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REPORT FROM

Virtual ERS International Congress

Wednesday September 8, 2021

Spirometry and oscillometry: Updates in basic and advanced lung function

Tuesday offered a Skills Lab session which was chaired by Prof. Omar S. Usmani, UK. The Skills Lab session included lectures on spirometry by Andrew Kouri, Canada, and Laura Rangel, Mexico, and on oscillometry by Chung-Wai Chow and Ronald Dandurand, both from Canada.

Spirometry was introduced as the *"queen of respiratory function tests"*, however, especially during times of COVID-19, infection control has shown to be a challenge. This is due to aerosol generation and the increased particle concentrations measurable for up to fifty minutes after a performed spirometry test (Li et al., Chest. 2021 Apr;159(4):1570-1574). The presenters stressed the importance of personal protection equipment for the personnel and required providers of spirometers to evaluate the use of filters for their devices. Alternatively, "at home spirometry" was discussed using portable electronic spirometers and smart phone applications. Studies have shown a high correlation between home- and clinical-based spirometers (Kerwin et al. 2019; Watz et al. 2018). Due to less intense coaching during home-measurements, reduced values of FEV1 of ~50mL have been observed compared to nurse-led measurements.

Accurate interpretations of spirometry require validated reference equations. These equations need to take into consideration factors such as age, height, sex and race/ethnicity. The Global Lung Initiative (GLI) communicated in their latest update from 2012 that there is a potential bias in their reference equations caused by e.g. socioeconomic status or environmental factors. Drs Kouri and Rangel emphasised that the definitions of races/ethnicities can vary between population databases, and underlined that indigenous populations are still lacking reference equations.

The presentation on oscillometry started with a definition: Oscillometry is the imposition of a sinusoidal current of air into the open mouth of a subject. Oscillometry was also described as "Cinderella waiting for her prince". The experts gave several examples for oscillometric traces of ventilatory inhomogeneity, peripheral as well as central obstruction. Several misperceptions on oscillometry were addressed, e.g. the misperception of the lack of reference values and equations. These have been published by Kalchiem-Dekel et al. (Respir Med. 2018 Mar;136:37-47) and others. It is however correct that cut-off values for diagnosis have not yet been defined. Oscillometry is sometimes perceived to be less reliable, which again is a misperception: The variability between measurements is below 10%, and the variance is caused by a higher sensitivity compared to spirometry. Next, the presenters clarified that impulse oscillometry (IOS) is not different from forced oscillation technique (FOT), but a subclass of the latter using a train of impulses to probe the respiratory system rather than single impulses.

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Deconstructing the GINA staircase: the new house of asthma

During the session on Clinical challenges beyond guidelines, Prof. Paul O´Byrne from Canada summarised the evolution of the GINA recommendations for treatment of asthma and gave the background to the latest changes for treatment of step 1 asthma implemented in 2021. From the "staircase" of the stepwise increase in treatment published in 1995, several maturations and changes have been implemented, emphasising the importance of a cycle of assessment- treatment adjustment- review of the response as recommended in 2018. In this context, Prof. O´Byrne stressed the importance of assuring that the diagnosis of asthma is correct. In 2021, a major change in the recommended step 1 treatment of mild asthma was made, the recommended treatment now being ICS/formoterol as needed, alternatively ICS maintenance treatment. Prof. O´Byrne stressed that this alternative is only to be chosen if the patient will certainly adhere to treatment.

Several observations gave rise to these changes.

The regular use of SABA has been shown to worsen asthma control (Sears et al., Lancet 1990), enhance exercise-bronchoconstriction (Inman et al., AJRCCM 1996) and promote airway inflammation (Gauvreau et al., AJRCCM 1997). Overuse of SABA is associated with increased exacerbation risk and asthma mortality (Nwaru et al., Eur Resp J 2020).

The change in recommendations was supported by evidence from large clinical trials and real-world data. The benefit of using ICS in mild asthma was demonstrated in the three-year START trial (Reddel et al, Lancet 2017), which found that 20% of mild asthmatics per year not treated with ICS will experience a severe exacerbation requiring OCS treatment. With ICS maintenance treatment, exacerbations will occur in 5% in of mild asthmatics, and 8% of asthmatics defined by having symptoms twice a week.

The recommendation to treat mild asthma with ICS/formoterol as needed is based on the SYGMA trials and subsequent analyses, published by O´Byrne et al. NEJM 2018, Bateman et al. NEJM 2018, and Bateman et al., Annals ATS 2021 in press. In these trials, the asthma exarcerbation rate was massively reduced by both low-dose ICS maintenance and ICS/formoterol as needed, compared to SABA as needed. However, patients frequently using SABA reliever medication improved magnificently more when treated with a combination of ICS/formoterol as needed compared to ICS maintenance treatment (O´Byrne et al., Lancet Resp Med 2021). Moreover, in a large unblinded study conducted in a primary care setting, the reduction of severe exacerbations was only achieved by treatment with ICS/formoterol as needed, but not with low-dose ICS maintenance treatment (Beasley et al., NEJM 2019).

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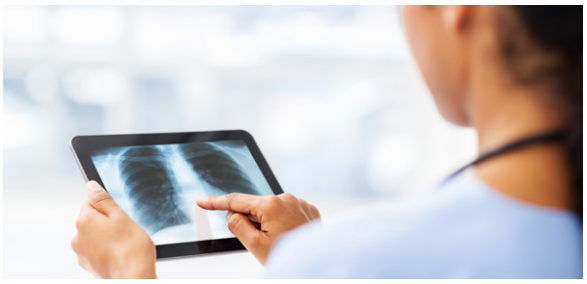
The expression of IL17RA (the common subunit of IL-17A and IL-25 receptor) on sputum macrophages in asthma patients

At the morning session *"Pearls in immunology, outcome studies and clinical trials in asthma, alpha-1 antitrypsin deficiency and COPD"* Patrycja Nejman-Gryz from Poland presented a study on the expression of the IL17RA receptor on asthmatic and control CD206+ macrophages from induced sputum with regard to IL-17/IL-25 background and in relation to clinical features.



Members of the IL-17 cytokine family, in particular IL-25 and IL-17A, play an important role in the development of asthma. IL-17A promotes inflammation through the induction of chemokines responsible for neutrophil recruitment, whereas IL-25 is associated with type-2 immune responses. The receptor for IL-17A and IL-25, called IL17RA/RB, is located on macrophages. Macrophages play a central role in the development of allergic airway diseases and are the most abundant immune cells in the lung. The three main subtypes of macrophages have been characterized; M1 and M2 are associated with inflammatory responses, and M2-like act as anti-inflammatory cells. M2-polarized cells have increased expression of CD206 (mannose receptor) and are more abundant in airway wall tissue of asthmatic compared to heathy subjects. Also, it has been shown that higher CD206 concentration is associated with more severe asthma.

In a study on adult patients with stable asthma (n=34) and healthy controls (n=34), Nejman-Gryz and colleagues presented evidence for a greater expression of IL17RA on CD206-positive sputum macrophages in the asthma group compared to control group, suggesting that IL-17A and/or IL-25 play a role in asthma pathobiology. The allergic background of asthma was associated with elevated numbers of CD206+/IL17RA+ macrophages and elevated levels of IL-25 in the sputum. Moreover, they showed that the expression of IL17RA on CD206+ macrophages in the Th2-dependent atopic environment is related to IL-25, but not to IL-17A. Hence, macrophages may represent potential therapeutic target not only in controlling Th1 pathologies, but also related to Th2-pathologies.

Ingvild Bjellmo Johnsen
Medical Advisor

IL-4Ra signaling is required for thymic stromal lymphopoietin (TSLP)-induced type 2 airway inflammation

Later during the same session, Subhashini Srivatsan from the US talked about the functional contributions of IL-4Ra and TSLP pathways to T2 airway inflammation.

TSLP is produced by airway epithelial cells and promotes T2 responses, including differentiation and proliferation of Th2 cells and IL-4 secretion. Applying two different pre-clinical allergic mouse models; house dust mite (HDM) and Ovalbumin (OVA), Srivatsan and colleagues demonstrated that TSLP requires signaling from the IL-4Rα receptor to induce features characterizing T2 airway inflammation, including goblet cell metaplasia, lung tissue eosinophilia and IgE production. On the other hand, IL-4 or IL-13 were found to promote T2 lung inflammation independent of TSLP. Blocking TSLP led to efficient modulation of T2 lung inflammation in the OVA-model whereas IL-4Rα blockade limited disease more effectively. In the HDM model, blocking IL-4Rα significantly blunted T2 lung inflammation, again independent of TSLP.

In summary these findings suggest that whilst TSLP can promote T2 airway inflammation, T2 inflammation can occur in the absent of TSLP signaling. However, the present data highlights a central role of IL-4 and IL-4Ra signalling in maintaining airway health.

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Type 2 biomarker expression (FeNO and blood eosinophils) is higher in severe adult-onset than in severe early-onset asthma

At the end of the session, Marek Lommatzsch from Germany presented a late breaking abstract comparing the expression of type 2 biomarkers (FeNO and blood eosinophils) in severe adult-onset and severe early-onset asthma.

Severe early-onset asthma was defined as a symptom onset before the age of 18, whereas severe adult-onset asthma was defined as a symptom onset after the age of 18. It is well known that patients with early-onset asthma often have allergies, while allergies are rare in patients with adult-onset asthma. However, it has not been explicitly studied before whether there are differences in FeNO levels and blood eosinophil levels between these groups.

Lommatzsch and colleagues studied 220 biologic-naive patients with severe asthma from the outpatient clinic for severe asthma in Rostock, Germany. Among the 220 patients, 50 had severe early-onset asthma and 170 had severe adult-onset asthma. The study showed that patients with severe adult-onset asthma had significantly higher FeNO levels and blood eosinophils as compared to patients with severe early-onset asthma. In contrast there was a trend to lower serum IgE levels in patients with severe adult-onset asthma as compared to patients with severe early-onset asthma. When looking at phenotypes (as defined by the UK severe asthma registry), it was a higher likelihood of a type 2 high phenotype in patients with severe adult-onset asthma as compared to patients with severe early-onset asthma. A type 2 low phenotype was rare in both groups. Within the adult-onset asthma group the type 2 high phenotype was significantly more prevalent among patients without allergies than among patients with allergies.

In conclusion, patients with severe adult-onset asthma have higher FeNO levels and blood eosinophils and a higher likelihood of a type 2 high phenotype than in patients with severe early-onset asthma. Interestingly, it was found a clear dissociation between IgE and allergies on the one hand and FeNo and blood eosinophils on the other hand in patients with severe adult-onset asthma.

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E-poster: COPD burden, epidemiology and management

E- poster 3501. To achieve only primary education is associated with COPD and poor prognosis Anne Lindberg (Boden, Sweden), Linnea Hedman, Caroline Stridsman, Christian Schyllert, Eva Rönmark, Helena Backman

The aim for this study was to evaluate the impact on the level of education among individuals with COPD and normal lung function in relation to prognosis in a Swedish cohort.

The study included 625 persons who had COPD (FEV1/VC < 0,7 post-bronchodilator) and 666 persons that had normal lung function, NLF (FEV1/VC > 0,7 and FVC > 80% of predicted). These were divided into groups who obtained primary education or secondary/tertiary education. Results showed that the mean number of school years were significantly lower (9,5 y vs. 10 y, p=0,004) and reaching primary education as the highest level (OR 1,32, p=0,047) more frequent in the COPD patients compared to NLF, independent of age, sex and smoking habits. There was also a significant difference in cumulative mortality in NLF (27,4%) compared to COPD (43,7%), p<0,001. A Caplan-Mayer plot over 13-year survival associated with educational level and NLF or COPD showed that survival was worst in COPD patients with only primary education. The study concluded that COPD was associated with achieving only primary education which also worsened the prognosis.

E-poster 3504. The association of comorbidity clusters with long-term survival and incidence of exacerbation in a COPD cohort. The HUNT Study, Norway. Sigrid Anna Vikjord (Levanger, Norway), Ben Michael Brumpton, Xiao-Mei Mai, Lowie Vanfleteren, Arnulf Langhammer

Another poster from this session presented a study where they have looked on how comorbidities were associated with long-time survival and exacerbation in a COPD. Participants with potential COPD were recruited form the HUNT study which is a large total population-based cohort from the 1980ies, covering 125 000 Norwegian participants. The patients were followed-up after 25 years. Different comorbidities were identified and clustered using self-organizing maps. Data regarding severe exacerbations and mortality were collected from hospital data and registries. Five distinct clusters were identified: “less comorbidities”, “psychological”, “cardiovascular”, “metabolic” and “cachectic”. Results showed that when using the “less comorbidities” as a reference, individuals in the “psychological” and the “cachectic” cluster had increased all-cause mortality and were associated with a higher risk of having severe COPD exacerbations.

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