4.3 (95% CI, 1.9 to 6.6), respectively. There was a mean improvement in maximum workload of 5.2 W (95% CI, 0.9 to 9.4) at 1 year. Also, shortness of breath questionnaire scores had a mean decrease of -17.3 points (95% CI, -21.8 to -13) at 6 months and -13.9 points (95% CI, -18.4 to -9.3) at 1 year. CONCLUSIONS: LVRS is an effective operation with overall improvement in functional status and quality of life in appropriately selected patients.

Houssaini, A., M. Breau, et al. (2018). **"mTOR pathway activation drives lung cell senescence and emphysema."** JCI Insight **3**(3)Chronic obstructive pulmonary disease (COPD) is a highly prevalent and devastating condition for which no curative treatment is available. Exaggerated lung cell senescence may be a major pathogenic factor. Here, we investigated the potential role for mTOR signaling in lung cell senescence and alterations in COPD using lung tissue and derived cultured cells from patients with COPD and from age- and sex-matched control smokers. Cell senescence in COPD was linked to mTOR activation, and mTOR inhibition by low-dose rapamycin prevented cell senescence and inhibited the proinflammatory senescence-associated secretory phenotype. To explore whether mTOR activation was a causal pathogenic factor, we developed transgenic mice exhibiting mTOR overactivity in lung vascular cells or alveolar epithelial cells. In this model, mTOR activation was sufficient to induce lung cell senescence and to mimic COPD lung alterations, with the rapid development of lung emphysema, pulmonary hypertension, and inflammation. These findings support a causal relationship between mTOR activation, lung cell senescence, and lung alterations in COPD, thereby identifying the mTOR pathway as a potentially new therapeutic target in COPD.

Huang, J., T. Zeng, et al. (2019). **"Clinical significance of high-mobility group box-1 (HMGB1) in subjects with type 2 diabetes mellitus (T2DM) combined with chronic obstructive pulmonary disease (COPD)."** J Clin Lab Anal **33**(6): e22910.

BACKGROUND: Simple method to predict type 2 diabetes mellitus (T2DM) combined with chronic obstructive pulmonary disease (COPD) is in great need clinically. This study aims to assess the clinical significance of high-mobility group box-1 (HMGB1) in predicting T2DM combined with COPD in Chinese patients with T2DM or COPD. METHODS: Serum concentrations of glycated hemoglobin (HbA1C), fasting plasma glucose (FPG), fasting insulin (FINS), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), C-reactive protein (CRP), fibrinogen (FIB), HMGB1, white blood cell count (WBC), neutrophil% (NEU%), and lung function text such as forced expiratory volume 1/forced vital capacity (FEV1/FVC) and forced expiratory volume 1% predicted value (FEV1%pred) were measured in 126 T2DM patients, 118 COPD patients, 112 T2DM combined with COPD patients, and 120 healthy controls. Logistic regression was used to estimate the risk factors for T2DM combined with COPD. RESULTS: High-mobility group box-1 elevated in patients with T2DM combined with COPD, significantly higher than other subjects ($P < 0.05$), and differences in HMGB1 also existed between patients with T2DM or COPD and healthy individuals ($P < 0.01$). HMGB1 was positively correlated with HOMA-IR, FBG, and HbA1c ($P < 0.01$) and negatively correlated with FEV1/FVC and FEV1%pred ($P < 0.01$). Logistic regression showed that HMGB1 was identified to be independent risk

factor for T2DM combined with COPD. CONCLUSION: High-mobility group box-1 was independent risk factor for T2DM combined with COPD and can be served to predict the occurrence of T2DM combined with COPD.

Hwang, Y. I. (2019). **"Reducing chronic obstructive pulmonary disease mortality in Korea: early diagnosis matters."** Korean J Intern Med **34**(6): 1212-1214.

Jacobs, D. M., K. Noyes, et al. (2018). **"Early Hospital Readmissions after an Acute Exacerbation of Chronic Obstructive Pulmonary Disease in the Nationwide Readmissions Database."** Ann Am Thorac Soc **15**(7): 837-845.

RATIONALE: Understanding the causes and factors related to readmission for an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) within a nationwide database including all payers and ages can provide valuable input for the development of generalizable readmission reduction strategies. OBJECTIVES: To determine the rates, causes, and predictors for early (3-, 7-, and 30-d) readmission in patients hospitalized with AECOPD in the United States using the Nationwide Readmission Database after the initiation of the Hospital Readmissions Reduction Program, but before its expansion to COPD. METHODS: We conducted an analysis of the Nationwide Readmission Database from 2013 to 2014. Index admissions and readmissions for an AECOPD were defined consistent with Hospital Readmissions Reduction Program guidelines. We investigated the percentage of 30-day readmissions occurring each day after discharge and the most common readmission diagnoses at different time periods after hospitalization. The relationship between predictors (categorized as patient, clinical, and hospital factors) and early readmission were evaluated using a hierarchical two-level logistic model. To examine covariate effects on early-day readmission, predictors for 3-, 7-, and 30-day readmissions were modeled separately. RESULTS: There were 202,300 30-day readmissions after 1,055,830 index AECOPD admissions, a rate of 19.2%. The highest readmission rates (4.2-5.5%) were within the first 72 hours of discharge, and 58% of readmissions were within the first 15 days. Respiratory-based diseases were the most common reasons for readmission (52.4%), and COPD was the most common diagnosis (28.4%). Readmission diagnoses were similar at different time periods after discharge. Early readmission was associated with patient (Medicaid payer status, lower household income, and higher comorbidity burden) and clinical factors (longer length of stay and discharge to a skilled nursing facility). Predictors did not vary substantially by time of readmission after discharge within the 30-day window. CONCLUSIONS: Thirty-day readmissions after an AECOPD remain a major healthcare burden, and are characterized by a similar spectrum of readmission diagnoses. Predictors associated with readmission include both patient and clinical factors. Development of a COPD-specific risk stratification algorithm based on these factors may be necessary to better predict patients with AECOPD at high risk of early readmission.

John, C., N. F. Reeve, et al. (2019). **"Cohort Profile: Extended Cohort for E-health, Environment and DNA (EXCEED)."** Int J Epidemiol **48**(3): 678-679j.

Khan, R. A., H. M. Waseem, et al. (2019). **"Plasma surfactant Protein-D levels in healthy subjects and COPD patients."** J Pak Med Assoc **69**(4): 494-498.

OBJECTIVE: To compare plasma surfactant protein-D levels in healthy smokers and Chronic obstructive pulmonary disease patients. METHODS: The comparative study was conducted at the University of Health Sciences, Lahore, Pakistan, from January to December 2015, and comprised chronic obstructive pulmonary disease patients and healthy smokers of either gender aged 40-80 years. Plasma surfactant protein-D levels of male and female subjects were estimated and compared with lung function and tobacco exposure. Blood samples were collected after complete history, physical examination and spirometry. Plasma levels were measured using enzyme-linked immunosorbent assay. Plasma cotinine levels were also measured for the determination of tobacco as well as biomass exposure along with pack years. SPSS 20 was used for data analysis.. RESULTS: Of the 84 subjects, there were 42(50%) patients and as many controls. Both groups had 21(50%) males and as many females. There was no significant difference in the plasma surfactant protein-D levels of males and females in the patient group compared to their counterparts in the control group ($p>0.05$). Females developed the disease at a younger age compared to males ($p=0.04$). There was no significant difference in terms of pack-years and cotinine levels between the groups ($p>0.05$) and lung function showed greater deterioration in the females compared to males with similar tobacco exposure ($p<0.05$).. CONCLUSIONS: The gender did not affect plasma surfactant protein-D levels.

Kinoshita, Y., K. Watanabe, et al. (2019). **"Distribution of emphysema and fibrosis in idiopathic pulmonary fibrosis with coexisting emphysema."** Histopathology **74**(7): 1103-1108.

AIMS: Combined pulmonary fibrosis and emphysema (CPFE) is a syndrome that results from tobacco smoking. Emphysema and fibrosis in CPFE patients have been considered to exist separately, with emphysema in the upper lobes and interstitial pneumonia in the lower lobes. The aim of this study was to examine the intrapulmonary distribution of fibrosis and emphysema in clinically diagnosed patients with idiopathic pulmonary fibrosis (IPF) and coexisting emphysema. METHODS AND RESULTS: Among IPF patients (n = 40) who had been autopsied or pneumonectomised for lung transplantation from 1993 to 2018, we retrospectively selected patients with IPF and coexisting emphysema (n = 19) on the basis of the appearance on chest computed tomography (IPF patients with emphysema). We then histologically determined the intrapulmonary distribution of emphysema and fibrosis in the upper lobes and the lower lobes separately. In 15 of the 19 IPF patients with emphysema (79%), fibrosis and emphysema coexisted in the upper lobes and the lower lobes. No patients showed emphysema exclusively in the upper lobes and fibrosis exclusively in the lower lobes. CONCLUSIONS: In the autopsied and pneumonectomised specimens of IPF patients with emphysema, craniocaudal separation of emphysema and fibrosis (emphysema in the upper lobes and interstitial pneumonia in the lower lobes) was histologically rare; coexistence or collision of fibrosis and emphysema in each lobe was common.

Krishnamurthy, S., Y. Sivagnaname, et al. (2019). **"Identification of subclinical cognitive impairment in chronic obstructive pulmonary disease using auditory P300 event related potential."** Monaldi Arch Chest Dis **89**(2)Adequate cognitive functioning in chronic obstructive pulmonary disease (COPD) patients is essential to understand the nature of the disease, adherence to treatment, and for leading a better quality of life. While cognitive impairment in severe forms of COPD have been well documented, identification of subclinical cognitive impairment in stable COPD patients remains crucial for planning prevention strategies. Hence the present study aimed to study and compare the cognitive function between the COPD patients, and normal individuals. The cognitive function was assessed in 42 stable COPD patients and 42 normal individuals with Mini Mental State Examination (MMSE), and auditory P300 event related potentials. Baseline characteristics and the cognitive parameters were compared between the COPD patients and the normal individuals; a $p<0.05$ was considered statistically significant. The latency of the P300 waves was significantly ($p<0.05$) prolonged (304.27+/-20.73 in COPD, 291.11+/-24.53 in normal individuals), and the amplitude (4.36+/-1.56 in COPD, 5.46+/-3.12 in normal individuals) was significantly reduced in the COPD patients compared to the normal individuals. MMSE scores were also significantly ($p<0.001$) different between the COPD patients (26.97+/-0.89), and the normal individuals (27.80+/-0.83). Cognition may be affected even at the earlier stages of the disease among the COPD patients, as evident by changes in the P300 values. Auditory P300 event related potential may be used as an adjunct to the routine MMSE examination, as it serves as an effective tool in identifying the cognitive impairment in different stages of COPD. This may help the patients to adopt prevention strategies that help to avoid adverse effects on cognition in future.

Lademann, M., M. Lademann, et al. (2019). **"Incorporating symptom data in longitudinal disease trajectories for more detailed patient stratification."** Int J Med Inform **129**: 107-113.

OBJECTIVE: Use symptoms to stratify temporal disease trajectories. MATERIALS AND METHODS: We use data from the Danish National Patient Registry to stratify temporal disease pairs by the symptom distributions they associate to. The underlying data comprise of 6.6 million patients collectively assigned with 7.5 million symptoms from chapter XVIII in the WHO International Classification of Disease version 10 terminology. RESULTS: We stratify 33 disease pairs into 67 temporal disease-symptom-disease trajectories from three main diagnoses (two diabetes subtypes and COPD), where the symptom significantly changes the risk of developing the subsequent diseases. We combine these trajectories into three temporal disease networks, one for each main diagnosis. We confirm apparent relations between diseases and symptoms and discovered that multiple symptoms decrease the risk for diabetes progression. CONCLUSION: Symptoms can be used to stratify disease trajectories, and we suggest that this approach can be applied to temporal disease trajectories systematically using structured claims data. The method can be extended to also use text-mined symptoms from unstructured data in health records.

Ladjemi, M. Z., C. Martin, et al. (2019). **"Increased IgA Expression in Lung Lymphoid Follicles in Severe Chronic Obstructive Pulmonary Disease."** Am J Respir Crit Care Med **199**(5): 592-602.

RATIONALE: Accumulation of B cells and lymphoid follicles (LFs) has been described in chronic obstructive pulmonary disease (COPD) airways, but the functional status of lung B cells remains poorly known. OBJECTIVES: To characterize LFs for expression of IgA, the main mucosal antibody. METHODS: The presence of B cells and LFs, including intrafollicular IgA expression, were determined in the lung from patients with COPD (n = 37) versus control subjects (n = 34) by immunohistochemistry. We also evaluated follicular IgA responses in the lungs from mice infected with Pseudomonas aeruginosa (PAO1) (n = 10 per group) and in smoking mice. MEASUREMENTS AND MAIN RESULTS: Whereas in smokers B-cell numbers slightly increased, robust increases in B-cell and LF numbers (mainly in distal airways) were only observed in severe COPD. Most follicular B cells were IgM(+) (70-80%), but IgA(+) (and not IgG(+)) B-cell numbers were increased in LFs from severe COPD compared with control subjects (twofold, 44.7% vs. 25.2%), and this was significant in distal but not proximal airways. Follicular IgA response was also observed in PAO1-infected mouse lungs, but not after smoke exposure. Moreover, follicular IgA expression associated with expression of IL-21, which was very potent to activate immunoglobulin production in vitro. CONCLUSIONS: This study shows that IgA production occurs in peribronchiolar LFs from severe COPD, where IL-21-producing T cells are present, and presumably represents a feature of exacerbated mucosal adaptive immune responses against microbial and/or self-antigens.

Lee, R., D. Lee, et al. (2019). **"Patients With Chronic Obstructive Pulmonary Disease Are at Higher Risk for Pneumonia, Septic Shock, and Blood Transfusions After Total Shoulder Arthroplasty."** Clin Orthop Relat Res **477**(2): 416-423.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) has been associated with several complications after surgery, including pneumonia, myocardial infarction, septic shock, and mortality. To the authors' knowledge, there has been no work analyzing the impact of COPD on complications after total shoulder arthroplasty (TSA). Although previous work has elucidated the complications COPD has on TKA and THA, extrapolating the results of lower extremity arthroplasty to TSA may prove to be inaccurate. Compared with lower extremity arthroplasty, TSA is a relatively new procedure that has only recently gained popularity. Therefore, this study seeks to elucidate COPD's effects on complications in TSA specifically so that postoperative care can be tailored for these patient populations. Assessing these patients may enable surgeons to implement preoperative precautionary measures to prevent serious adverse events in these patients. QUESTIONS/PURPOSES: What serious postoperative complications are patients with COPD at risk for within the 30-day postoperative period after TSA? METHODS: The American College of Surgeons National Surgical Quality Improvement Program(R) (ACS-NSQIP) database was queried to identify 14,494 patients who had undergone TSA between 2005 and 2016, excluding patients who had undergone hemiarthroplasties of the shoulder and revision shoulder arthroplasties. The ACS-NSQIP database was utilized in this study for the comprehensive preoperative and postoperative medical histories it provides for each patient for 274 characteristics. Among the 14,494 patients undergoing TSA, 931 (6%) patients who had a history of COPD were identified, and the two cohorts-COPD and non-COPD-were analyzed for differences in their demographic factors, comorbidities, and acute complications occurring within 30 days of their procedure. Univariate analyses were utilized to assess differences in the prevalence of demographic features, comorbidities, and perioperative/postoperative outcomes after surgery. Multivariate regression analyses were used to assess COPD as an independent risk factor associated with complications. RESULTS: COPD is an independent risk factor for three complications after TSA: pneumonia (odds ratio [OR], 2.793; 95% confidence interval [CI], 1.426-5.471; p = 0.003), bleeding resulting in transfusion (OR, 1.577; 95% CI, 1.155-2.154; p = 0.004), and septic shock (OR, 9.259; 95% CI, 2.140-40.057; p = 0.003). CONCLUSIONS: In light of the increased risk of these serious complications, surgeons should have a lower threshold of suspicion for infection in patients with COPD after TSA so that adequate measures can be taken before developing severe infectious complications including pneumonia and septic shock. Surgeons may also consider administering tranexamic acid in patients with COPD undergoing TSA to reduce the amount of blood transfusions necessary. Future work through randomized control trials analyzing (1) the effectiveness of more aggressive infection prophylaxis in decreasing the risk of pneumonia/septic shock; and (2) the use of tranexamic acid in decreasing blood transfusion requirements in patients with COPD undergoing TSA is warranted. LEVEL OF EVIDENCE: Level III, therapeutic study.

Lee, S. J., S. S. Yun, et al. (2019). **"Validity of the GOLD 2017 classification in the prediction of mortality and respiratory hospitalization in patients with chronic obstructive pulmonary disease."** Int J Chron Obstruct Pulmon Dis **14**: 911-919.

Background: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) released an updated document in 2017 that excluded the spirometric parameter in the classification of patients. The validity of this new classification system in predicting mortality and respiratory hospitalization is still uncertain. Methods: Outpatients (n=149) with chronic obstructive pulmonary disease (COPD) who underwent spirometry and six-minutes walking test from October 2011 to September 2013 were enrolled. The overall mortality and rate of respiratory hospitalization over a median of 61 months were analyzed. Kaplan-Meier survival analyses, receiver operaing curve analyses with areas under the curve (AUCs), and logistic regression analyses for GOLD 2007, GOLD 2011, GOLD 2017, and/or BODE index were performed to evaluate their abilities to predict mortality and respiratory hospitalization. Results: Forty-two (53.2%) patients in 2011 GOLD C or D group were categorized into 2017 GOLD A or B group. The odds ratios of GOLD 2017 group C and group D relative to group A were 7.55 (95% CI, 1.25-45.8) and 25.0 (95% CI, 6.01-102.9) for respiratory hospitalization. Patients in GOLD 2017 group A and group B had significantly better survival (log-rank test, p<0.001) compared with patients in group D; however, survival among patients in GOLD 2007 groups and GOLD 2011 groups was comparable. The AUC values for GOLD 2007, GOLD 2011, GOLD 2017, and BODE index were 0.573, 0.624, 0.691, 0.692 for mortality (p=0.013) and 0.697, 0.707, 0.741, and 0.754 for respiratory hospitalization (p=0.296), respectively. Conclusion: The new GOLD classification may perform better than the previous classifications in terms of predicting mortality and respiratory hospitalization.

Liao, K. M., C. J. Tseng, et al. (2019). **"Outcomes of laparoscopic cholecystectomy in patients with and without COPD."** Int J Chron Obstruct Pulmon Dis **14**: 1159-1165.

Objective: The aim of this study was to investigate the outcomes of patients with COPD after laparoscopic cholecystectomy (LC). Patients and methods: All COPD patients who underwent LC from 2000 to 2010 were identified from the Taiwanese National Health Insurance Research Database. The outcomes of hospital stay, intensive care unit (ICU) stay, and use of mechanical ventilation and life support measures in COPD and non-COPD populations were compared. Results: A total of 3,954 COPD patients who underwent LC were enrolled in our study. There were significant differences in the hospitalization period, ICU stay, and use of mechanical ventilation and life support measures between the COPD and non-COPD populations. The mean hospital stay, ICU stay and number of mechanical ventilation days in the COPD and non-COPD groups were 7.81 vs 6.01 days, 5.5 vs 4.5 days and 6.40 vs 4.74 days, respectively. The use of life support measures, including vasopressors and hemodialysis, and the rates of hospital mortality, acute respiratory failure and pneumonia were also increased in COPD patients compared with those in non-COPD patients. Conclusion: COPD increased the risk of mortality, lengths of hospital and ICU stays, ventilator days and poor outcomes after LC in this study.

Lin, T. L., W. W. Chen, et al. (2019). **"Correlations between serum amyloid A, C-reactive protein and clinical indices of patients with acutely exacerbated chronic obstructive pulmonary disease."** J Clin Lab Anal **33**(4): e22831.

BACKGROUND: To explore the correlations between SAA, CRP, and clinical indices of patients with acutely exacerbated chronic obstructive pulmonary disease (AECOPD). METHODS: A total of 120 patients with AECOPD and another 120 with remitted COPD were enrolled in an AECOPD group and a COPD remission group, respectively. Meanwhile, 120 healthy subjects were included as a control group. SAA, CRP, PCT, Fbg, IL-8, IL-6, TNF-alpha, and IP-10 levels were detected. FEV1 and FEV1 /FVC were measured. RESULTS: Compared with control group, the serum levels of SAA, CRP, PCT, Fbg, IL-8, IL-6, TNF-alpha, and IP-10 significantly increased in COPD remission group ($P < 0.05$). The levels of AECOPD group significantly exceeded those of COPD remission group ($P < 0.05$). The levels of AECOPD patients with different GOLD grades were significantly different ($P < 0.05$). AECOPD group had significantly lower FEV1 and FEV1 /FVC than those of COPD remission group ($P < 0.05$). The CAT score of AECOPD patients was (18.41 +/- 2.55) points. The levels of SAA, CRP, PCT, Fbg, IL-8, IL-6, TNF-alpha, and IP-10 were negatively correlated with FEV1 and FEV1 /FVC, and positively correlated with CAT score. The area under receiver operating characteristic curve of SAA was largest (0.931). The cutoff values for SAA, CRP, PCT and Fbg were 18.68 mg/L, 14.70 mg/L, 0.39 mug/L, 3.91 g/L, 0.46 mug/L, 24.17 mug/L, 7.18 mg/L, and 83.19 ng/L, respectively. CONCLUSIONS: Serum levels of SAA, CRP, PCT, Fbg, IL-8, IL-6, TNF-alpha, and IP-10 in AECOPD patients were elevated, which may undermine pulmonary functions. SAA can be used as an effective index for AECOPD diagnosis and treatment.

Liu, V. X., K. L. Winthrop, et al. (2018). **"Association between Inhaled Corticosteroid Use and Pulmonary Nontuberculous Mycobacterial Infection."** Ann Am Thorac Soc **15**(10): 1169-1176.

RATIONALE: Nontuberculous mycobacterial (NTM) pulmonary disease prevalence is increasing. OBJECTIVES: To determine the association between the use of inhaled corticosteroids and the likelihood of NTM pulmonary infection among individuals with treated airway disease. METHODS: We conducted a case-control study of subjects with airway disease with and without NTM pulmonary infection (based on mycobacterial respiratory cultures) between 2000 and 2010 in northern California. We quantified the use of inhaled corticosteroids, other airway disease medications, and healthcare use within 6 months of NTM pulmonary infection identification. We used 1:10 case-control matching and conditional logistic regression to evaluate the association between the duration and cumulative dosage of inhaled corticosteroid use and NTM pulmonary infection. RESULTS: We identified 248 cases with NTM pulmonary infection with an estimated rate of 16.4 cases per 10,000 subjects treated for airway disease. The median interval between treated airway disease cohort entry (defined as date of patient filling the third airway disease treatment prescription) and NTM case identification was 1,217 days. Compared with control subjects, subjects with NTM pulmonary infection were more likely to use airway disease medications including systemic steroids; they were also more likely to use health care. Any inhaled corticosteroids use between 120 days and 2 years before cohort entry was associated with substantially increased odds of NTM infection. For example, the adjusted odds ratio for NTM infection among inhaled corticosteroid users in a 2-year interval was 2.51 (95% confidence interval, 1.40-4.49; $P < 0.01$). Increasing cumulative inhaled corticosteroid dose was also associated with greater odds of NTM infection. CONCLUSIONS: Inhaled corticosteroid use, and particularly high-dose inhaled corticosteroid use, was associated with an increased risk of NTM pulmonary infection.

Locke, E. R., R. M. Thomas, et al. (2019). **"Using Video Telehealth to Facilitate Inhaler Training in Rural Patients with Obstructive Lung Disease."** Telemed J E Health **25**(3): 230-236.

BACKGROUND: Proper inhaler technique is important for effective drug delivery and symptom control in chronic obstructive pulmonary disease (COPD) and asthma, yet not all patients receive inhaler instructions. INTRODUCTION: Using a retrospective chart review of participants in a video telehealth inhaler training program, the study compared inhaler technique within and between monthly telehealth visits and reports associated with patient satisfaction. MATERIALS AND METHODS: Seventy-four (N = 74) rural patients prescribed >/=1 inhaler participated in three to four pharmacist telehealth inhaler training sessions using teach-to-goal (TTG) methodology. Within and between visit inhaler technique scores are compared, with descriptive statistics of pre- and postprogram survey results including program satisfaction and computer technical issues. Healthcare utilization is compared between pre- and post-training periods. RESULTS: Sixty-nine (93%) patients completed all three to four video telehealth inhaler training sessions. During the initial visit, patients demonstrated improvement in inhaler technique for metered dose inhalers (albuterol, budesonide/formoterol), dry powder inhalers (formoterol, mometasone, tiotropium), and soft mist inhalers (ipratropium/albuterol) ($p < 0.01$ for all). Improved inhaler technique was sustained at 2 months ($p < 0.01$). Ninety-four percent of participants were satisfied with the program. Although technical issues were common, occurring among 63% of attempted visits, most of these visits (87%) could be completed. There was no significant difference in emergency department visits and hospitalizations pre- and post-training. DISCUSSION: This study demonstrated high patient acceptance of video telehealth training and objective improvement in inhaler technique. CONCLUSIONS: Video telehealth inhaler training using the TTG methodology is a promising program that improved inhaler technique and access to inhaler teaching for rural patients with COPD or asthma.

Louvaris, Z., H. Habazettl, et al. (2018). **"Near-infrared spectroscopy using indocyanine green dye for minimally invasive measurement of respiratory and leg muscle blood flow in patients with COPD."** J Appl Physiol (1985) **125**(3): 947-959.

Reliability of near-infrared spectroscopy, measuring indocyanine green (ICG) for minimally invasive assessment of relative muscle blood flow during exercise has been examined in fit young individuals but not in chronic obstructive pulmonary disease (COPD). Here we ask whether it could be used to evaluate respiratory and locomotor muscle perfusion in COPD patients. Vastus lateralis muscle blood flow (MBF, the reference method calculated from arterial and muscle ICG concentration curves) and a blood flow index [BFI, calculated using only the (same) muscle ICG concentration curves] were compared in 10 patients (forced expiratory volume in 1 s: 51 +/- 6% predicted) at rest and during cycling at 25, 50, 75, and 100% of peak work rate (WRpeak). Intercostal muscle MBF and BFI were also compared during isocapnic hyperpnea at rest, reproducing ventilation levels up to those at WRpeak. Intercostal and vastus lateralis BFI increased

with increasing ventilation during hyperpnea (from 2.5 +/- 0.3 to 4.5 +/- 0.7 nM/s) and cycling load (from 1.0 +/- 0.2 to 12.8 +/- 1.9 nM/s), respectively. There were strong correlations between BFI and MBF for both intercostal (r = 0.993 group mean data, r = 0.872 individual data) and vastus lateralis (r = 0.994 group mean data, r = 0.895 individual data). Fold changes from rest in BFI and MBF did not differ for either the intercostal muscles or the vastus lateralis. Group mean BFI data showed strong interrelationships with respiratory and cycling workload, and whole body metabolic demand (r ranged from 0.913 to 0.989) simultaneously recorded during exercise. We conclude that BFI is a reliable and minimally invasive tool for evaluating relative changes in respiratory and locomotor muscle perfusion from rest to peak exercise in COPD patient groups. NEW & NOTEWORTHY We show that noninvasive near-infrared spectroscopic (NIRS) detection of indocyanine green dye (ICG) after peripheral venous injection adequately reflects intercostal and locomotor muscle perfusion during exercise and hyperpnea in patients with chronic obstructive pulmonary disease (COPD). Mean, individual, and fold change responses from rest to exercise or hyperpnea correlated closely with the reference method, which requires arterial sampling. NIRS-ICG is a reliable, robust, and essentially noninvasive tool for assessing relative changes in intercostal and locomotor muscle perfusion in COPD patient groups.

Mathew, A. R., S. P. Bhatt, et al. (2019). **"Life-Course Smoking Trajectories and Risk for Emphysema in Middle Age: The CARDIA Lung Study."** Am J Respir Crit Care Med **199**(2): 237-240.

Matthees, N. G., J. A. Mankin, et al. (2019). **"Pneumomediastinum in blunt trauma: If aerodigestive injury is not seen on CT, invasive workup is not indicated."** Am J Surg **217**(6): 1047-1050.

BACKGROUND: Pneumomediastinum following blunt trauma is often observed on CT imaging, and concern for associated aerodigestive injury often prompts endoscopy and/or fluoroscopy. In recent years, adoption of multi-detector CT technology has resulted in high resolution images that may clearly identify aerodigestive injuries. The purpose of this study was to evaluate the utility of multi-detector CT in the identification of blunt aerodigestive injuries. METHODS: Over five years, patients with pneumomediastinum following blunt trauma were identified from the registry of a level 1 trauma center. All CT imaging of trauma patients during this time period was accomplished with 64-slice scanners. RESULTS: 127 patients with blunt traumatic pneumomediastinum were identified. Five airway injuries were identified, and all injuries were evident on CT imaging. No patient was found to have airway injury by endoscopy that was not evident on CT. No patient had an esophageal injury. CONCLUSION: Multi-detector CT imaging identifies aerodigestive injuries associated with pneumomediastinum following blunt trauma. The absence of a recognizable aerodigestive injury by CT effectively rules out the presence of such injury.

Media, A. S., M. Persson, et al. (2019). **"Chronic obstructive pulmonary disease and comorbidities' influence on mortality in non-small cell lung cancer patients."** Acta Oncol **58**(8): 1102-1106.

Background: In Denmark, lung cancer is the most common cause of cancer-related death and chronic obstructive pulmonary disease (COPD) is the most common comorbidity in patients with non-small cell lung cancer (NSCLC). The aim of this study was to investigate the influence of COPD and other common comorbidities on NSCLC mortality. Methods: Patients (n = 534) diagnosed with NSCLC at Aalborg University Hospital from 2008-2010 were included retrospectively in this study. Patient records were assessed and the population was dichotomized in COPD and non-COPD subgroups. Comorbidities i.e., ischemic heart disease, hypertension, diabetes mellitus, apoplexia, former malignancy, interstitial lung disease and psychiatric comorbidity were registered and a comorbidity count were calculated. Survival was assessed with log-rank test and uni- and multivariate regression analysis were performed for COPD-status and comorbidity count adjusting for age, gender, BMI, smoking exposure, cancer stage, method of treatment and eastern cooperative cancer group (ECOG) performance status score. Results: Of 534 NSCLC patients included, 470 were divided into COPD and non-COPD subgroups, 70% with COPD (329/470) and 30% without COPD (141/470). Only 32.5% of the patients in the COPD-group had previously diagnosed COPD. Log-rank test did not show statistically significant difference in survival between the COPD and non-COPD groups (p = .215). Multivariate Cox regression analysis did not show statistically significant association between overall 5-year mortality and the presence of COPD (HR-adj = 0.808, 95% CI = 0.612; 1.068) or other comorbidities (HR-adj = 1.101, 95% CI = 0.979; 1.237) when adjusted for age, BMI, gender, smoking exposure, ECOG performance status, treatment and TNM-stage. Conclusion: Our findings do not suggest that COPD nor other common comorbidities are significantly associated with higher mortality in NSCLC patients.

Millares, L., S. Pascual, et al. (2019). **"Relationship between the respiratory microbiome and the severity of airflow limitation, history of exacerbations and circulating eosinophils in COPD patients."** BMC Pulm Med **19**(1): 112.

BACKGROUND: The respiratory microbiome is altered in COPD patients but its relationship with core components of the disease, such as the severity of airflow limitation, the frequency of exacerbations or the circulating levels of eosinophils, is unclear. METHODS: Cross-sectional study comprising 72 clinically stable COPD patients (mean age 68 [SD 7.9] years; FEV1 48.7 [SD 20.1]% of reference) who provided spontaneous sputum samples for 16S rRNA gene amplification and sequencing. The microbiome composition was analysed with QIIME. RESULTS: We observed that: (1) more severe airflow limitation was associated with reduced relative abundance (RA) of Treponema and an increase in Pseudomonas; (2) patients with >/=2 exacerbations the previous year showed a significantly different bacterial community with respect to non-exacerbators (p = 0.014), with changes in 13 genera, including an increase of Pseudomonas, and finally, (3) peripheral eosinophils levels >/=2% were associated with more diverse microbiome [Chao1 224.51 (74.88) vs 277.39 (78.92) p = 0.006; Shannon 3.94 (1.05) vs 4.54 (1.06) p = 0.020], and a significant increase in the RAs of 20 genera. CONCLUSION: The respiratory microbiome in clinically stable COPD patients varies significantly according to the severity of airflow limitation, previous history of exacerbations and circulating eosinophils levels.

Nyberg, A., D. Saey, et al. (2018). **"Cardiorespiratory and muscle oxygenation responses to low-load/high-repetition resistance exercises in COPD and healthy controls."** J Appl Physiol (1985) **124**(4): 877-887.

Single-limb exercises have been used as a strategy to improve aerobic exercise tolerance in patients with chronic obstructive pulmonary disease (COPD) by alleviating the cardiopulmonary demand. We asked whether this strategy would also apply to cardiorespiratory demand and amount of work performed during single-limb and two-limb low-load/high-repetition resistance exercises in 20 patients with COPD [forced expiratory volume in 1 s (FEV1) = 1.0 liters, 38% of predicted] and 15 age-, sex-, and activity-matched healthy controls. Peak ventilation, peak oxygen consumption (Vo2), and peak heart rate (HR) were assessed to document cardiorespiratory demand during shoulder flexion and knee extension exercises while exercise tolerance was assessed by the total amount of work achieved. In addition, changes in myoglobin-deoxyhemoglobin level (Deltadeoxy-[Hb/Mb]) were measured during single-limb knee extension. In COPD, single-limb shoulder flexion and knee extension elicited higher localized workloads than two-limb exercises (21 and 24% higher workloads for the former exercise) while cardiopulmonary demand was 8-16% higher during two-limb exercises. When expressed as a percentage of peak values achieved during incremental cycle ergometry, peak VO2 and HR were similarly high during single-limb shoulder flexion and knee extension exercises, representing 90% of peak HR and 60% of peak VO2. Apart from single-limb knee extension, cardiorespiratory demand per kilogram work during low-load/high-repetition knee extension and shoulder flexion exercises was higher in patients with COPD than in healthy controls (range 27-122%, P < 0.0125). Deltadeoxy-[Hb/Mb] of the quadriceps during knee extension was similar between the two groups, while Deltadeoxy-[Hb/Mb] per kilogram work was higher in patients with COPD. We conclude that 1) in patients with COPD, single-limb exercises resulted in lower peak cardiorespiratory demand as well as higher localized workloads compared with two-limb exercises; 2) compared with healthy controls, the cardiorespiratory demand, either expressed per unit of work or relative to peak capacity, was higher in patients with COPD than in controls during low-load/high-repetition resistance exercises, irrespective of the involvement of one or two limbs or of the upper or lower extremity; 3) quadriceps muscle deoxygenation per unit of work during low-load/high-repetition knee extension was increased in COPD compared with controls; and 4) single- and two-limb low-load/high-repetition knee extension and shoulder flexion resistance exercises imposed a similar burden on the cardiorespiratory system, resulting in a higher cardiorespiratory demand per kilogram work performed during shoulder flexion compared with knee extension, in both COPD and healthy controls. NEW & NOTEWORTHY In chronic obstructive pulmonary disease (COPD), single-limb knee extension and shoulder flexion resulted in a lower peak cardiorespiratory response as well as larger localized exercise workloads compared with two-limb exercises. Cardiorespiratory and quadriceps deoxygenation cost per kilogram work was greater in COPD compared with healthy controls, despite similar acute responses. Compared with knee extension, shoulder flexion imposed a similar burden on the cardiorespiratory system in patients with COPD and healthy controls.

Occhipinti, M., M. Paoletti, et al. (2019). **"Spirometric assessment of emphysema presence and severity as measured by quantitative CT and CT-based radiomics in COPD."** Respir Res **20**(1): 101.

BACKGROUND: The mechanisms underlying airflow obstruction in COPD cannot be distinguished by standard spirometry. We ascertain whether mathematical modeling of airway biomechanical properties, as assessed from spirometry, could provide estimates of emphysema presence and severity, as quantified by computed tomography (CT) metrics and CT-based radiomics. METHODS: We quantified presence and severity of emphysema by standard CT metrics (VIDA) and co-registration analysis (ImbioLDA) of inspiratory-expiratory CT in 194 COPD patients who underwent pulmonary function testing. According to percentages of low attenuation area below - 950 Hounsfield Units (%LAA-950insp) patients were classified as having no emphysema (NE) with %LAA-950insp < 6, moderate emphysema (ME) with %LAA-950insp >/= 6 and < 14, and severe emphysema (SE) with %LAA-950insp >/= 14. We also obtained stratified clusters of emphysema CT features by an automated unsupervised radiomics approach (CALIPER). An emphysema severity index (ESI), derived from mathematical modeling of the maximum expiratory flow-volume curve descending limb, was compared with pulmonary function data and the three CT classifications of emphysema presence and severity as derived from CT metrics and radiomics. RESULTS: ESI mean values and pulmonary function data differed significantly in the subgroups with different emphysema degree classified by VIDA, ImbioLDA and CALIPER ($p < 0.001$ by ANOVA). ESI differentiated NE from ME/SE CT-classified patients (sensitivity 0.80, specificity 0.85, AUC 0.86) and SE from ME CT-classified patients (sensitivity 0.82, specificity 0.87, AUC 0.88). CONCLUSIONS: Presence and severity of emphysema in patients with COPD, as quantified by CT metrics and radiomics can be estimated by mathematical modeling of airway function as derived from standard spirometry.

Paulin, L. M., B. M. Smith, et al. (2018). **"Occupational Exposures and Computed Tomographic Imaging Characteristics in the SPIROMICS Cohort."** Ann Am Thorac Soc **15**(12): 1411-1419.

RATIONALE: Quantitative computed tomographic (CT) imaging can aid in chronic obstructive pulmonary disease (COPD) phenotyping. Few studies have identified whether occupational exposures are associated with distinct CT imaging characteristics. OBJECTIVES: To examine the association between occupational exposures and CT-measured patterns of disease in the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study). METHODS: Participants underwent whole-lung multidetector helical CT at full inspiration and expiration. The association between occupational exposures (self-report of exposure to vapors, gas, dust, or fumes [VGDF] at the longest job) and CT metrics of emphysema (percentage of total voxels < -950 Hounsfield units at total lung capacity), large airways (wall area percent [WAP] and square-root wall area of a single hypothetical airway with an internal perimeter of 10 mm [Pi10]), and small airways (percent air trapping [percent total voxels < -856 Hounsfield units at residual volume] and parametric response mapping of functional small-airway abnormality [PRM fSAD]) were explored by multivariate linear regression, and for central airway measures by generalized estimating equations to account for multiple measurements per individual. Models were adjusted for age, sex, race, current smoking status, pack-years of smoking, body mass index, and site. Airway measurements were additionally adjusted for total lung volume. RESULTS: A total of 2,736 participants with available occupational exposure data (n = 927 without airflow obstruction and 1,809 with COPD) were included. The mean age was 64 years, 78% were white, and 54% were male. Forty percent reported current smoking, and mean (SD) pack-years was 49.3 (26.9). Mean (SD) post-bronchodilator forced expiratory volume in 1 second (FEV1) was 73 (27) % predicted. Forty-nine percent reported VGDF exposure. VGDF exposure was associated with higher emphysema (beta = 1.17; 95% confidence interval [CI], 0.44-1.89), greater large-airway disease as measured by WAP (segmental beta = 0.487 [95% CI, 0.320-0.654]; subsegmental beta = 0.400 [95% CI, 0.275-0.527]) and Pi10 (beta = 0.008; 95% CI, 0.002-0.014), and greater small-airway disease was measured by air trapping (beta = 2.60; 95% CI, 1.11-4.09) and was nominally associated with an increase in PRM fSAD (beta = 1.45; 95% CI, 0.31-2.60). These findings correspond to higher odds of percent emphysema, WAP, and air trapping above the 95th percentile of measurements in nonsmoking control subjects in individuals reporting VGDF exposure. CONCLUSIONS: In an analysis of SPIROMICS participants, we found that VGDF exposure in the longest job was associated with an increase in emphysema, and in large- and small-airway disease, as measured by quantitative CT imaging.

Pedro, P. I., L. Maia Santos, et al. (2019). **"Benefits of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease and interstitial lung disease with the same dyspnea severity."** Pulmonology **25**(2): 117-118.

Poznanski, M., E. Brzezianska-Lasota, et al. (2019). **"Serum levels and gene expression of pentraxin 3 are elevated in COPD."** Adv Med Sci **64**(1): 85-89.
PURPOSE: Pentraxin 3 (PTX-3) is an acute phase protein that belongs to the pentraxin superfamily. It is synthesized locally at the site of inflammation and its levels are related to the damage of blood vessels. There are only a few studies examining the relationship between PTX-3 and chronic obstructive pulmonary disease (COPD). The aim of this study was to evaluate the serum levels of PTX-3 and relative PTX-3 gene expression in COPD patients and their correlations with cigarette smoking history and lung function. MATERIALS/METHODS: A total number of 34 participants were enrolled into this study. Only stable patients without comorbidities were recruited. After obtaining written informed consent all planned procedures were performed (pre- and post-bronchodilator spirometry, blood samples for PTX-3 serum levels and PTX-3 gene expression measurements, demographical data, medical history, COPD patients were also asked for CAT and MMRC questionnaires). RESULTS: PTX-3 serum levels were significantly higher in the COPD group (29.22 (5.47) ng/ml vs. 14.64 (3.64) ng/ml). PTX-3 gene relative quantification (RQ) values were also significantly higher in the COPD group (0.15 (1.33) vs. -2.80 (1.99)). No differences in CRP serum levels were found between the control group and the COPD group. CONCLUSIONS: Our study demonstrates that serum levels of PTX-3 and the relative expression values of its gene are elevated in COPD, and can be related to cigarette smoking history.

Qi, X., H. Chen, et al. (2019). **"LncRNAs NR-026690 and ENST00000447867 are upregulated in CD4(+) T cells in patients with acute exacerbation of COPD."** Int J Chron Obstruct Pulmon Dis **14**: 699-711.
Objective: The aim of the study was to determine the expression profile of long noncoding RNAs (lncRNAs) in CD4(+) T cells from COPD patients and explore the clinical value of the lncRNAs. Methods: First, microarray analysis was performed. Differentially expressed lncRNAs were validated by quantitative real-time reverse transcription-PCR (qRT-PCR) in samples from 56 patients with acute exacerbations of COPD (AECOPD), 56 patients with stable COPD, and 35 healthy controls. Meanwhile, the clinical value was tested by receiver operating characteristic curve analysis. The functions of lncRNAs were analyzed by the Gene Ontology and Kyoto Encyclopedia of Genes and Genomes database. The potential target genes that might be regulated by NR-026690 and ENST00000447867 were identified by the lncRNA-mRNA network and competing endogenous RNA network. The transcriptional expression level of rap guanine nucleotide exchange factor 3 (RAPGEF3) was tested by qRT-PCR. The correlation of the expression between NR-026690, ENST00000447867, and RAPGEF3 was analyzed by Spearman's correlation test. Results: We found that the relative expression levels of ENST00000447867 and NR-026690 in the CD4(+) T cells of AECOPD patients were significantly higher than in the stable COPD patients and control subjects by microarray and qRT-PCR validation. The transcriptional expression level of RAPGEF3 in the CD4(+) T cells was significantly higher in the AECOPD group compared to the control group ($P<0.01$) and the stable COPD group ($P<0.05$). RAPGEF3 expression was positively associated with NR-026690 ($r=0.4925$, $P<0.01$) and ENST00000447867 ($r=0.4065$, $P<0.01$). Conclusion: NR-026690 and ENST00000447867 might be potential biomarkers for COPD. They might affect RAPGEF3 as miRNA sponges to regulate COPD development.

Rayyan Assi, H., A. Ziv, et al. (2019). **"The metabolic syndrome and its components are differentially associated with chronic diseases in a high-risk population of 350 000 adults: A cross-sectional study."** Diabetes Metab Res Rev **35**(4): e3121.
AIMS: We compared strengths of associations conferred by the metabolic syndrome (MetS) and its components across four chronic disease categories (cancer, cardiovascular diseases [CVDs], chronic kidney disease [CKD], and chronic obstructive pulmonary disease [COPD]) in a community-dwelling high-risk population. METHODS: This is a cross-sectional analysis of Israeli adults insured in a single health maintenance organization during 2010 to 2013 and having greater than or equal to two MetS components (hypertension, dysglycemia, low high-density lipoprotein level, high plasma triglyceride level, and obesity). Data regarding MetS components, chronic disease prevalence, and sociodemographic variables were retrieved from electronic health records and disease registries. RESULTS: Among 347 244 eligible members, 54.2% had MetS. MetS was negatively associated with cancer, (prevalence ratio [PR] = 0.86; 95% confidence interval, 0.79-0.93) and positively associated with CKD (PR = 1.07, [1.01-1.13]). Some MetS components conferred different associations across the chronic

diseases: a high triglyceride level was positively associated with cancer (PR = 1.15, 1.12-1.18) and CKD (PR = 1.37, 1.32-1.41) but negatively associated with CVD (PR = 0.88, 0.86-0.90) and COPD (PR = 0.93, 0.88-0.98). In the presence of MetS, those with dysglycemia had higher cancer prevalence than those with normoglycemia (PR-interaction MetS*dysglycemia on cancer = 1.14, 1.06-1.22). Likewise, in the presence of MetS, men were more likely than women to present with CVD (PR-interaction MetS*sex on CVD = 1.12, [1.05-1.20]). CONCLUSIONS: Prevalences of the MetS and MetS components distribute unequally across four chronic diseases. MetS including dysglycemia may warrant screening for cancer, and MetS in males may indicate the presence of CVD. Longitudinal studies may reveal if MetS is associated with different risks or merely indicates better prognosis once having a chronic illness.

Reddy, R. S., K. A. Alahmari, et al. (2019). **"Reliability of Chest Wall Mobility and Its Correlation with Lung Functions in Healthy Nonsmokers, Healthy Smokers, and Patients with COPD."** Can Respir J **2019**: 5175949.

Chest wall circumference measurements are common evaluation methods in clinical settings by therapists in order to obtain chest wall mobility. Previous published results have been conflicting, and there is a lot of variability in the method of testing, which needs testing in different conditions. Seventy subjects (25 healthy nonsmokers, 25 healthy smokers, and 20 COPD) aged between 18 and 70 years participated in the study. Upper and lower chest expansion (CE) measurements (2 levels) are performed with cloth inch tape. Intrarater (between day) and interrater (within-day) reliability of CE measurements was evaluated by two examiners. Lung function parameters, forced expiratory volume in first second (FEV1), forced vital capacity (FVC), FEV1/FVC, and vital capacity (VC) were measured using a computerized spirometer (Spiro lab 3). The intrarater reliability for upper and lower CE showed very good agreement with intraclass correlation (ICC) values between 0.90 and 0.93 for upper CE and 0.85 to 0.86 for lower CE. The interrater reliability for upper CE showed good to very good agreement with ICC values ranging between 0.78 and 0.83, and lower CE showed very good agreement with ICC values ranging between 0.82 and 0.84. Upper and lower CE showed a significant and positive correlation with all lung function parameters, with strong correlation with FEV1/FVC (r = 0.68). Upper and lower CE measurements with inch tape showed good intra- and interrater reliability and reproducibility in healthy nonsmokers, healthy smokers, and COPD subjects. Compared to upper, lower CE correlated well with the lung function parameters. Upper and lower CE may be more useful in clinical practice to evaluate chest mobility and to give indirect information on lung function but interpretation with caution is required when considering implementation into clinical setting.

Ren, Y., Y. Zhang, et al. (2019). **"The cullin4A is up-regulated in chronic obstructive pulmonary disease patient and contributes to epithelial-mesenchymal transition in small airway epithelium."** Respir Res **20**(1): 84.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a common respiratory disease with high morbidity and mortality. The most important pathophysiological change of COPD is airway obstruction. Airway obstruction can cause airflow restriction and obstructive ventilation dysfunction. Currently, many studies have shown that there is EMT phenomenon in the process of airway remodeling of COPD. Cullin4A (CUL4A) is an E3 ubiquitin ligase that interacts with other factors to form the E3 complex. Studies have shown that CLU4A is associated with EMT in non-small cell lung cancer and other cancers. However, its relationship with EMT in COPD has not been reported systematically. In this study, we detected the expression of CUL4A in lung epithelium of COPD patients. In addition, the regulatory effect and mechanism of CUL4A on EMT in COPD were clarified in small airway epithelial cells. METHODS: The expression of CUL4A was assessed by immunohistochemistry in lung epithelium specimens from smokers, non-smokers and patients with chronic obstructive pulmonary disease. The role of CUL4A on cigarette smoke extract (CSE)-induced epithelial-mesenchymal transition (EMT) in human small airway epithelial cells (HSAEpiCs) was assessed by silencing or overexpression CUL4A in vitro. Cigarette smoke is recognized as a high-risk factor in the induction of COPD, and its damage to the airway involves airway damage, airway inflammation and airway remodeling. RESULTS: The results shown that CUL4A expression in small airway epithelium was significantly increased in patients with COPD. We also observed a significant negative association between CUL4A and FEV1%, a useful clinical marker for the diagnosis and evaluation of COPD severity, in small airway epithelial cells. In vitro, CSE-induced EMT is associated with high expression of CUL4A, and targeted silencing of CUL4A with shRNA inhibits CSE-induced EMT in human small airway epithelial cells. CONCLUSIONS: Our results showed that CUL4A was overexpressed in lung epithelium of COPD patients, and CUL4A could regulate EMT of human small

airway epithelium, which revealed a new mechanism of remodeling of small airway epithelium of COPD patients.

Sand, J. M. B., P. Lamy, et al. (2018). **"Development of a Neo-Epitope Specific Assay for Serological Assessment of Type VII Collagen Turnover and Its Relevance in Fibroproliferative Disorders."** Assay Drug Dev Technol **16**(2): 123-131.

Type VII collagen is the main component of the anchoring fibrils connecting the basement membrane to the underlying interstitial matrix. Mutations in the type VII collagen gene cause dystrophic epidermolysis bullosa. Increased levels of type VII collagen in the skin have been reported in patients with systemic sclerosis (SSc), whereas reduced levels in the airways have been related to asthma. This indicates that type VII collagen plays an important part in upholding tissue integrity and that its remodeling may lead to pathological states. The aim of this study was to investigate the role of type VII collagen remodeling in fibroproliferative disorders. We produced monoclonal antibody targeting a specific fragment of type VII collagen (C7M) released to the systemic circulation and developed a neo-epitope specific competitive enzyme-linked immunosorbent assay (ELISA). Biological relevance was evaluated in serum from patients with SSc or chronic obstructive pulmonary disease (COPD). The C7M ELISA was technically robust and specific for the C7M neo-epitope. Serum C7M levels were significantly elevated in two cohorts of patients with SSc and in patients with COPD as compared with healthy individuals ($P < 0.0001$). The C7M ELISA enabled quantification of type VII collagen turnover in serum. Elevated serum C7M levels indicated that the turnover rate of type VII collagen was significantly increased in patients with SSc or COPD, suggesting a pathological role. Thus, the C7M ELISA may become useful in future investigations of type VII collagen turnover in fibroproliferative disorders, and it may prove a valuable tool for evaluating novel anti-fibrotic drugs.

Sansgiry, S. S., A. Bhansali, et al. (2019). **"Effect of coverage gap on healthcare utilization among Medicare beneficiaries with chronic obstructive pulmonary disorder."** Curr Med Res Opin **35**(2): 321-328.

OBJECTIVE: To evaluate the association between the Medicare coverage gap with hospitalization, emergency room (ER) visits, and time to hospitalization in chronic obstructive pulmonary disease (COPD) patients. METHODS: Retrospective cohort study using data from a Medicare Advantage (MA) plan. Patients with >/=1 claim for COPD at baseline, >/=65 years, continuous 24-months enrollment and without any cancer/end stage renal disease diagnosis were eligible. Patients not reaching the coverage gap (no coverage gap) were matched and compared to those reaching the coverage gap and those reaching catastrophic coverage in separate analyses. Chi-square tests and Cox proportional hazards model were used to compare outcomes across matched cohorts. RESULTS: In total, 3142 COPD patients were identified (79% no coverage gap, 10% coverage gap, and 11% catastrophic coverage). Compared to the no coverage gap group, a larger number of beneficiaries in the coverage gap group had >/=1 hospitalization (26% vs 32%, $p < .05$), >/= 1 ER visits (43% vs 49%, $p < .05$), and >/=1 hospitalization/ER (total visit) (47% vs 54%, $p < .05$), respectively. Compared to the no coverage gap group, a greater number of beneficiaries in catastrophic coverage had >/=1 ER visit (45% vs 53%, $p < .05$) or >/=1 total visits (48% vs 56%, $p < .05$), respectively. Time to hospitalization was shorter among those entering the coverage gap as compared to the no coverage gap [Hazards Ratio (HR) = 1.5; $p = .040$]. CONCLUSIONS: COPD patients entering the coverage gap and catastrophic coverage were associated with increased utilization of healthcare services. Entering the coverage gap was also associated with shorter time to hospitalization as compared to the no coverage gap.

Sapmaz, E., H. Isik, et al. (2019). **"A comparative study of pneumomediastinums based on clinical experience."** Ulus Travma Acil Cerrahi Derg **25**(5): 497-502.

BACKGROUND: Pneumomediastinum (PM) is the term which defines the presence of air in the mediastinum. PM has also been described as mediastinal emphysema. PM is divided into two subgroups called as Spontaneous PM (SPM) and Secondary PM (ScPM). METHODS: A retrospective comparative study of the PM diagnosed between February 2010 and July 2018 is presented. Forty patients were compared. Clinical data on patient history, physical characteristics, symptoms, findings of examinations, length of the hospital stay, treatments, clinical time course, recurrence and complications were investigated carefully. Patients with SPM, Traumatic PM (TPM) and Iatrogenic PM (IPM) were compared. RESULTS: SPM was identified in 14 patients (35%). In ScPM group, TPM was identified in 16 patients (40%), and IPM was identified in 10 patients (25%). On the SPM group, the most frequently reported symptoms were chest pain, dyspnea, subcutaneous emphysema and cough. CT was performed to all patients to confirm the diagnosis and to assess the possible findings. All patients prescribed prophylactic antibiotics

to prevent mediastinitis. CONCLUSION: The present study aimed to evaluate the clinical differences and managements of PMs in trauma and non-trauma patients. The clinical spectrum of pneumomediastinum may vary from benign mediastinal emphysema to a fatal mediastinitis due to perforation of mediastinal structures. In most series, only the SPM was evaluated in many aspects, but there are fewer studies comparing the evaluation and management of traumatic and non-traumatic PMs. The patients with TPM who have limited trauma to the thorax and who do not have mediastinal organ injury in their imaging studies can be followed up and treated like SPM patients who do not have mediastinal organ injury, and both have good clinical course.

Shah, P., A. McWilliams, et al. (2019). **"A comparison of methodologies for the real-time identification of hospitalized patients with acute exacerbations of COPD."** Int J Chron Obstruct Pulmon Dis **14**: 693-698.

Background: COPD is a lung disease characterized by chronic, irreversible airway obstruction that can precipitate into acute exacerbations of COPD (AECOPD) often requiring hospitalization. Improving these outcomes will require proactive innovations in care delivery to at-risk populations. Data-driven models to identify patients with AECOPD on admission to the hospital are needed, but do not exist. Objective: This study aimed to compare the performance of several models designed to identify patients with AECOPD within 24 hours of hospital admission. Methods: Clinical factors associated with admissions for AECOPD that are available within 24 hours of an encounter were combined into six different models and then tested retrospectively to evaluate each model's performance in predicting AECOPD. The data set incorporated billing and clinical data from patients who were older than 40 years of age with an inpatient or observation encounter in 2016 at one of the nine hospitals within a large integrated healthcare system. Results: Of the 116,329 encounters, 6,383 had a billing diagnosis for AECOPD. The models showed a wide range of sensitivity (0.473 vs 0.963) and positive predictive value (0.190 vs 0.827). Conclusion: It is possible to leverage clinical and administrative data to identify patients admitted with AECOPD in real-time for quality improvement or research purposes. Because models relied on clinical data, local variation in care delivery also likely contributed to performance variation across hospitals. These findings emphasize the importance of testing model performance on local data and choosing the model that best aligns with the specific goals of the targeted initiative.

Shah, S., C. M. Blanchette, et al. (2019). **"Survival associated with chronic obstructive pulmonary disease among SEER-Medicare beneficiaries with non-small-cell lung cancer."** Int J Chron Obstruct Pulmon Dis **14**: 893-903.

Objective: We investigated the impact of preexisting COPD and its subtypes, chronic bronchitis and emphysema, on overall survival among Medicare enrollees diagnosed with non-small-cell lung cancer (NSCLC). Methods: Using SEER-Medicare data, we included patients >/=66 years of age diagnosed with NSCLC at any disease stage between 2006 and 2010 and continuously enrolled in Medicare Parts A and B in the 12 months prior to diagnosis. Preexisting COPD in patients with NSCLC were identified using ICD-9 codes. Kaplan-Meier method and log-rank tests were used to examine overall survival by COPD status and COPD subtype. Multivariable Cox proportional hazards models were fit to assess the risk of death after cancer diagnosis. Results: We identified 66,963 lung cancer patients. Of these, 22,497 (33.60%) had documented COPD before NSCLC diagnosis. For each stage of NSCLC, median survival was shorter in the COPD compared to the non-COPD group (Stage I: 692 days vs 1,130 days, P<0.0001; Stage II: 473 days vs 627 days, P<0.0001; Stage III: 224 days vs 229 days; P<0.0001; Stage IV: 106 days vs 112 days, P<0.0001). For COPD subtype, median survival for patients with preexisting chronic bronchitis was shorter compared to emphysema across all stages of NSCLC (Stage I: 672 days vs 811 days, P<0.0001; Stage II 582 days vs 445 days, P<0.0001; Stage III: 255 days vs 229 days, P<0.0001; Stage IV: 105 days vs 112 days, P<0.0001). In Cox proportional hazard model, COPD patients exhibited 11% increase in risk of death than non-COPD patients (HR: 1.11, 95%CI: 1.09-1.13). Conclusion: NSCLC patients with preexisting COPD had shorter survival with marked differences in early stages of lung cancer. Chronic bronchitis demonstrated a greater association with time to death than emphysema.

Shi, Q. F., Y. Sheng, et al. (2019). **"The v-DECAF score can predict 90-day all-cause mortality in patients with COPD exacerbation requiring invasive mechanical ventilation."** Clin Respir J **13**(7): 438-445.

INTRODUCTION: The DECAF score is a simple and effective tool for predicting mortality in patients hospitalized with acute exacerbations of chronic obstructive pulmonary disease (AECOPD); however, the DECAF score has not been validated in AECOPD patients requiring invasive mechanical ventilation (IMV). We devised the ventilator (v)-DECAF score, in which "anemia" replaces "acidaemia," for use in AECOPD patients requiring IMV. The objective of this study was to compare the predictive efficacy of the v-DECAF score and the DECAF score. METHODS: This study prospectively recruited 112 consecutive AECOPD patients requiring IMV from a single center. The clinical endpoint was 90-day all-cause mortality. Demographic and clinical data were recorded, as well as APACHE II, GCS, CURB-65, BAP-65 and DECAF scores, and the newly devised v-DECAF score. The discriminatory value of the scoring systems in predicting 90-day all-cause mortality was determined using the area under the receiver operating characteristic (AUROC) curve. RESULTS: In multivariate logistic regression analysis, the v-DECAF score was an independent predictor of 90-day all-cause mortality (odds ratio 3.004, 95% CI 1.658-5.445, P < 0.001). The AUROC of the v-DECAF and DECAF scores were 0.852 (95% CI 0.766-0.938) and 0.777 (95%CI: 0.676-0.878), respectively. The v-DECAF score had a better predictive value for 90-day all-cause mortality compared to the DECAF score (Z = 2.338, P = 0.019). CONCLUSION: The v-DECAF score had good discriminatory power in predicting 90-day all-cause mortality in AECOPD patients requiring IMV.

Sipos, I. H., S. Labor, et al. (2019). **"Dynamics of exhaled breath temperature after smoking a cigarette and its association with lung function changes predictive of COPD risk in smokers: a cross-sectional study."** Arh Hig Rada Toksikol **70**(2): 123-129.

Exhaled breath temperature (EBT) is a biomarker of inflammation and vascularity of the airways already shown to predict incident COPD. This cross-sectional study was aimed to assess the potential of EBT in identifying "healthy" smokers susceptible to cigarette smoke toxicity of the airways and to the risk of developing COPD by analysing the dynamics of EBT after smoking a cigarette and its associations with their demographics (age, smoking burden) and lung function. The study included 55 current smokers of both sexes, 29-62 years of age, with median smoking exposure of 15 (10-71.8) pack-years. EBT was measured at baseline and 5, 15, 30, 45, and 60 min after smoking a single cigarette. Lung function was measured with spirometry followed by a bronchodilator test. To compare changes in EBT between repeated measurements we used the analysis of variance and the area under the curve (EBTAUC) as a dependent variable. Multivariate regression analysis was used to look for associations with patient characteristics and lung function in particular. The average (+/-SD) baseline EBT was 33.42+/-1.50 degrees C. The highest significant increase to 33.84 (1.25) degrees C was recorded 5 min after the cigarette was smoked (p=0.003), and it took one hour for it to return to the baseline. EBTAUC showed significant repeatability (ICC=0.85, p<0.001) and was significantly associated with age, body mass index, number of cigarettes smoked a day, baseline EBT, and baseline FEF75 (R2=0.39, p<0.001 for the model). Our results suggest that EBT after smoking a single cigarette could be used as early risk predictor of changes associated with chronic cigarette smoke exposure.

Song, J., Q. H. Wang, et al. (2018). **"Role of microRNA-218-5p in the pathogenesis of chronic obstructive pulmonary disease."** Eur Rev Med Pharmacol Sci **22**(13): 4319-4324.

OBJECTIVE: Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease characterized by inflammatory cell activation and the release of inflammatory mediators. By measuring microRNA expression in the plasma of COPD subjects, we aimed to identify the clinical relevance of plasma miRNA levels in these patients. PATIENTS AND METHODS: A total of 40 COPD patients and 40 healthy controls were enrolled in the study. The COPD model of C57BL/6 mice was also developed by exposing them to cigarette smoke (CS). The expression of microRNA-218-5p was detected by qRT-PCR in all the subjects and mice. The serum level of IL-18 and TGF-beta1 was also detected via ELISA kit. To investigate the effects of miR-218-5p, 10 mg/kg of miR-218-5p inhibitor (miR-218-5p antagonist), a scrambled control or PBS (solvent) was intranasally administered on the first and the fourth exposure day, before the start of CS exposure. RESULTS: The results showed that miR-218-5p was significantly down-regulated in patients with COPD, compared to normal subjects. There was a negative correlation between the plasma miR-218-5p level and the duration of disease since diagnosis in COPD ex-smokers. CS-induced COPD mice experiments with a miR-218-5p inhibitor demonstrated a protective role of miR-218-5p in cigarette smoke-induced inflammation and COPD. CONCLUSIONS: These findings supported that miR-218-5p may, therefore, play an important role in the pathogenesis of COPD.

Sorensen, D. and H. Svenningsen (2018). **"Adherence to home-based inspiratory muscle training in individuals with chronic obstructive pulmonary disease."** Appl Nurs Res **43**: 75-79.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is an incurable progressive illness characterized by airflow limitation and respiratory failure. Inspiratory muscle training (IMT) combined with pulmonary rehabilitation increases inspiratory muscle strength and endurance, and it decreases dyspnoea. Little is known about IMT adherence, and in the present study, we aimed to evaluate adherence to home-based IMT used with automatic internet-based feedback, in patients with chronic obstructive pulmonary disease. METHOD: The adherence was evaluated at an individual level by completing a before-and-after comparison between two groups. Over a 12-week study period, the participants performed two daily sessions of 30 breaths with a mechanical threshold loading training device. They were randomly assigned to either a group of people who self-reported their perceived exertion during breathing and who received automatic internet-based feedback regarding their next threshold loadings, or a group of people who performed IMT with 30% maximal inspiratory pressure and who received no feedback. RESULTS: The group of patients who self-reported their perceived exertion showed significantly better training adherence compared with the group of patients who received no feedback. CONCLUSION: Adherence was greater among patients who self-reported their perceived breathing exertion and received automatic internet-based feedback on the next threshold loadings compared with patients who self-reported training sessions without feedback.

Sundar, I. K., K. P. Maremanda, et al. (2019). **"Mitochondrial dysfunction is associated with Miro1 reduction in lung epithelial cells by cigarette smoke."** Toxicol Lett **317**: 92-101.

Cigarette smoke (CS) is known to cause mitochondrial dysfunction leading to cellular senescence in lung cells. We determined the mechanism of mitochondrial dysfunction by CS in lung epithelial cells. CS extract (CSE) treatment differentially affected mitochondrial function, such as membrane potential, mitochondrial reactive oxygen species (mtROS) and mitochrondrial mass as analyzed by FACS, and were associated with altered oxidative phosphorylation (OXPHOS) protein levels (Complexes I-IV) in primary lung epithelial cells (SAEC and NHBE), and (complexes I and II) in BEAS2B cells. There were dose- and time-dependent changes in mitochondrial respiration (oxygen consumption rate parameters i.e. maximal respiration, ATP production and spare capacity, measured by the Seahorse analyzer) in control vs. CSE treated BEAS2B and NHBE/DHBE cells. Electron microscopy (EM) analysis revealed perinuclear clustering by localization and increased mitochondrial fragmentation by fragement length analysis. Immunoblot analysis revealed CS-mediated increase in Drp1 and decrease in Mfn2 levels that are involved in mitochondrial fission/fusion process. CSE treatment reduced Miro1 and Pink1 abundance that play a crucial role in the intercellular transfer mechanism and mitophagy process. Overall, these findings highlight the role of Miro1 in context of CS-induced mitochondrial dysfunction in lung epithelial cells that may contribute to the pathogenesis of chronic inflammatory lung diseases.

Tanabe, N., S. Sato, et al. (2019). **"Associations of airway tree to lung volume ratio on computed tomography with lung function and symptoms in chronic obstructive pulmonary disease."** Respir Res **20**(1): 77.

BACKGROUND: Decreased airway lumen size and increased lung volume are major structural changes in chronic obstructive pulmonary disease (COPD). However, even though the outer wall of the airways is connected with lung parenchyma and the mechanical properties of the parenchyma affect the behaviour of the airways, little is known about the interactions between airway and lung sizes on lung function and symptoms. The present study examined these effects by establishing a novel computed tomography (CT) index, namely, airway volume percent (AWV%), which was defined as a percentage ratio of the airway tree to lung volume. METHODS: Inspiratory chest CT, pulmonary function, and COPD Assessment Tests (CAT) were analysed in 147 stable males with COPD. The whole airway tree was automatically segmented, and the percentage ratio of the airway tree volume in the right upper and middle-lower lobes to right lung volume was calculated as the AWV% for right lung. Low attenuation volume % (LAV%), total airway count (TAC), luminal area (Ai), and wall area percent (WA%) were also measured. RESULTS: AWV% decreased as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric grade increased ($p < 0.0001$). AWV% was lower in symptomatic (CAT score >/= 10) subjects than in non-symptomatic subjects ($p = 0.036$). AWV% was more closely correlated with forced expiratory volume in 1 s (FEV1) and ratio of residual volume to total lung capacity (RV/TLC) than Ai, Ai to lung volume ratio, and volume of either the lung or the airway tree. Multivariate analyses showed that lower AWV% was associated with lower FEV1 and higher RV/TLC, independent of LAV%, WA%, and TAC. CONCLUSIONS: A disproportionally small airway tree with a relatively large lung could lead to airflow

obstruction and gas trapping in COPD. AWV% is an easily measured CT biomarker that may elucidate the clinical impacts of the airway-lung interaction in COPD.

Tian, Y., T. Zeng, et al. (2019). **"Clinical significance of BPI-ANCA detecting in COPD patients with Pseudomonas aeruginosa colonization."** J Clin Lab Anal **33**(6): e22908.

BACKGROUND: Antineutrophil cytoplasmic autoantibodies against neutrophil granule bactericidal/permeability-increasing protein (BPI-ANCA) has been found in many inflammatory diseases, such as COPD, which can reduce the killing effect of BPI on Gram-negative bacteria. This study was aimed to assess the clinical significance of BPI-ANCA detecting in COPD patients with Pseudomonas aeruginosa (P aeruginosa) colonization. METHODS: A total of 216 COPD patients with lung P aeruginosa colonization, 244 patients with P aeruginosa infection from June 2015 to June 2018, and 100 healthy individuals were included. Serum BPI-ANCA, tumor necrosis factor (TNF)-alpha, and interleukin (IL)-6 and IL-1beta levels were detected by ELISA, and the lung function of the patients was measured at stable clinical stages. Patients with COPD were grouped according to BPI-ANCA detection and GOLD criteria, and serum TNF-alpha, IL-6, and IL-1beta levels and indices reflecting lung function were compared and analyzed between groups. RESULTS: Positive rate of BPI-ANCA in COPD patients with P aeruginosa colonization was 48.15%; and compared with BPI-ANCA(-) group, FEV1 %pred and FEV1 /FVC(%) in BPI-ANCA(+) patients were significantly decreased, while TNF-alpha, IL-6, and IL-1beta levels were elevated. There were 31.73% and 36.54% BPI-ANCA(+) patients with severe and very severe airflow limitation, respectively, which was significantly higher than that in the BPI-ANCA(-) group. FEV1 %pred and FEV1 /FVC(%) were negatively correlated with TNF-alpha, IL-6, IL-1beta, and NEU%. C-reactive protein (CRP) was negatively correlated with FEV1 %pred, yet not significantly correlated with FEV1 /FVC(%). CONCLUSION: BPI-ANCA positivity is associated with inflammatory status in COPD patients with pulmonary P aeruginosa colonization and can be used as a potential biomarker assessing disease severity.

To, T., J. Zhu, et al. (2018). **"Asthma and Chronic Obstructive Pulmonary Disease Overlap in Women. Incidence and Risk Factors."** Ann Am Thorac Soc **15**(11): 1304-1310.

RATIONALE: Women with asthma are at a high risk of developing chronic obstructive pulmonary disease (COPD) or asthma and COPD overlap syndrome (ACOS) as they age, which is a condition associated with a high mortality rate, low quality of life, and high healthcare costs. However, factors influencing the development of ACOS remain unclear. OBJECTIVES: To quantify the risk of developing COPD in women in Ontario with asthma and identify factors that are associated with increased risk. METHODS: Data for women in Ontario with asthma who participated in the Canadian National Breast Screening Study from 1980 to 1985 were linked to health administrative databases, and participants were followed from 1992 to 2015. A competing risks survival model was used to measure the associations between sociodemographic, lifestyle, and environmental risk factors and time to COPD incidence, accounting for death as a competing risk. RESULTS: A total of 4,051 women with asthma were included in the study, of whom 1,701 (42.0%) developed COPD. The mean age at the study end date was 79 years. Low education, high body mass index, rurality, and high levels of cigarette smoking were associated with ACOS incidence, whereas exposure to fine particulate matter, a major air pollutant, was not. CONCLUSIONS: Individual risk factors appear to play a more significant role in the development of ACOS in women than environmental factors, such as air pollution. Prevention strategies targeting health promotion and education may have the potential to reduce ACOS incidence in this population.

Toledo-Pons, N., J. F. M. van Boven, et al. (2019). **"ACO: Time to move from the description of different phenotypes to the treatable traits."** PLoS One **14**(1): e0210915.

BACKGROUND: Asthma-COPD overlap (ACO) is a term that encompasses patients with characteristics of two conditions, smoking asthmatics or COPD patients with asthma-like features such as high bronchodilator response or blood eosinophil count >/=300 cells/muL. The aim of this study was to compare the different phenotypes inside the ACO definition in a real-life population cohort. METHODS: We analyzed patients from the MAJORICA cohort who had a diagnosis of asthma and/or COPD based on current guidelines, laboratory data in 2014 and follow-up until 2015. Prevalence of ACO according to the different criteria, demographic, clinical and functional characteristics, prescriptions and use of health resources data were compared between three groups. RESULTS: We included 603 patients. Prevalence of smoking asthmatics was 14%, COPD patients with high bronchodilator response 1.5% and eosinophilic COPD patients 12%. Smoking asthmatics were younger and used more rescue inhalers, corticosteroids and health resources. Conversely, eosinophilic COPD patients were older than the other groups, often treated with corticosteroids and had lower use of health resources. Most of the COPD patients with high

bronchodilator response were included in the eosinophilic COPD group. CONCLUSIONS: ACO includes two conditions (smoking asthmatics and eosinophilic COPD patients) with different medication requirement and prognosis that should not be pooled together. Use of >/=300 blood eosinophils/muL as a treatable trait should be recommended.

Voorham, J., N. Roche, et al. (2018). **"Real-world effectiveness evaluation of budesonide/formoterol Spiromax for the management of asthma and chronic obstructive pulmonary disease in the UK."** BMJ Open **8**(10): e022051.

OBJECTIVES: Budesonide/formoterol (BF) Spiromax ((R)) is an inhaled corticosteroid/long-acting beta2-agonist fixed-dose combination (FDC) inhaler, designed to minimise common inhaler errors and provide reliable and consistent dose delivery in asthma and chronic obstructive pulmonary disease (COPD). We evaluated non-inferiority of BF Spiromax after changing from another FDC inhaler, compared with continuing the original inhaler. METHODS: Patients with asthma and/or COPD who switched to BF Spiromax were matched (1:3) with non-switchers. Data were obtained from the Optimum Patient Care Research Database and Clinical Practice Research Datalink in the UK. The primary end point was the proportion of patients achieving disease control (using the risk domain control (RDC) algorithm); secondary end points were: exacerbation rate, short-acting beta2-agonist (SABA) use and treatment stability (achieved RDC; no maintenance treatment change). Non-inferiority was defined as having 95% CI lower bound above -10%, using conditional logistic regression and adjusted for relevant confounders. RESULTS: Comparing 385 matched patients (asthma 253; COPD 132) who switched to BF Spiromax with 1091 (asthma 743; COPD 348) non-switchers, non-inferiority of BF Spiromax in RDC was demonstrated (adjusted difference: +6.6%; 95% CI -0.3 to 13.5). Among patients with asthma, switchers to BF Spiromax versus BF Turbuhaler((R)) reported fewer exacerbations (adjusted rate ratio (RR) 0.76;95% CI 0.60 to 0.99; p=0.044); were less likely to use high daily doses of SABA (adjusted OR 0.71;95% CI 0.52 to 0.98; p=0.034); used fewer SABA inhalers (adjusted RR 0.92;95% CI 0.86 to 0.99; p=0.019); and were more likely to achieve treatment stability (adjusted OR 1.44;95% CI 1.02 to 2.04; p=0.037). No significant differences in these end points were seen among patients with COPD. CONCLUSIONS: Among UK patients with asthma and COPD, real-world use of BF Spiromax was non-inferior to BF Turbuhaler in terms of disease control. Among patients with asthma, switching to BF Spiromax was associated with reduced exacerbations, reduced SABA use and improved treatment stability versus continuing on BF Turbuhaler.

Wang, C., Y. Cui, et al. (2019). **"Continuous hemodiafiltration as a rescue therapy for patients with cardiopulmonary failure caused by enterovirus-71: a retrospective observational study in a PICU."** BMC Infect Dis **19**(1): 866.

BACKGROUND: Hand, foot and mouth disease (HFMD) remains a burdensome health issue in mainland China. Enterovirus71 (EV-A71) is the main pathogen of severe HFMD. Continuous hemofiltration improves fluid overload, restores kidney function and alleviates inflammatory reactions. The aim of the present study was to evaluate the effects of continuous veno-venous hemodiafiltration (CVVHDF) on severe HFMD caused by EV-A71(EV-A71-HFMD) in a pediatric intensive care unit (PICU). METHODS: A retrospective observational study was performed in a tertiary university PICU from January 2012 to December 2016. Children with severe EV-A71-HFMD complicated by cardiopulmonary failure were included. The patients were divided into a CVVHDF group and a conventional therapy (control) group (non-CVVHDF). The demographics, characteristics, and outcomes between the groups were collected and analyzed. RESULTS: Twenty-nine patients with severe EV-A71-HFMD were enrolled. The 28-day mortality was 17.6% (3/17) in the CVVHDF group and 33.3% (4/12) in the non-CVVHDF group, with no statistical significance between the two groups (P = 0.403). The median interval between CVVHDF initiation and PICU admission was 6 (4,8.5) hrs, and the median duration of CVVHDF was 48 (36, 64) hrs. The left ventricular ejection fraction (LVEF) and cardiac index (CI) in the CVVHDF group were improved after treatment. The plasma levels of catecholamines and renin-angiotensin-aldosterone system (RAAS) substances in the CVVHDF group were significantly decreased after treatment. The decreased catecholamines and RAAS substances included adrenalin (169.8 [145.5, 244.6] vs. 148.0 [109.0, 208.1] ng/L, P = 0.033), dopamine (152.7 [97.0, 191.1] vs. 96.0 [68.0, 160.9] ng/L, P = 0.026), angiotensin II (185.9 [125.2, 800.0] vs. 106.0 [90.8, 232.5] ng/L, P = 0.047), aldosterone (165.7 [94.0, 353.3] vs. 103.3 [84.3, 144.3] ng/L, P = 0.033), and renin (1.12 [0.74, 3.45] vs. 0.79 [0.52, 1.25] mug/L/h, P = 0.029), CONCLUSIONS: CVVHDF reduced the levels of catecholamines and RAAS substances and improved cardiovascular function. Continuous hemodiafiltration may represent a potential therapy in patients with severe EV-A71-HFMD complicated with cardiopulmonary failure.

Wang, F., Z. Liang, et al. (2019). **"Reproducibility of fluid-phase measurements in PBS-treated sputum supernatant of healthy and stable COPD subjects."** Int J Chron Obstruct Pulmon Dis **14**: 835-852.

Purpose: The purpose of this study was to investigate the reproducibility of fluid-phase measurements in PBS-treated sputum supernatant, processed using the two-step method, of healthy and stable COPD individuals. Methods: Nine healthy subjects and 23 stable COPD patients provided sputum twice within 6 days. A two-step sputum processing method was used to obtain PBS-treated supernatant and sputum cells. Soluble protein markers and IgG and IgM autoantibody profiles in PBS supernatant were analyzed using customized microarrays. Repeatability of measurements was assessed by paired-sample testing and an intraclass correlation coefficient, then graphically reported by Bland-Altman plot. Results: There was no significant difference between the repeated detection of 8/10 types of soluble protein markers, all 13 types of IgG autoantibodies, and 12/13 types of corresponding IgM autoantibodies in PBS supernatant. The repeatability of measurements in PBS supernatant was substantial to very good for interleukin 6 (IL6), IL8, IL13, IL10, IL33, vascular endothelial growth factor, soluble receptor for advanced glycation end-products, and tumor necrosis factor-alpha; for IgG autoantibodies against aggrecan, centromere protein B (CENP-B), collagen II, collagen IV, cytochrome C, elastin, heat shock protein 47 (HSP47), HSP70, and La/Sjogren syndrome type B antigen; for IgM autoantibodies against CENP-B, collagen I, collagen II, collagen IV, cytokeratin 18, and HSP70; and for sputum neutrophils, macrophages and eosinophils count. Bland-Altman plots suggested good consistency within repeated measurements. Stable COPD patients differed from healthy subjects in the proportion of neutrophils and eosinophils; relative fluorescence intensity of anti-cytochrome C IgG, anti-aggrecan IgM, and anti-cytochrome C IgM. There was a significant positive correlation for stable COPD patients between sputum anti-collagen II IgG and post-bronchodilator FEV1%. Conclusion: We confirmed fluid-phase measurements in PBS-treated sputum supernatant by high-throughput techniques with good repeatability. We demonstrated the presence of IgG and IgM autoantibodies to multiple antigens in the airways of COPD patients.

Wells, J. M., M. M. Parker, et al. (2018). **"Elevated circulating MMP-9 is linked to increased COPD exacerbation risk in SPIROMICS and COPDGene."** JCI Insight **3**(22)BACKGROUND: Matrix metalloprotease 9 (MMP-9) is associated with inflammation and lung remodeling in chronic obstructive pulmonary disease (COPD). We hypothesized that elevated circulating MMP-9 represents a potentially novel biomarker that identifies a subset of individuals with COPD with an inflammatory phenotype who are at increased risk for acute exacerbation (AECOPD). METHODS: We analyzed Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) and Genetic Epidemiology of COPD (COPDGene) cohorts for which baseline and prospective data were available. Elevated MMP-9 was defined based on >95th percentile plasma values from control (non-COPD) sample in SPIROMICS. COPD subjects were classified as having elevated or nonelevated MMP-9. Logistic, Poisson, and Kaplan-Meier analyses were used to identify associations with prospective AECOPD in both cohorts. RESULTS: Elevated MMP-9 was present in 95/1,053 (9%) of SPIROMICS and 41/140 (29%) of COPDGene participants with COPD. COPD subjects with elevated MMP-9 had a 13%-16% increased absolute risk for AECOPD and a higher median (interquartile range; IQR) annual AECOPD rate (0.33 [0-0.74] versus 0 [0-0.80] events/year and 0.9 [0.5-2] versus 0.5 [0-1.4] events/year for SPIROMICS and COPDGene, respectively). In adjusted models within each cohort, elevated MMP-9 was associated with increased odds (odds ratio [OR], 1.71; 95%CI, 1.00-2.90; and OR, 3.03; 95%CI, 1.02-9.01), frequency (incidence rate ratio [IRR], 1.45; 95%CI, 1.23-1.7; and IRR, 1.24; 95%CI, 1.03-1.49), and shorter time-to-first AECOPD (21.7 versus 31.7 months and 14 versus 21 months) in SPIROMICS and COPDGene, respectively. CONCLUSIONS: Elevated MMP-9 was independently associated with AECOPD risk in 2 well-characterized COPD cohorts. These findings provide evidence for MMP-9 as a prognostic biomarker and potential therapeutic target in COPD. TRIAL REGISTRATION: ClinicalTrials.gov: NCT01969344 (SPIROMICS) and NCT00608764 (COPDGene). FUNDING: This work was funded by K08 HL123940 to JMW; R01HL124233 to PJC; Merit Review I01 CX000911 to JLC; R01 (R01HL102371, R01HL126596) and VA Merit (I01BX001756) to AG. SPIROMICS (Subpopulations and Intermediate Outcomes in COPD Study) is funded by contracts from the NHLBI (HHSN268200900013C, HHSN268200900014C,HHSN268200900015C HHSN268200900016C, HHSN268200900017C, HHSN268200900018C, HHSN268200900019C, and HHSN268200900020C) and a grant from the NIH/NHLBI (U01 HL137880), and supplemented by contributions made through the Foundation for the NIH and the COPD Foundation from AstraZeneca/MedImmune; Bayer; Bellerophon Therapeutics; Boehringer-Ingelheim Pharmaceuticals Inc.; Chiesi Farmaceutici; Forest Research Institute Inc.; GlaxoSmithKline; Grifols Therapeutics Inc.; Ikaria Inc.; Novartis Pharmaceuticals Corporation; Nycomed GmbH; ProterixBio; Regeneron Pharmaceuticals Inc.; Sanofi; Sunovion; Takeda Pharmaceutical Company; and Theravance Biopharma and Mylan. COPDGene is funded by the NHLBI (R01 HL089897

and R01 HL089856) and by the COPD Foundation through contributions made to an Industry Advisory Board composed of AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pfizer, Siemens, and Sunovion.

Xu, R., Y. Zhang, et al. (2019). **"ASSOCIATION OF BONE MINERAL DENSITY WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN POSTMENOPAUSAL WOMEN."** Rev Invest Clin **71**(3): 204-210.

Background: Osteoporosis (OP) is common in patients with chronic obstructive pulmonary disease (COPD). The relationship between OP and COPD has been primarily studied in male patients, and few reports are available in postmenopausal women. Objective: The purpose of this study was to investigate the association between bone mineral density (BMD) and COPD in postmenopausal women. Methods: This cross-sectional study included 133 clinically stable female ex-smokers with confirmed COPD, and 31 age-matched "ex-smoker" female controls. We analyzed groups according to their airway obstruction category. BMD was measured on dual-energy X-ray absorptiometry images of the left femoral neck. Results: Patients with COPD had lower T-scores and higher prevalence of osteopenia/OP than the control group. In the COPD group, the airway obstruction category was significantly associated with the T-score after adjustment for confounders. Multivariate logistic regression analysis showed COPD was an independent marker for increased risk of osteopenia/OP in postmenopausal women. Conclusions: COPD and airway obstruction category were strongly related to BMD. Postmenopausal women with COPD, especially those with severe airway obstruction, had a higher prevalence rate and a higher risk of osteopenia and OP than female controls without COPD.

Xu, W., R. Li, et al. (2019). **"Increased IFN-gamma-producing Th17/Th1 cells and their association with lung function and current smoking status in patients with chronic obstructive pulmonary disease."** BMC Pulm Med **19**(1): 137.

BACKGROUND: Th17 cells are believed to be important proinflammatory cells in the pathogenesis of chronic obstructive pulmonary disease (COPD). Recent evidence demonstrates that Th17 cells display substantial developmental plasticity, giving rise to Th17/Th1 cells that secret both IL-17 and IFN-gamma and are more pathogenic in inflammatory diseases. The aim of this study was to examine the distribution of circulating Th17/Th1 subpopulation and its association with disease severity in patients with COPD. METHODS: Blood samples were obtained from 21 never-smokers, 31 smokers with normal lung function and 83 patients with COPD. The frequencies of Th17 cells and the Th17/Th1 subset were measured using flow cytometry. Plasma concentrations of IL-6, transforming growth factor (TGF)-beta1 and IL-12 were determined by ELISA. The associations of Th17/Th1 cells with lung function and smoking were evaluated. RESULTS: In peripheral blood, significantly increased proportions of Th17/Th1 cells among CD4 cells and Th17 cells were found in COPD patients compared with never-smokers and smokers with normal lung function. The percentages of Th17/Th1 cells showed correlations with forced expiratory volume in 1 (FEV1) % predicted value ($r = -0.244$, $p < 0.05$), and higher proportions of Th17/Th1 cells in GOLD stage IV patients compared with stage I patients. The percentages of Th17/Th1 cells were significantly higher in current smokers compared with ex-smoker COPD patients, and positively correlated with pack-years of smoking ($r = 0.352$, $p < 0.01$). The plasma concentrations of IL-6, TGF-beta1 and IL-12 were significantly increased in patients with COPD compared with never-smokers and smokers with normal lung function. CONCLUSION: Our results revealed correlations of proportions of IFN-gamma-producing Th17/Th1 cells with lung function and smoking, suggesting that increased Th17/Th1 cells may play a role in COPD progression.

Yamamura, K., J. Hara, et al. (2019). **"The prevalence and clinical features of asthma-COPD overlap (ACO) definitively diagnosed according to the Japanese Respiratory Society Guidelines for the Management of ACO 2018."** J Med Invest **66**(1.2): 157-164.

Background Asthma-COPD overlap (ACO) is a disease that shares clinical features of both asthma and COPD. The purpose of this study is to investigate the prevalence and clinical features of ACO. Methods We retrospectively reviewed data for 170 patients with persistent airflow limitation and diagnosed them according to "The Japanese Respiratory Society Guidelines for the Management of ACO 2018". Results Of the 170 patients, 111 were diagnosed as follows : COPD (74 patients, 66.6%), ACO (34 patients, 30.6%), and asthma (3 patients, 2.8%). There was no significant difference in clinical features between ACO and COPD patients. The following pulmonary function tests were significantly lower in ACO than in COPD patients : forced expiratory volume in 1 second/forced vital capacity, peak expiratory flow, maximal mid-expiratory flow, and the maximum expiratory flow at 50%and75%. The following respiratory impedance parameters were significantly higher in ACO than in COPD patients : respiratory

resistance (Rrs) at 5 Hz (R5), Rrsat 20 Hz (R20), R5-R20, and low-frequency reactance area. Conclusions About 30% of patients with persistent airflow limitation were diagnosed with ACO. ACO patients had lower lung function and higher respiratory impedance compared with COPD patients. J. Med. Invest. 66 : 157-164, February, 2019.

Yang, L., K. Hsu, et al. (2019). **"Changes in ventilation and perfusion following lower lobe endoscopic lung volume reduction (ELVR) with endobronchial valves in severe COPD."** Clin Respir J **13**(7): 453-459.

BACKGROUND: We have previously reported significant improvements in ventilation and perfusion (VQ) and V/Q matching in the contralateral lung, especially the non-targeted lower zone in patients with severe COPD following upper lobe ELVR with endobronchial valves. However, V/Q changes after lower lobe ELVR have not been described. METHODS: Seven patients with lower lobe heterogeneous emphysema underwent unilateral lower lobe ELVR at Macquarie University Hospital. Lung function tests, 6-minute walk tests (6MWT), St George's Respiratory Questionnaire (SGRQ) and planar differential VQ scans were performed at baseline and at 1, 3 and 12 months post-ELVR. RESULTS: Compared to baseline, patients showed significant improvements in FEV1 (0.83 +/- 0.09L-0.97 +/- 0.12L, p < 0.05), 6MWD (200.33 +/- 56.54 m-274.24 +/- 48.03 m, p < 0.05) and SGRQ (61.13 +/- 5.33-42.86 +/- 6.99, p < 0.05) at 3 months after ELVR. This improvement was maintained at 12 months. There was a corresponding significant improvement in the differential ventilation (30.21 +/- 3.04%-37.82 +/- 3.76%, p < 0.05) and perfusion (31.77 +/- 2.53%-35.60 +/- 2.58%, p < 0.05) of the contralateral non-targeted upper zone. CONCLUSIONS: Within the limitations of a small sample size, we have found that in heterogeneous severe COPD patients undergoing ELVR targeting the lower lobes, there are clinical and PFT improvements similar to that reported in ELVR targeting upper lobes. Contralateral improvement in V/Q matching also occurs following lower lobe ELVR with the greatest improvement in the contralateral upper zone, suggesting the contralateral upper lobe should be the least affected lobe if the lower lobe is targeted in ELVR. These findings need to be confirmed in a study with a larger number of patients.

Yasuura, Y., T. Maniwa, et al. (2019). **"Quantitative computed tomography for predicting cardiopulmonary complications after lobectomy for lung cancer in patients with chronic obstructive pulmonary disease."** Gen Thorac Cardiovasc Surg **67**(8): 697-703.

OBJECTIVES: In lung cancer resection, chronic obstructive pulmonary disease is a risk factor for post-operative complications. Few studies on post-operative complications of lung cancer resection have considered radiographic emphysematous change as an index. Here, we have examined the relationship between the regional ratio of the emphysematous area in pre-operative computed tomography images and cardiopulmonary complications in patients with chronic obstructive pulmonary disease who underwent lung cancer resection. METHODS: We retrospectively evaluated 159 patients with chronic obstructive pulmonary disease who underwent lobectomy for lung cancer at Shizuoka Cancer Center Hospital, Shizuoka, Japan, between 2002 and 2011. Pre-operative factors, including the proportion of the emphysematous area measured by computed tomography as a percentage of the low attenuation area (LAA%), as well as intraoperative factors were analyzed. Cardiopulmonary complications, including pyothorax, pneumonia and atelectasis, acute pulmonary injury, indwelling chest tube, long duration of oxygen supply, and arrhythmia, were evaluated. RESULTS: Cardiopulmonary complications were observed among 61 patients (38%). Univariate analysis revealed that patient age, percentage of forced expiratory volume in 1 s, LAA%, and volume of blood loss were significantly associated with cardiopulmonary complications. Multivariate analysis indicated patient age and LAA% as being significant independent predictors of cardiopulmonary complications. CONCLUSIONS: The regional ratio of the emphysematous area is useful for predicting cardiopulmonary complications in patients with chronic obstructive pulmonary disease who undergo lobectomy for lung cancer. In such patients who are also >/= 70 years of age and exhibit LAA% >/= 1.0%, careful intra- and post-operative management is warranted.

Yormaz, B., D. Findik, et al. (2019). **"Differences of viral panel positive versus negative by real-time PCR in COPD exacerbated patients."** Tuberk Toraks **67**(2): 124-130.

Introduction: Exacerbations of chronic obstructive pulmonary disease (COPD) are often caused by respiratory tract infections. The aim of this study was to investigate the clinical, laboratory and computed tomography features of patients with hospitalized COPD exacerbations in which respiratory viruses were detected using a real-time polymerase chain reaction (PCR) technique. Materials and Methods: This retrospectively planned study included patients hospitalized in the chest diseases clinic due to exacerbation of COPD between November 2018-February 2019. The study included patients who had

virus-specific real-time PCR, and computed tomography scans of the chest. Result: A total of 110 patients were included in the study. Respiratory viruses were identified in the nasopharyngeal swabs of 50 patients (45.5%) using the real-time PCR method, with rhinovirus (25%), influenza A (13.1%) and coronavirus (11.8%) being the most commonly isolated agents. The mean age of the patients was 68.28 +/- 9.59 years in the virus-positive group and 68.20 +/- 8.27 years in the virus-negative group (p= 0.963). Gender distribution, rate of smokers, exposure to biofuels, blood leukocyte count, neutrophil percentage, C-reactive protein (CRP) level, FEV1/FVC ratio did not significantly differ between the two groups (p> 0.05). Procalcitonin (PCT) and FEV1 values were significantly lower (p= 0.001 and p= 0.028, respectively) and the number of exacerbations was significantly higher in the virus-positive group (p= 0.001). The length of hospital stay was longer in the virus-positive group than in the virus-negative group (p= 0.012). Among the findings of computed tomography (CT) of the chest, bronchial wall thickening, cystic bronchiectasis, and emphysema did not differ significantly (p> 0.05). The rate of infiltrative lesions (tree-in-bud opacity, ground-glass opacity, atypical pneumonia) was significantly higher in the virus-positive group (p= 0.020). Conclusions: Viral respiratory tract infections should be considered in hospitalized patients with an exacerbation of COPD who have a history of frequent exacerbations, normal PCT value, and the absence of consolidation in CT scan of the chest. The use of broadspectrum antibiotic therapy should be avoided in patients with these features.

Yuan, W., S. Nie, et al. (2019). **"Anticholinergics aggravate the imbalance of the autonomic nervous system in stable chronic obstructive pulmonary disease."** BMC Pulm Med **19**(1): 88.

BACKGROUND: Inhaled anticholinergics, recommended as first-line maintenance treatment for patients with moderate-to-severe chronic obstructive pulmonary disease (COPD), has been demonstrated to be associated with an increased risk of cardiovascular diseases. Nevertheless, why COPD patients using inhaled anticholinergics have this higher risk remains unknown. One of mechanisms may be an autonomic imbalance because anticholinergics yield reduced vagal nervous activity. To test our hypothesis, we studied heart rate recovery (HRR) after exercise, recognized as a marker of cardiac autonomic function, in COPD patients using and not using inhaled anticholinergics. METHODS: Sixty patients with COPD were involved in this study (mean FEV1 = 1.57 +/- 0.42 L), including 24 patients who had received tiotropium for more than 1 year and 36 patients not using tiotropium as a control group. A maximal cardiopulmonary exercise test was performed. HRR was defined as the difference between peak exercise and at 1-min recovery heart rate. RESULTS: HRR was significantly lower in patients using tiotropium than in the controls (16 +/- 6 vs 22 +/- 8 beats/min, respectively, p < 0.05). Multivariate regression analysis revealed that tiotropium use and peak VCO2 were independent predictors of HRR in these COPD patients. CONCLUSIONS: These findings suggest that anticholinergics bronchodilators reduce HRR after exercise in COPD patients. This has the potential to aggravate autonomic nervous imbalance. Therefore, we recommend that COPD patients taking anticholinergic bronchodilators should be considered for monitoring of cardiac function and prescribers should be alert for cardiovascular events that may arise from autonomic nervous imbalance.

Zhang, Y., P. Lin, et al. (2018). **"Serum cytokine profiles in patients with chronic obstructive pulmonary disease associated pulmonary hypertension identified using protein array."** Cytokine **111**: 342-349.

Pulmonary hypertension (PH) is a common complication of chronic obstructive pulmonary disease (COPD) and is a significant risk factor for hospitalization and shortened life expectancy. Therefore, developing new serum biomarkers for early diagnosis and prognosis of COPD associated PH is crucial. In the present study, a solid-phase antibody array simultaneously detecting multiple proteins was used to search specific COPD associated PH biomarkers, with COPD patients and healthy subjects as control groups. As a result, compared to the COPD and healthy groups, the levels of MCP-4, SDF-1 alpha, CCL28, Adipsin, IL-28A, CD40 and AgRP were uniquely altered in COPD patient serum with pulmonary hypertension. Among these proteins, CCL28, MCP-4, CD40, AgRP and IL-28A were identified to be differentially expressed in COPD patients with hypertension, indicating that these cytokines may serve as novel biomarkers for the diagnosis and prognosis of COPD associated pulmonary hypertension.

Zhang, Y. B., H. Y. Zuo, et al. (2018). **"Correlation between peripheral skeletal muscle functions and the stable phase of COPD in older patients."** Eur Rev Med Pharmacol Sci **22**(16): 5317-5326.

OBJECTIVE: To establish normal values for detection indexes of peripheral skeletal muscle dysfunction (quadriceps femoris) of healthy older subjects, and investigate the functional status of the peripheral skeletal muscle of patients with stable phase COPD. PATIENTS AND METHODS: Patients with stable phase COPD and healthy subjects of similar age were included. The assessments of strength and myoelectricity of the

quadriceps femoris were recorded. The twitch tension of the quadriceps femoris (TwQ), quadriceps maximum voluntary contraction (QMVC), and endurance time (Tf) were measured. The multiple-parameter malnutrition index (MNI) was used for overall evaluation of the nutritional status of patients. The femoral muscle volume was estimated. All subjects were subjected to a routine pulmonary function test including indexes such as FEV1, FVC, FEV1/FVC (%), and PEF. Enzyme-linked immunoassay (ELISA) was used to measure the levels of myostatin, tumor necrosis factor-alpha, TNF-like apoptosis-inducing factor (TWEAK), surface active protein D (SPD), C-reactive protein (CRP), interleukin (IL)-1beta, and IL-6. The cell immunohistochemical method was used to detect the expression of nuclear factor Kappa B (NF-kappaB). RESULTS: There were significant differences in body weight, BMI, femoral muscle volume, and physical activity scores between the two groups ($p<0.01$). The MNI of patients in the COPD group was significantly higher than that in the control group ($p<0.01$). The QMVC of 51 male and 16 female patients decreased. All eight tested cytokines increased in the COPD group but there were only significant differences in four cytokines ($p<0.05$). CONCLUSIONS: Chronic systemic inflammation is a major risk factor of skeletal muscle dysfunction (SMD) in COPD patients. The levels of SPD, myostatin, TWEAK, and TNF-alpha decreased significantly in COPD patients.

Zhao, J., M. Li, et al. (2019). **"Role of PM2.5 in the development and progression of COPD and its mechanisms."** Respir Res **20**(1): 120.

BACKGROUND: A multitude of epidemiological studies have shown that ambient fine particulate matter 2.5 (diameter < 2.5um; PM2.5) was associated with increased morbidity and mortality of chronic obstructive pulmonary disease (COPD). However, the underlying associated mechanisms have not yet been elucidated. We conducted this study to investigate the role of PM2.5 in the development of COPD and associated mechanisms. METHODS: We firstly conducted a cross-sectional study in Chinese han population to observe PM2.5 effects on COPD morbidity. Then, in vitro, we incubated human bronchial epithelial cells to different concentrations of PM2.5 for 24 h. The expression levels of IL-6 and IL-8 were detected by ELISA and the levels of MMPs, TGF-beta1, fibronectin and collagen was determined by immunoblotting. In vivo, we subjected C57BL/6 mice to chronic prolonged exposure to PM2.5 for 48 weeks to study the influence of PM2.5 exposure on lung function, pulmonary structure and inflammation. RESULTS: We found that the effect of PM2.5 on COPD morbidity was associated with its levels and that PM2.5 and cigarette smoke could have a synergistic impact on COPD development and progression. Both vitro and vivo studies demonstrated that PM2.5 exposure could induce pulmonary inflammation, decrease lung function, and cause emphysematous changes. Furthermore, PM2.5 could markedly aggravated cigarette smoke-induced changes. CONCLUSIONS: In short, we found that prolonged chronic exposure to PM2.5 resulted in decreased lung function, emphysematous lesions and airway inflammation. Most importantly, long-term PM2.5 exposure exacerbateed cigarette smoke-induced changes in COPD.